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Application of Organ-on-Chip in Drug Discovery

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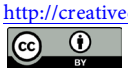

Abstract

Nowadays the pharmaceutical industry is facing long and expensive drug discovery processes. Current preclinical drug evaluation strategies that utilize oversimplified cell cultures and animal models cannot satisfy the growing demand for new and effective drugs. The microengineered biomimetic system, namely organ-on-chip (OOC), simulating both the biology and physiology of human organs, has shown greater advantages than traditional models in drug efficacy and safety evaluation. The microengineered co-culture models recapitulate the complex interactions between different types of cells *in vivo*. Organ-on-chip system has also avoided the substantial interspecies differences in key disease pathways and disease-induced changes in gene expression profiles between human and other animal models. Biomimetic microsystems representing different organs have been integrated into a single microdevice and linked by a microfluidic circulatory system in a physiologically relevant manner. In this review, I outline the current development of organ-on-chip, and their applications in drug discovery. This human-on-chip system can model the complex, dynamic process of drug absorption, distribution, metabolism and excretion, and more reliably evaluate drug efficacy and toxicity. I also discuss, for the next generation of organ-on-chip, more research is required to identify suitable materials that can be used to mass produce organs-on-chips at low cost, and to scale up the system to be suitable for high-throughput analysis and commercial applications. There are more aspects that need to be further studied, thereby bring a much better tool to patients, drug developers, and clinicians.

Keywords

Organ-on-Chip, Drug Discovery, Microfluidic Platforms, Automated, Microengineered Models

1. Introduction

The pharmaceutical industry is confronting pressing challenges because of in-

creasing costs, and the drug discovery is less efficient. Since drug failures in trials have to do with the limited predictive ability of present preclinical models, the drug discovery researchers have affirmed the urgent necessities for new testing approaches, which can make dependable predictions of drug efficacy and safety in humans [1].

Researchers find that microengineered cell culture models can provide effective solutions to those needs mentioned above. These models reconstitute physiologically important features of one or more human tissues or organs and their interactions, exerting microfabrication and microfluidics technologies to precisely control the cellular microenvironment and to better present various human physiological situations. The advanced progress has resulted in the development of promising microdevices, known as organs-on-chips that can simulate both the biology and physiology of human organs *in vitro* [1]-[5].

Organ-on-chips are microengineered biomimetic systems that represent foremost functional miniaturized units of living human organs, which also are a multi-channel 3-D microfluidic cell culture chip [1] [6] [7]. They are usually composed of transparent 3D polymeric microchannels arranged by alive human cells and duplicate three vital aspects of complete organs: 1) the 3D microarchitecture defined by the spatial distribution of multiple tissue types; 2) functional tissue-tissue interactions and interfaces; 3) dynamic mechanical and biochemical stimuli found in specific organs [1]. These special chips could be used as specialized *in vitro* models for simulations, mechanistic studies and pharmacological adjustments of complicated biological processes, which will be powerful tools for drug delivery, analyte-specific monitoring, and medical diagnostics via more precise investigations and therapies [1] [4] [6] [8] [9] [10].

The goal of organ-on-chips is not about building an intact living organ but about synthesizing the most basic functional units of tissues and organs. The simplest chip is a single, perfused microfluidic chamber containing a cultured cell, such as endothelial cells, that functions as a certain tissue type. As for other more complex designs, there are more than one microchannels connected by porous membranes, with different cell types arranged on opposite sides, to reconstruct the interfaces between different tissues [11]. These systems involve physical forces, including physiologically related fluid shear stress and mechanical compression, and they also allow analysis of responses of a specific organ, like recruitment of circulating immune cells, in reaction to drugs, toxins or other environmental disturbances [11].

In this review, I have summarized many information and progress in organ-on-chip. First, I describe the characteristics of organ-on-chip, the microfabrication methods and materials that are used to produce these chips, and some cases about existed chips that nowadays have been used in studying vital human tissues and organs *in vitro*. Second, compared with traditional models of drug discovery, novel organ-on-chip technology shows advantages in mimicking complex *in vivo* conditions and the analysis of complicated physiology issues, and organ-on-chips focus on using human induced pluripotent stem cells (hiPSCs)

to predict human response to any treatments, which contributes to the development of personalized drugs. And I introduce two case studies and further study—human-on-a-chip. Finally, I discuss more challenges that must be overcome to ensure that organ chip models meet the needs of patients, drug developers, and clinicians in future drug development, and this new field has more possibilities to develop with other cross-disciplines.

