Potential of multi-organ chip models to replace animal trials in COVID-19 contribution

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Abstract: When people feel ill, most of us turn to medicine to help us get better. But there are years of intensive research behind each drug-it takes an average of 12 years for a drug to get from the lab to the medicine cabinet. Moreover, any new drug must undergo extensive testing, including laboratory and clinical trials, to ensure the safety and effectiveness of the drug before approval. According to statistics, 86% of drug candidates entering clinical trials will never enter the market. Traditional preclinical models, which are usually tested in human cells or animals, have many uncertainties, such as genetic variation between patients, and animal tests have the opportunity to show different responses from humans, adding to the challenge of predicting efficacy and toxicity under clinical trials. Furthermore, the use of laboratory animals, animal protection, ethical issues also become. So, the field of organ chips deserves attention and has the potential to be another way to save lives in a technologically advanced future. The following articles will explore in depth the potential of the multi-MOC (organ on a chip) model, especially in terms of potential contribution and expectations for COVID-19 (Coronavirus Disease 2019).

1. Introduction

The "Multiple Organ on a Chip" (MOC), also known as the "Body on a Chip," combines microscale technology with mathematical PK-PD modeling, with independent chambers connected through microfluidic-flow channels to accurately simulate blood circulation, allowing researchers to track the dynamic response of multiple organs to drug compounds [1]. At the same time, the organ chip is an emerging frontier crossover science and technology, it integrates physics, chemistry, engineering and biology and other multidisciplinary methods, can be a few square centimeters of the size of the flow chip bionic construction of a variety of human tissue and organ miniature models in hope of reflecting the key structure and biological function of human organs. Hence, the effectiveness of preclinical human drug response prediction making progression is critical to eliminate the expenditure arising from clinical trial failures. In other words, organ chips are fundamental for preclinical analysis with greater predictive power. Micro-engineered bionic systems that represent essential functioning units of living human organs make up the organs on the chip. They are generally composed of three-dimensional transparent polymeric microchannels arranged by living human cells [1]. These microchannels replicate three important aspects of a complete organ: the three-dimensional microstructure defined regarding the spatial distribution of multiple types of tissues; Functional tissue interface; and complex organ. In defined concepts, mechanical and biochemical microenvironment [2]. As organ chip technology takes progressions, the construction of multiple organs on one chip has become a heated research topic. Eventually, the human chip would be capable of supporting more than 10 types of organs, including the liver, intestine, heart, kidney, brain, lung, reproductive system, immune system, vascular system, and skin. It is the objective of a human chip to control how the drug reacts to the "core" of the chip and ultimately study the pharmacological and toxic reactions from the drug on respective organs or throughout the system. The "multi-organ chip" is capable of building multiple tissues and organs in different functional areas simultaneously, and connecting them through the chip pipeline (which is a simulation of human blood vessels) [2] to simulate the absorption,

metabolism, transformation and excretion of specific substances in the human body. COVID-19 (Coronavirus Disease 2019) infection has led to a global pandemic. Being a vital target, Lung is subjective to SARS-COV-2 infection. At present, the clinical treatment of COVID-19 is mainly comprehensive treatment, but there is still a lack of specific drugs. Although previous cell and animal models have been used for COVID-19 research, there are still many limitations to some extent. At present, there is still a lack of research models that can reflect the human response to COVID-19 infection at the tissue and organ level, which is one of the bottlenecks that seriously restricts the current COVID-19 drug development process. Organ chips can reproduce the human body's response to various external stimuli in an unprecedented way in vitro, which has a wide potential in life science research, disease research and new drug research and development.

2. Application and Design of Multi-Organ Chip Model

2.1. Design of multi-organ chip model

The current organic chip system could be divided into two basic aspects: a single organ chip that integrates the sole category of tissue or organ and a multi-organ chip that consists of minimal two different types of tissue compartments or organs. In turn, there are two types of single-organ systems, namely the tissue-specific and universal single-organ chips. Although the organ/tissue specified chip geometry is precisely customized according to the needs of a specific tissue (Fig. 1), the general geometry is suitable for all tissue methods and allows for rapid time to market [3].

