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REVIEW ARTICLE

Organ on Chips: A New Paradigm for Alternative Animal Model in Drug Development

Sarika Pulichintha, Satwika Bonthu, N. V. L. V. Suvarchala Reddy*, M. Ganga Raju

Department of Pharmacology, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad, Telangana, India

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ABSTRACT

Organs-on-chips (OoC) are microfluidic devices that incorporate electronic gadgets or tissues growing in them. Chips are developed to regulate biological microbial environments and specific tissues to optimize the human body. OoCs have received interest as a next-generation experimental platform for studying human pathophysiology and the effects of treatments on the body by combining developments in tissue engineering and microfabrication. Several successful devices based on various organs have been constructed, including lungs on a chip, liver on a chip, kidneys on a chip, hearts on a chip, intestines on a chip, and skin on a chip. The Food and Drug Administration has also shown trust in this technology and has formed agreements with industry and other entities that employ it. The history, concepts, method of preparation of organ on chips, examples of organ on a chip, and applications of the organ on a chip model in various scientific domains such as disease model development, drug screening, pharmacology, customized medicine, and dentistry are discussed in this review. Particularly given the challenges posed by the current spread of the COVID-19 virus, integrating multiple chip modules into a single integrated chip should be a priority for diagnosis and treatment. The market demand for organic product development is expected to increase in the future.

Keywords: Kidney, Liver, Lung, Microfluidics, Organ on chips, Product development

HISTORY

In the early 2000s, Huh *et al*. sought to simulate the fluid accumulation seen in *in vitro* models of lung disease.[1] Therefore, they developed the first organ-on-a-chip technology for lung visualization. Dr. Takayama presented the gadget at Harvard's Wyss Institute, where he was joined by Donald Ingber, MD, Sc.D., who expressed amazement upon hearing the same "clicking" sound he hears when identifying patients' bodies. No one knows much about the lungs as a phenomenon because researchers can't get their hands on a set to investigate.

Huh *et al*., researchers from the early 2000s, attempted to simulate the excess fluid seen in *in vitro* models of lung illness. As a result, they developed the first organ-on-a-chip system specifically for lung visualization.[2] Prof. Dr. Donald Ingber, Sc.D. Dr. Takayama, then presented his findings at Harvard's Wyss Institute, where he was similarly surprised to hear the device produce the same "click" when it recognized the patient's body. Lungs are an inexplicable phenomenon because the lungs themselves cannot be studied.[3]

Organ-Chips integrate cell culture and microfluidics to mimic the physiological forces of various

***Corresponding Author:**
N. V. L. V. Suvarchala Reddy,
E-mail: suvarchalakiran@gmail.com

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organ tissues and disease states, such as intestinal peristalsis, pulmonary ventilation, and vascular blood flow.[4] These chips, about the size of a thumb drive, are made of a flexible material and have microfluidic channels on both their upper and lower surfaces. A thin, porous membrane separates the channels, serving as a communication link between the cells [Figure 1]. The membrane is covered by an extracellular matrix (ECM) that is unique to the tissue being developed.

To grow functional organs on a chip, researchers use an automated fluid flow and cyclic mechanical deformation system called a microfluidic platform. Because of this, the cells on the chip can mimic the actions of pharmaceuticals, medications, and other chemicals as if they were actually within the body. Spot microscopy, wastewater analysis, and other functional test organisms allow scientists to gather data in real-time.