1.1. Microfabrication

The word "chip" in organ-on-a-chip originates from the original manufacturing approach, an improved form of photolithographic etching used to produce computer microchips, which enables to control the shapes and sizes of surface features on the same scale [11]. Photolithography technology also has other usages in some areas, like patterning proteins and cells. Nevertheless, microfluidic culture systems are often made by "soft lithography", and this technique is an alternative to photolithography which can be used to pattern surfaces needed in biochemistry and biology. Besides, soft lithography is cheap and experimentally simple, which can replicate patterns etched into silicon chips in more biocompatible and flexible materials [11] [12] [13]. In the process of soft photolithography, this special chip is done by pouring a liquid polymer, such as poly-dimethylsiloxane (PDMS), on an etched silicon substrate which is formed through soft lithography technology and polymerizing into an optically transparent, rubber-like material, thereby creating a "stamp" (**Figure 1**). Subsequently, both ends of the polymer block are opened for filling the fluids. Cells that flow into the channel adhere to the ECM substrate, and then the channel is continuously perfused with culture medium [11]-[17]. A pivotal feature of PDMS culture systems is their optical clarity, allowing real-time, high-resolution optical imaging of how cell responses to environmental cues [11].

Organ-on-chip platforms are designed to enhance preclinical models for analyzing responses to novel drug compounds in some organs [18]. With the increment of organoid models' size and volume, the distance between the core and the surface which contacts the fresh medium is larger, and the growing cells cannot get enough oxygen and nutrients from the simple diffusion process. Also,

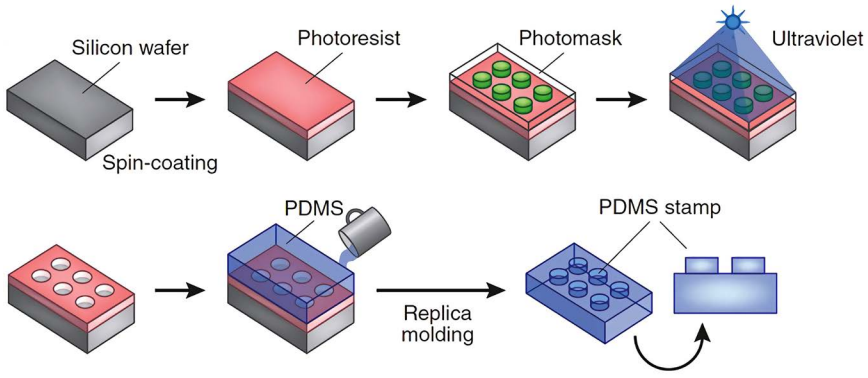

Figure 1. Fabrication methods for microfluidic chips [11].

this process limits the amount of waste being removed from cells in the core. However, only cells in contact with fresh medium can survive. In these systems, the most important thing is to build structures and parameters that are similar to the conditions in the body. The use of microfluidics technology allows people to perform tissue culture in controlled and adjustable environments to optimize temperature, pH, nutrient supply, and waste disposal. Organ-on-chip systems can also be equipped with diverse sensors and actuators and integrated with them, so that they can more accurately monitor and control key parameters in the human body, various physical and electrical stimuli, nutrition exchange, etc. [19].

1.2. Existing Organ on Chip

With the advance in modern techniques, various companies of the pharmaceutical industry have shown exponential achievements in developing more effective and lower cost drug discovery models just in recent years. And relying on this organ-on-chip technology, the integrated organ systems, such as heart, lungs, liver and so on, are generated to provide an optimal *in vitro* model for drug discovery [20] [21] [22] [23].