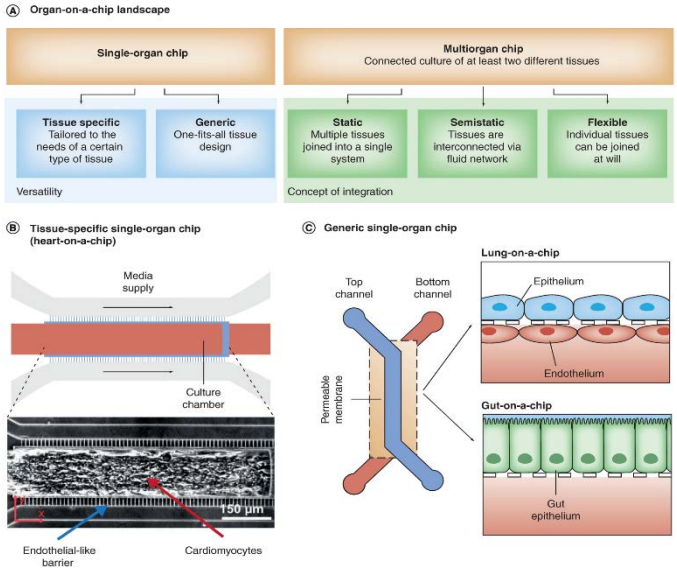

Figure 1. The general concept of the organ-on-a-chip technology [3].

Static system: several organizations are integrated in an interconnected device. (Fig. 1B) Semi-static system: the tissue is connected to the Transwell®-based tissue insert through a network of fluids. Flexible system: Specific individual organ (Fig. 1C)/ tissue platforms are connected by flexible micro-connectors. (Fig. 1A) Reprinted with permission from the Royal Society of Chemistry [4]; (Fig. 1B) Reprinted with permission from Royal Society of Chemistry [5].

2.2. Application of multi-organ chip model

Human organs chip technology research innovation based on full understanding of the complex tissues and organs of human body structure and physiological characteristics, on the basis of it for drug research and development, disease research, chemicals, toxins and cosmetics testing and other fields provides a close physical model in vitro, with wide application value in many fields.

The common areas for application of multi-organ chip models lie within various aspects. In terms of drug development, medical researchers could apply multi-organ chips to drug testing, building disease models, and drug screening. For special patients, they may also customize their medicine to

cater to special demands. Moreover, multi-organ chips could also be used for special diseases such as metastasis of cancer and detection of biomarkers.

3. MOC'S Contribution to COVID-19

3.1. The application of human organ chips in terms of enabling rapid drug repurposing for COVID-19

The Wyss Institute in Boston has identified the antimalarial drug amodiaquine as an effective inhibitor of SARS-CoV-2, the virus that generates COVID19 [4]. The human respiratory chip reconstructs the interface between the respiratory tract and blood vessels of the human lung, allowing researchers to study how different drugs and pathogens (such as viruses) affect lung function (Fig. 2). Wyss's team examined eight types of existing drugs, which include hydroxychloroquine and chloroquine. In this research, it is identified that these drugs are active against SARS-CoV-2 in routine cell culture tests. When they tested it on a rather sophisticated microfluidic lung airway chip infected with the pseudo-SARS-CoV-2 virus. In the research, it has been found that most drugs, including hydroxychloroquine and chloroquine, were ineffective. One exception is the antimalarial drug, amodiaquine, which is very effective in preventing the entry of the virus. These results were subsequently verified in cell cultures using infectious small animal models of the SARS-CoV-2 and COVID19 viruses. Amodikine is currently undergoing clinical trials for COVID19 in multiple locations in Africa. The drug is inexpensive and easily available.

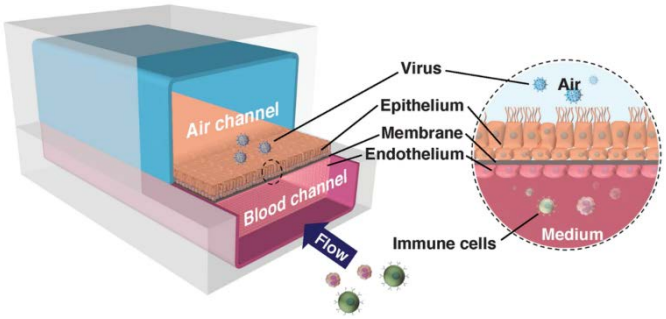

Figure 2. The Human Breath chip recreates the interface between the respiratory tract and human pulmonary blood vessels [4].

After confirming that the patient was not pneumonia but rather the mysterious new coronavirus (COVID19), the research team quickly turned their attention to the new SARS-CoV-2 virus. The ACE2 receptor protein (green) used by the SARS-CoV-2 virus to channel through the cell layer is highly expressed on the surface of human airway cells, which are grown on airway microchips. Airway microarray cells also have high levels of angiotensin converting enzyme 2 (ACE2) receptor protein, which plays a central role in lung physiology and is used by SARS-CoV-2 to infect cells. To solve this problem, we engineered a SARS-CoV-2 pseudovirus to express the SARS-CoV-2 spike protein so that we can determine that the drug interferes with the protein-binding ability of the ACE2 receptor in human lung cells, "said Bai, postdoctoral researcher and co-author from the Wyss Institute. The second objective is to show that this type of research can be done by other organic chip researchers who also have the technology but lack the necessary laboratory facilities to study infectious viruses with high potential. Using pseudoviruses, researchers can study SARS-CoV-2 infection. They first filled the vascular canals of the airway chip with various applicable drugs that have went through approval, including amodiaquine, trephine, cofen, chloroquine, hydroxychloroquine, Abby, verapamil, and amiodarone. The proposed drugs have shown the activity of other related viruses in previous studies. Twenty-four hours later, they introduced the SARS-CoV-2 pseudovirus into the airways of the airway chip to simulate airborne viral infections, such as coughing or sneezing. For instance, The ACE2 receptor protein (green) used by the SARS-CoV-2 virus to enter cells is highly expressed on the surface of human airway cells that grow on airway chips. This faithful imitation of human biology allows us to study how viruses interact with their host cells (Fig. 3).

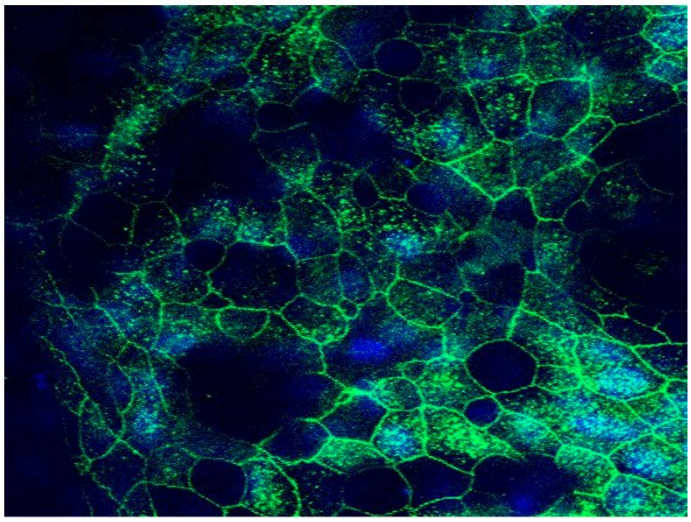

Figure 3. The ACE2 receptor protein (green) used by the SARS-CoV-2 virus[4]

3.2. MOC's COVID-19 solution highlights the model dilemma in biomedical research and simulates COVID-19 infection, inducing lung damage and immune responses