Take the lung organ-on-chips for example. Alveolar tissue and blood vessels are usually essential in the study of pulmonary drug discovery [20]. Therefore, in the lung models currently being studied for disease pathogenesis and drug screening, alveoli, the minimum functional unit of the lung, are used to simulate cyclic expansion by mechanical stretch to the gas-exchange surface [20] [24]. Researchers will use these chip models to address previous problems, such as a lack of interaction between the immune system and lung tissue, which may contribute to some compelling breakthroughs and could change the prospects for finding promising future treatments for diseases [20] [24]. Take the lung organ-on-chips for example. Alveolar tissue and blood vessels are usually essential in the study of pulmonary drug discovery [20]. Therefore, in the lung models currently being studied for disease pathogenesis and drug screening, alveoli, the minimum functional unit of the lung, are used to simulate cyclic expansion by mechanical stretch to the gas-exchange surface [20] [24]. Researchers will use these chip models to address previous problems, such as a lack of interaction between the immune system and lung tissue, which may contribute to some compelling breakthroughs and could change the prospects for finding promising future treatments for diseases [20] [24]. For instance, in 2017, Benam and other researches created a microfluidic device that interfaces a differentiated mucociliary bronchiolar epithelium, through engineering a small airway, an air-blood barrier, to study of physiological and pathophysiological mechanisms. This model avoids the recent main limitation of the airway mucosa, generalizing the roles of the true interactive immune system and endothelial tissues. And those tissues undergo shear stresses from blood flow, simulating as the airway. This improved lung-on-a-chip model makes it possible for further study of lung diseases related to immune systems, like comorbidities of chronic obstructive pulmonary disease

(COPD) and asthma [20] [24] [25]. In other words, several the resulting lung-on-a-chip models contribute to the development of the biologically inspired OOCs we have today [3] [24] [25].

2. OOC Application on Drug Discovery

Relevant data show that the drug development process is becoming longer and more expensive, which takes 12 years. The average cost of developing each clinically available drug is more than $1.7 billion. However, under the condition of high research expenses, the number of newly approved drugs is relatively small every year [26] [27] [28]. Nowadays, the use of physiologically-based pharmacokinetic (PBPK) modeling and simulation approaches have made significant advances in predicting the key pharmacokinetic (PK) parameters from human *in vitro* data, which becomes an important tool in drug development and regulation [29] [30] [31]. However, such approaches fail to integrate organ-specific differentials in drug clearance, distribution, and absorption which are caused by the differences in cell uptake, transport, and metabolism, therefore being unable to provide insight into pharmacodynamic (PD) parameters [29]. Plus, a new drug, approved by the Food and Drug Administration (FDA), must pass the preclinical evaluation phase and the clinical evaluation phase. One mainly relies on *in vitro* cell culture platforms and *in vivo* animal models, and another refers to the drug administration on human bodies [26]. The successful transition ratios to the next phases are approximately 65, 32, and 60 percent for phase I, phase II, and phase III, independently. Thus, the drug candidates which can be approved by the FDA are less than 1 in 10 [2] [32]. Among the major causes of failures, low pass nonclinical/clinical safety (>50%) and efficacy (>10%) are the most prominent, outperforming all other factors combined [2] [32] [34]. These major reasons mentioned above not only lead to the failure of drug development but also result in the withdrawal of approved drugs from the market [2].

2.1. Limitations of Traditional Drug Discovery

The final goal of almost all biomedical researches is to understand the pathology of human disease, thereby developing more effective patterns of diagnosis, prevention, and treatment. However, researchers cannot do basic diseases examinations with human bodies, due to kinds of reasons, so they have to rely on other alternative investigating models which have the same physiological environment as human disease [34]. The traditional preclinical drug development strategy that has been well acknowledged globally to predict the pharmacological parameters, and toxicological issues, is to utilize traditional simplified *in vitro* cell culture dishes and animal models [34] [35]. Though people have learned a lot about precious conclusions related to human disease from the disease models in animals, such as transgenic mice, some models fail to entirely and accurately reconstitute the human condition and exist several limitations separately [34]. As for the cells model, when the cells are taken out of their native environment,

they will not work as to how they function in the human bodies, owing to the environmental differences between the dishes and in the body. In terms of animal models, the obtained data from animal models cannot be precisely extrapolated to humans because it sometimes results in the distinct safe starting doses for clinical trials due to vast differences in different species' genomes.

In addition, traditional methods gradually cannot satisfy the growing demand for new and effective drugs. What's more, during using traditional disease models, drug development will be time-consuming because of those inaccuracies caused by different species' genes as well as raising ethical concerns [35]. In a word, traditional methods cannot reproduce the functions of the complicated biological structures, preventing people from getting timely and accurate analysis about diseases. These results have brought a heavy burden on the health care sector in the whole society and subsequently overwhelming the drug development progress [35].