COVID-19 infection, inducing lung damage and immune responses Scientists struggled to find suitable animal models to study SARS-CoV-2 infection. In these models, human ACE2 is expressed under specific promoters in tissues, and mice are susceptible to SARS-CoV-2 infection. Selected 2D cell culture remains essential in human physiology research (Patpo) as it allows rapid and economical detection of high throughput. SARS-CoV-2 is the selected cell type for cell detection based on subtortic 2 (TMPRSS2) expression of transmembrane protease2 (TMPRSS2) [6]. Biology and synthetic microfabrication have promoted the development of microfluidics of tissues, organoids, and organ sonar models that can restore cytopathological and inflammatory characteristics of viral infection. Therefore, lung oral steroids are currently used in drug regeneration studies, among which imatinib tyrosine kinase inhibitors have been identified as strong SARS-CoV-2 cell invasion inhibitors 5. Single-layer cultures and individual 3D organ models are simplified but can provide powerful tools for the first study of virus-cost interactions and drug detection. These organs also help study virus-cost interactions, test new antiviral drugs, and monitor the emergence of drug resistance [7]. In this study, we first constructed the humanoid alveolar functional unit using multi-organ chip technology, and further carried out the Novel Coronavirus infection experiment [8]. Experiments in the porous membrane on either side of the chip (alveolar side/vascular side) microcavity, through human alveolar epithelial cells and pulmonary microvascular endothelial cells, and to dynamic culture of human peripheral blood immune cells, contain a variety of human cells, mechanical fluid and tissue interface complex factors such as the function of the alveolar capillary barrier, then on chip coronavirus infection experiments (Fig. 4). In addition, the study found that the virus infection can also cause the chip side of immune cells in peripheral blood vessels in the vascular endothelial cell adhesion, and release a large number of inflammatory factors (such as IL-1 beta, IL-6, IL-8, TNF alpha), the coronavirus infection cutting-edge, probably by activating the body's immune cells release a large number of lung tissue inflammation factors, Induce pulmonary microvascular endothelial injury. Using multiple organ chip technology, based on human COVID19 disease model of organizational levels, in vitro to coronary pulmonary barrier dysfunction caused by viral infections, immune cell adhesion, inflammation factors and lung endothelial cell injury and a series of key pathophysiologic process, reflect the coronavirus infection of many complex factors involved in mediating cell pathogen, host interaction.

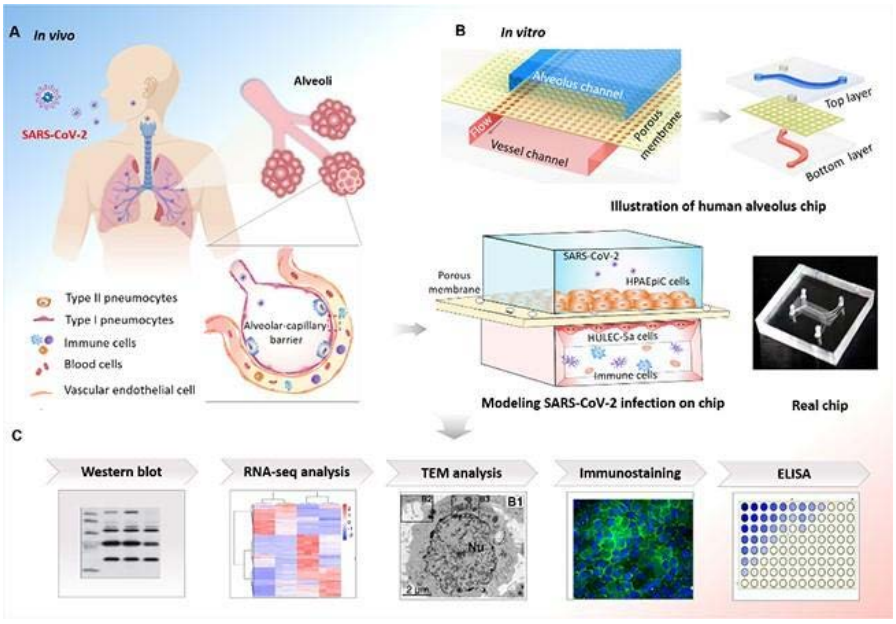

Figure 4. A screenshot of the official website of Kunming Institute of Zoology, Chinese Academy of Sciences [6].

3.3. Using multi-organ chips to find out how COVID-19 invades our bodies and quickly identify candidate antiviral therapies and precursors

To develop new coronavirus vaccines and antiviral drugs, scientists must first understand why the virus spreads so easily and quickly, and why our immune systems seem to have little resistance when it invades our bodies [5]. To understand how COVID19 enters the human body and causes harm, a team of top researchers from CRAFT Universities, Hospitals and the National Research Council of Canada (NRC), the University of Toronto, and NRC Collaborative Center Milica Radicic, Axel Guenther, Edmund Young from the school Developed a method for making miniature models of the nose, mouth, eyes, and lungs. Now, by creating miniature models of other human organs, researchers can learn more about how COVID19 works. "This method enables research surrounding this problem without touching the human body and potentially harming others," said Radic, president of Canada's Functional Cardiovascular Tissue Engineering Research. Using organic chips, scientists may witness the process of COVID19 as it COVID19 enters the human body. " Scientists found that clinically relevant doses of amodiaquine, an antimalarial drug, inhibited infection of infected chips with pseudo-SARSCoV2, while clinical doses of hydroxychloroquine and other antiviral drugs could prevent pseudo-SARSCoV2 from entering cell lines in static conditions. One of the fastest ways to meet the challenge of the pandemic is to reintroduce existing drugs that have been approved for other medical indications into antiviral or preventive drugs. According to research, the multi-organ chip can reproduce the physiology, disease state of human organs and the response to treatment to exposure to clinically relevant drugs with high fidelity [9-11]. In addition, the human lung bronchial airway chip (airway chip) can be used to simulate the in vitro response of human lungs to viral infections, combined with higher throughput cell-based tests and animal models, to determine existing approved treatments or treatments. Potential drugs. Prevent the spread of a pandemic caused by the influenza A virus or the SARS CoV2 virus. Currently, established cell lines, tissue-derived human cells and primary human organs, and in vitro human lung tissue cultures are being used for in vitro studies of respiratory virus infections and antiviral drug screening, although these all have obvious limitations (Table1) [15-17] Despite the fact that the lung organ of human is generates lung epithelium, such structure forbids culturing of epithelium at the air-fluid interface (ALI) and other physiology at the relevant organ level. Characteristically patterned lungs - for example, due to mucus layer formation, mucociliary clearance, epithelium-endothelial interaction, and recruitment of circulating immune cells [15-16], all of these cells are involved in the host's response to respiratory virus infections. a key role [12,13,17].

Table.1. Limitations of existing in vitro viral infection models

MODELS	LIMITATIONS
Cell lines	1.Minimal viral replication without the addition of exogenous proteases. 2.Cannot be used for analysis of virus tropism. 3.Lack host immune, tissue-level, or organ-level response. 4.Do not mimic the *in vivo* phenotype of human lung cells and tissues.
Ex vivo culture of human lung tissue	1.Short viability (4-10 days). 2.Limited availability of resources and expensive. 3.Uncontrolled region-to-region and donor-to-donor variation. 4.Poor reproducibility of experimental results. 5.Difficult to analyze mechanism of infection or host responses. 6.Not possible to study viral evolution.
Human organoids	1.Lack of physiologically relevant organ-level microenvironment. 2.Difficult to access the apical surface of the epithelium. 3. Lakhs of air-liquid interface. 4.Cannot study mucociliary clearance. 5.Lacks endothelium and circulating immune cells. 6.Absence of relevant mechanical cues. 7.Thick ECM gel complicates permeability and drug studies.