2.2. Advantages of OOC on Drug Discovery

Superior to the limitations of traditional drug discovery methods, organ-on-chip technology offers a new approach to study human physiology in an organ-specific context, and allows us to innovate *in vitro* disease models and replicates the native tissues and various cell-cell interactions via engineered biomaterials and microfluidic technologies, accelerating the assessment process of drugs [5] [35] [36].

In evaluating drug efficacy and safety, organs-on-chips have significant advantages over other *in vitro* cell culture models. 2D culture models are easier to be made and can provide a wealth of relatively inexpensive and non-time-consuming data. They contribute significantly to the early-stage assessments of drug toxicity, while these models fail to predict and analyze the response of real tissues to drugs and certain toxins *in vivo*. For 2D culture models poorly represent complex pathophysiology in patients, investigators need extra computer models and systematical biology approaches to analyze the drug response [1] [37] [38] [39]. Nevertheless, the advent of tissue engineering raises new possibilities for the research of complicated physiological and pathophysiological processes *in vitro* [38]. With the help of biomimetic 3D tissue structures with physiological barrier function, cell culture models recreate the interwoven set of biochemical and mechanical cues in the cellular microenvironment and recapitulate the complicated interactions between different cells *in vivo*, which can more accurately simulate and control drug delivery and infiltration *in vivo* [1] [38]. Therefore, unlike 2D culture models, organ-on-chips attempt to mimic complex *in vivo* conditions using a combination of microfluidics and biology, clinically relevant disease phenotypes and pharmacological responses that arise from structural and functional integration of multiple tissue types [1].

Compared with animal models, organs-on-chips also show advantages in the analysis of complex physiology issues. Based on recent systematic studies of the predictive value of traditional animal models, due to key genetic, molecular,

immune, and cellular differences between humans and animals, the poor correlation of data between different species underlines the urgency for novel methods to simulate intricate human-related conditions [1] [40] [41] [42].

Biomaterials and structures used in organ-on-chips also are critical merits. Organ-on-chips adopt PDMS materials. These materials have outstanding optical transparency, which allows investigators to get direct real-time visualization and quantitative high-resolution analysis of various biological processes, which is impossible in animal models [1]. Besides, the special design of separation channels for co-culture of organ-on-chips, for example, the upper and lower channels are separated by thin porous membranes, enables fluid flow into different tissues independently in a single device, and combines with the techniques of microfluidics and bio-microelectromechanical systems (BioMEMS) to create platforms where the cellular microenvironments and microenvironmental factors can be precisely controlled [1] [43].

In organ-on-chip, scientists will sample from specific human tissues to culture in conditioned media to analyze their metabolites and other secreted products, which may help drug testing [1] [11] [43]. However, each patient has unique genes, thereby having diverse tissue types. The different genes will cause patients to respond differently to drugs. Although patients exhibit similar symptoms, they may have different underlying causes for the disease. Yet, generally, based on their similar symptoms, they are more likely to receive the same medication, which could lead to the significant risk of taking the wrong therapy [44] [45]. Owing to drug developments related to various aspects, except individual genetic variations, many factors could hamper and change the way of drug development, such as epigenetic and environmental factors. These problems would have tremendous impacts on a patient's response to treatment, which remains to an extent unknown. Recently, OOC technology has drawn attention to be used to replace traditional drug discovery models and become personalized disease models by reflecting the genetic characteristics of cells in each patient [36]. While OOCs nowadays have generated different types of chips from many types of human and animal stem cells, researchers still face the challenge of predicting the personal safety risks of new heterogeneous organisms, in part due to the constrained availability of human cells to assess tissue-specific toxicity [36] [44]. But the advance in the production of human-induced pluripotent stem cells (hiPSCs) has the prospect to fill this gap. Since hiPSCs which are gained from patient's tissue or be directly obtained as pathogenic cells from patients can be cultured and differentiate into major and different cell types. These cells will be cultured in the devices (OOCs) that are made by various engineered biomaterials and 3D microfabrication techniques. The drug candidates will be tested and analyzed through a series of studies and *in vivo* tests in animals. After that, based on the responses received from the disease models to the animals, we determine the type of drug and dosage, therefore developing and generating personalized drugs for specific patients [36]. iPSC technology provides resources derived from the patients themselves for disease-specific drug development models, and hiPSC-integrated

OOCs give the possibilities of imitating human physiology for each individual, which establishes personalized drug testing platforms and generates a much better predictive tool (**Figure 2**) [36] [44] [45].

2.3. Case Study

2.3.1. Organ-on-a-Chip Technologies in Ophthalmic Drug Discovery and Disease Modeling

Eye diseases, causing visual impairment, are affecting many people around the world. However, owing to the lack of *in vitro* models to mimic the biology and physiology of human eyes, people cannot find any effective treatments for some eye diseases [46]. To study the principle of disease and solve the problem of vacancy of drugs, we urgently need new ophthalmic disease models which should be consistent with the physiology and structure of the human eye [46]. Existing ophthalmic models, such as explant cultures from human and non-human sources, traditional 2D and advanced 3D cell cultures, have gained achievements in specific applications, and these models would make up for each other's disadvantages. Nevertheless, they fail to rebuild the complicated bio-properties of human eyes and functional subunits. It is high costs and limited reproducibility that jeopardize the further developments of these existing systems [46]. Nowadays, ophthalmic organ-on-chip systems combined with stem cell technology and microengineered methods bring a promising future. These systems can mimic the *in vivo* microenvironment and overcome most of the shortcomings of present models to a large extent, thereby changing the approach of drug discovery and testing models of ophthalmic disease [46].

The study in 2017 has been showing prosperities in developing models of different human ocular structures, such as the cornea, the retina and so on. For example, a study by Bennet *et al.* introduced a corneal epithelium-on-a-chip

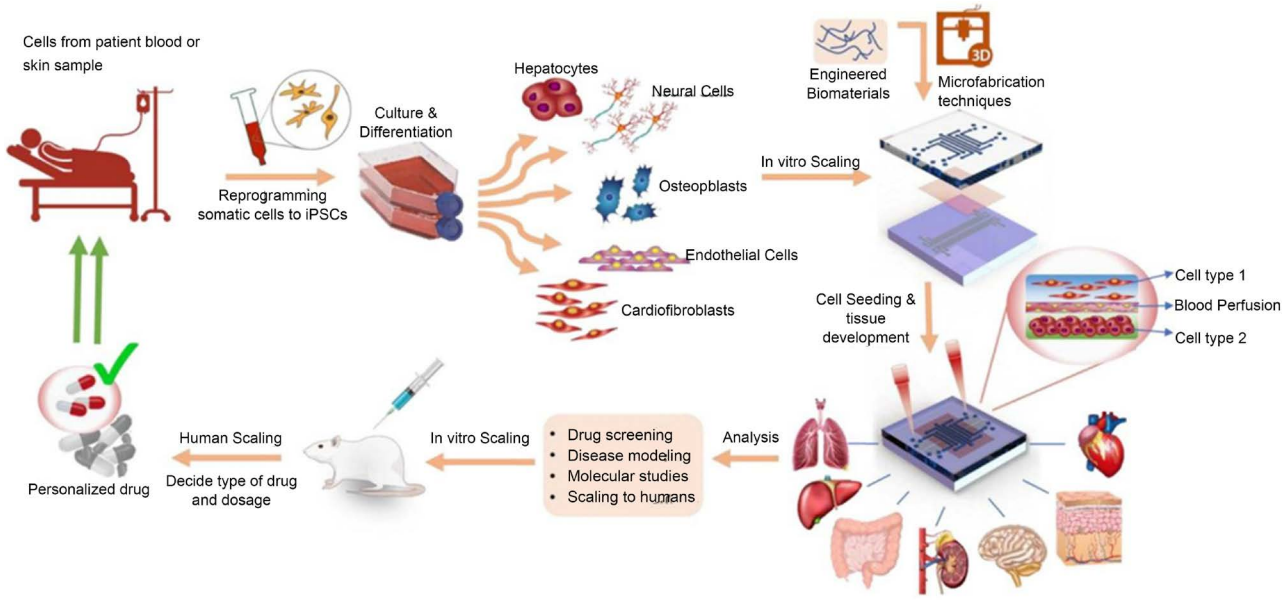

Figure 2. The cycle used in OOCs for personalized medicine [36].

system [46] [47]. The purpose of this model was to mimic the tear flow associated with the eye-blinking mechanism and the cellular environment because tear flow and blinking are two main factors influencing the residence time of drugs on the cornea. Thus, researchers analyzed drug mass transport by using different ocular drug formulations compared in three different conditions. Besides, they used two forms of topical eye drops: a suspension with a particle size of 1 - 3 μm (Pred Forte) and a liquid formulation (Zaditor) to study permeability across the rate-limiting barrier [47]. Finally, they got the conclusion that the result of the corneal chip study can support the ophthalmic drug test method, since the biology of the corneal epithelium is very similar with those of the human subjects, which is suitable for understanding ocular PK and physiology [47]. However, up to now, there are few reports concerning eye-on-a-chip models.