4. Comprehensive Evaluation of MOC

4.1. MOC accelerate drug development for COVID-19

In the face of COVID-19 novel coronavirus, it is difficult to eliminate the virus in a short period of time, and it may even coexist with human beings forever. Obviously, the speed of traditional drug development is difficult to fight against. In order to catch up with the NOVEL coronavirus mutation, we urgently need a technology - multi-organ chip to shorten the development cycle of Wuhan pneumonia drugs, accelerate clinical trials, and ensure safety and effectiveness. This technology will not only give scientists the opportunity to see the pathological changes in cells through a microscope, but also enable drug testing on animals and humans to accelerate drug development by screening candidate drugs for efficacy and toxicity at an early stage. Before the COVID-19 novel Coronavirus emerged, scientists have simulated a variety of human organ chips to promote drug development and customized medical treatment, such as the lungs, liver, eyes, female reproductive system and so on. While MOCS are not a complete replacement for human and animal testing at the moment, they could be a good substitute for some testing phases, giving people more opportunity to catch a virus and predict its success or failure.

4.2. The contribution of multi-organ chips to society is better than bad

Although organ chip made a major breakthrough in this field, organ compared chip, cell chip is closer to the real human body physiology, it provides a relatively simple organisms in vitro for extremely complex organisms in the body to carry out the simulation study way, to the study of drug safety, personalized modern pharmaceutical industry, such as precision medical treatment, and the bottleneck problems existing in clinical medicine, it has great scientific and practical value. Moreover, the emergence of multi-organ chips provides an excellent solution for the study of drug safety with high throughput, high reliability and high efficiency. We are committed to the research of drug screening and evaluation systems based on organ chips, shorten the drug development cycle and improve the input-output ratio, which has a great application value of the entire pharmaceutical

industry. However, there are still some challenges, such as using human self-organized cells to replace cancer cells, maintaining cell response to stimuli or control the quality of the microenvironment (metabolites, oxygen saturation, pH). However, with the development of technology, the contribution of multi-organ chips in the future is very optimistic to look forward to.

4.3. Multi-organ chip replaces animal toxicity testing

The US Food and Drug Administration (FDA) has begun testing a multi-organ chip. The FDA will test whether it can effectively model the human body's response to food and food-borne illness [18]. These tests will help the FDA determine whether chip data can be used instead of animal data when drug companies apply for approval of potentially toxic new compounds, such as food additives. Suzanne Fitzpatrick, senior advisor for toxicology in the FDA's Division of Food Safety, announced the FDA's move in a blog post on April 11. Lawrence Vernetti, a toxicologist at the University of Pittsburgh in Pennsylvania, is developing a different kind of multi-chips [19]. Animal metabolisms are very different from human metabolisms in some ways, such as the fact that chocolate is toxic to dogs. He says that while animals are often good models for predicting toxicity to humans, they are not foolproof. If the long-term goal is to reduce the number of animals used for toxicity testing, "we have to develop a system that allows the scientific community regulators to trust the data they give them." Kathy Guillermo, senior vice president of People for the Ethical Treatment of Animals (PETA), said to Nature during an interview, "No longer do animals have to suffer from toxic testing to improve human medicine. We are ecstatic that the FDA has acted. But it will take some time for organ chips to completely replace animal testing. Even if human liver chips can metabolize certain toxins, other organs, such as the heart, will react in unpredictable ways. Hamilton said that although researchers are trying to link up as many as 10 organ chips, there is still a lot of room for improvement before they can completely abandon animal research.

5. Conclusion

With the long-term development of technology, in the future, using the human organ chip can build a "human" life simulation system, which is likely to revolutionize the way people meet each other. And to provide people with a complete and systematic life. Although significant progress has been made in organ chip research, challenges still lie within its development, such as how to build an organ chip system that is more in line with human physiology, how to achieve multi-organ relevance and functional compatibility, how to achieve chip standardization and built-in detection and detection. Driven by high demand and application market, deep fusion of human organ chips and stem cells, omics technology, gene editing, synthetic biology, high-resolution imaging, big data and artificial intelligence will be the future development trends. If scientists can seize the opportunity in time, integrate many advantages into forward-looking design and increase investment, it will be conducive to the rapid development of human organ chips and drive the development of related industries. In this review, we mainly discuss the important contribution of MOC to society and human beings during COVID-19, and evaluate its value. The application of MOC shows its strong potential. In short, THE application of MOC will be more and more widespread, and it will be one of the major contributions of this epidemic. Its potential deserves more attention and expectations.

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