2.3.2. Cardiovascular Drug Discovery

In the past few years, innovative microfluidic designs have been developed, such as endothelialized microfluidic platforms or heart-on-the-chip systems, with biomimetic and high-throughput capabilities [48].

The biggest benefit of using microfluidics to assess the effects of the cardiovascular drug is their power to precisely regulate some fluid flow conditions, like flow rate, shear stress, and pulsatile flow [48]. And the advance in stem cell technology has enabled the iPSC of a specific patient to be used in building *in vitro* models of cardiac disease. For instance, by using iPSC-CMs and heart-on-chip technology, Wang *et al.* obtained iPSCs from patients with BTHS and differentiated into patient-specific iPSC-derived cardiomyocytes (CMs), engineering an *in vitro* disease model about the cardiomyopathy of Barth syndrome (BTHS). According to this study, seeding iPSC-derived CMs on MTFs successfully demonstrated the pathophysiology of BTHS cardiomyopathy [49] [50]. Compared to controls, the BTHS-derived cardiac microtissue impaired sarcomere structure. Moreover, compared with the control group under the same conditions, the MTF of BTHS iPSC-CM significantly reduced its shrinkage performance. Besides, this "BTHS on-chip cardiomyopathy" was used to test potential treatment options (e.g., pharmacology and genetic modification), demonstrating its suitability for identifying new therapeutic targets [49] [50] [51] [52]. Many researchers all show that the novel *in vitro* models of heart-on-a-chip paid to the way toward testing cardiotoxicity in human-relevant models and the advent of iPSC motivated research in this new field. These advances would contribute to the creation of physiologically and genetically related models of heart disease for drug discovery and toxicity, yet these models are still faced with diverse challenges and opportunities that needed us to overcome [49] [50] [51].

2.4. Further Study—Human-on-a-Chip

Despite significant progress in creating organ-on-chip and microengineered tissues, effective drug toxicity testing actually involves the implementation of each

organ and its interactions. Thus, all organs are functionally needed to be integrated into the human body in the future, establishing a microfluidic circulatory system, and researchers still have a lot of work to do in the development of complex and complete models that rebuild the metabolism and physiology of the entire organs [5] [43].

Thus, researchers have further put forward the concept of "human-on-chip" models. Interconnected isolation chambers compose the whole model, each compartment containing different cell types representing different human organs, and are connected by the microfluid circulation system in a microfabrication bioreactor. It can be closer to the physiological fluid flow conditions, realistic size ratios and multi-tissue interactions in ideally, which may help in developing associated with the physiological pharmacokinetic model [5] [53] [54]. The concept of man on the chip is shown in **Figure 3**. Biomimetic microsystems representing different organs are integrated into a microfabrication bioreactor and connected in a physiologically relevant way to simulate complicated and dynamic drug processes of absorption, distribution, metabolism, and excretion, allowing for more reliable evaluation of drug efficacy and toxicity [5].

The primary requirement for organ-on-chip systems in the future to be the major new drug screening and discovery methods is to accurately characterize the response of these microchips to pharmacological modulation and to verify their ability to predict the response of drugs with well-defined characteristics to humans. A key challenge will be to determine the best source of human cells for accurate response in the body. The second important issue lies in combining the scale-up of complex techniques with the integrated engineering systems, such as microengineered organ simulators with sensors to detect and measure various light, chemical, electrical and mechanical signals from cells to analyze their structures and functions. For another example, more reliable operations should rely on the development of automated control of flow and pressure by microfluidic

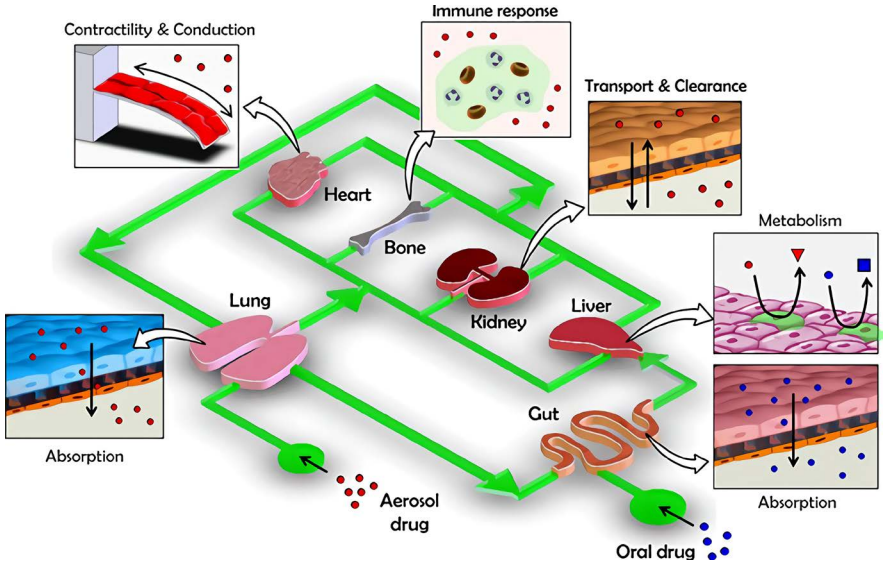

Figure 3. The human-on-a-chip concept [5].

devices equipped with microengineered valves and pumps, which paves the way for multiplexing these microsystems for high-throughput analysis and drug screening [5] [55] [56].

At present, laboratories are working hard to link more mechanically active organ-on-chip models through microfluidics technology to provide more complete biomimetic techniques for physiology, therefore achieving the goal of human-on-chip [5].

3. Discussion and Perspective

Although scientists have gained great progress in the field of organ-on-chip, this technology has become a useful tool for building *in vitro* human disease models and developing effective drugs. Many challenges still need to be overcome and the whole potential is yet to be realized before organs-on-chips have extensive use in research laboratories [5] [11] [19]. A fundamental problem in terms of the material used for fabrication, most chips are made out of PDMS because of its usability, high optical clarity, gas permeability, and biocompatibility. Despite many advisable properties of PDMS, it has poor chemical resistance to organic solvents, which enables it can absorb small hydrophobic molecules, like many drugs, fluorescent dyes, and chemical compounds. Therefore, it will lead to a significant influence on the precise chemical test of potential drugs. The material problem also involves that ECM-coated PDMS membranes, as tissue-tissue interfaces, could have different transport, mechanical and structural properties than natural basement membranes [11].

Another challenge refers to multisensory systems. Though some organ-on-chips have the ability to mimic specific organ-level functions, in a few current successful cases, several limitations of the current integrated multisensory combined with organ-on-chips platform still exist. Since we certitude that the integrated modular in-line fluid routing and sensing platform will be compatible with existing organ-on-a-chip models and promote their performances in drug screening by real-time, in situ monitoring of microenvironment biophysical and biochemical parameters [2] [11] [57].

Those challenges and problems also enable researches to determine the directions that they will continue studying in turn. First, doing more research to identify suitable materials can be used to mass-produce organs-on-chips at a low cost. Besides, future success will require automated instruments that are well developed with the user interfaces to provide systems-level microenvironmental control and supervise timely analysis of multiple, linked, alive organs-on-chips [11] [57]. Finally, we anticipate that the organs on the next generation of chips may be enlarged to accommodate high-throughput analysis and commercial applications. In order to integrate multiple organic types into a single chip, the media and physical conditions in a microfluidic platform may require optimization of each organic type and generalization of organ-organ interactions [19].

As a novel field, it is crucial that we have to across the initial prototyping stage

and gradually simplify the platform. These challenges mentioned above are necessary to transform the laboratory-derived idea called organs-on-chips into robust animal replacements in the pharmaceutical, biotechnology, chemistry, and environmental safety industries, which can more accurately model human systems to better predict drug efficacy and toxicity [2] [57].

4. Conclusion

In this paper, we have reviewed some characteristics and the future prospects of the OCC technology. The OCC system can generalize tissue- and organ-level functions *in vitro* disease models with different cell types, thereby rebuilding the authentic *in vivo* conditions of humans and allowing researches to do drug experiments. The future achievements in the OCC field could present exciting new avenues for drug discovery and development. Accordingly, there is a wealth of opportunities to participate in what we hope will be a surge of innovation to realize the tremendous potential that OCC technology holds.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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