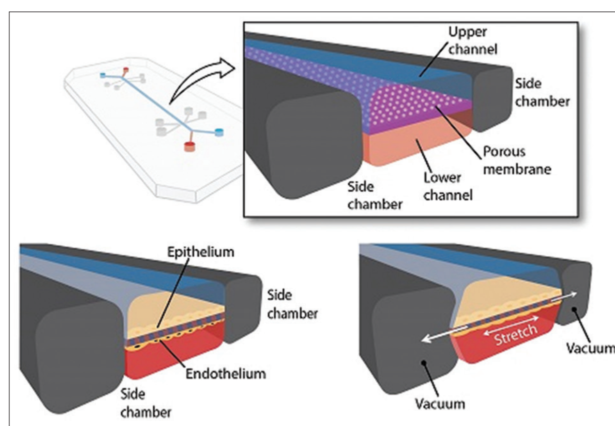

Figure 1: Organ on a chip

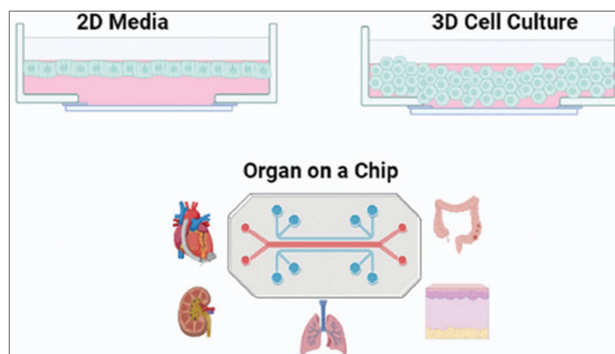

Figure 2: Method of preparation of organ on a chip

METHOD OF PREPARATION

The hydrodynamic element implies the use of microfluidics to transport cells of interest to a predetermined place, and it includes a culture fluid inflow and effluent liquid outflow system throughout the culture process. The other three key components of the OOAC are living cell tissues, stimulation or drug delivery, and sensing.[5] This part is known for its miniaturization, integration, and automation.[6] In the context of 2D or 3D systems, the term "living cell tissue component" refers to elements that coordinate the positioning of a specific type of cell. Hydrogels and other biocompatible materials are often used to achieve the desired three-dimensional configurations. Materials like this can withstand mechanical stress and be molded into complex three-dimensional shapes.[7] Although the 3D tissue structure more accurately mimics the *in vivo* situation compared to 2D models, due to the limitations of technology and cost, the assembly of the ECM, and the presentation and formation of the vasculature, living cells in organ tissues are still mostly cultivated in 2D, as shown in Figure 2. For some tissues, the physiological milieu that fosters micro-tissue growth and function can only be mimicked through the use of physical or chemical signals. Myocardial tissue maturation, for instance, can benefit from electrical stimulation.[8] A wide range of sources of signals can be used to build drug screening systems. As the element responsible for detecting and assembling data, integrated sensing outcome elements or a transparent chip-based visual function evaluation system may be used.[9] Peel *et al*. employed automated techniques to offer detailed cell phenotypes and statistical models for measurements while imaging multicellular OOACs.[10] Kane *et al*. developed a system for tracking cells in a three-dimensional microfluidic environment.[11] In these experiments, time-lapse microscopy was utilized as a quality control measure to examine cell electrical activity. For characterizing and accessing a relevant human-on-chip cell model, microsensor-mediated scanning of the metabolic state at distinct points in the system is required.

MODELS OF ORGANS ON A CHIP TYPES

Recently, scientists have created numerous organ-on-a-chip models, such as the kidney on a chip[12], lung on a chip[13], heart on a chip[14], skin on a chip[15], pancreas

on a chip[16], brain on a chip[17], and blood–brain barrier on a chip.[18] Some of the present constraints, including space and cost, were surmounted by microfluidic technologies that permitted the development of organ-on-a-chip models:

- Accessibility of the tissue to liquids in movement, which is frequently directed
- Nutrients entering and trash leaving
- A flow gradient can be produced, making dosage trials more feasible
- Numerous kinds of cells can be stacked to resemble organs
- The studies are conducted on human-derived cells, which are significantly more biologically relevant
- Unlike in animals, where additional mutations might interact, organ engineering can be done (with precise deletion or mutation) and investigated in isolation.

Organ-on-a-chip Microfluidic devices have revolutionized research in many fields, including high-throughput drug screening[18,19], single-cell analysis[20], cell-cell interaction[21], cell-ECM studies[22], cell co-culture[22], neuronal models[23], chemotaxis[24,25], drug screening[26], precision medicine[27], cancer cell migration[28], and axon growth.[29]

MODEL OF A LIVER ORGAN ON A CHIP

The liver plays a pivotal role in the metabolic cleansing of drugs and toxins. Multicellular functional communication is facilitated by the liver's series of complicated hepatic lobules.[30] Hepatocyte physiology maintenance over long time periods is difficult.[31] The first liver-based system was developed by Kane *et al*. [Figure 3], and it was composed of microfluidic holes in which 3T3-J2 fibroblasts and rat liver cells were co-cultured to simulate an airway interface.[32] The chip allowed for the constant and stable synthesis of albumin and metabolism in rat hepatocytes grown *in vitro*. Culture media was perfused from outside the gap in a chip constructed by Lee *et al*. to mimic the interstitial structure of endothelial cells and cultured primary hepatocytes.[33] Separation of the hepatocytes from the exterior sinusoidal region was made possible by the cord-based structures' permeable endothelial gap, which also allowed for efficient substance exchange. Electrophoresis was employed by Ho to generate radial electric field gradients, which he then used to pattern cells onto circular polydimethylsiloxane (PDMS) chips.[34] These cutting-edge methods successfully reproduced the lobule structure of the liver. Hegde developed a two-layer chip with a porous polyethylene terephthalate membrane between the channels, and then he continuously perfused rat primary hepatocytes coated in collagen and fibronectin into the bottom channel from the upper chamber.[35]

Physiological models have been made better with the help of 3D hepatocyte culture methods derived from microfluidic chips.[36] For *in vivo* perfusion of

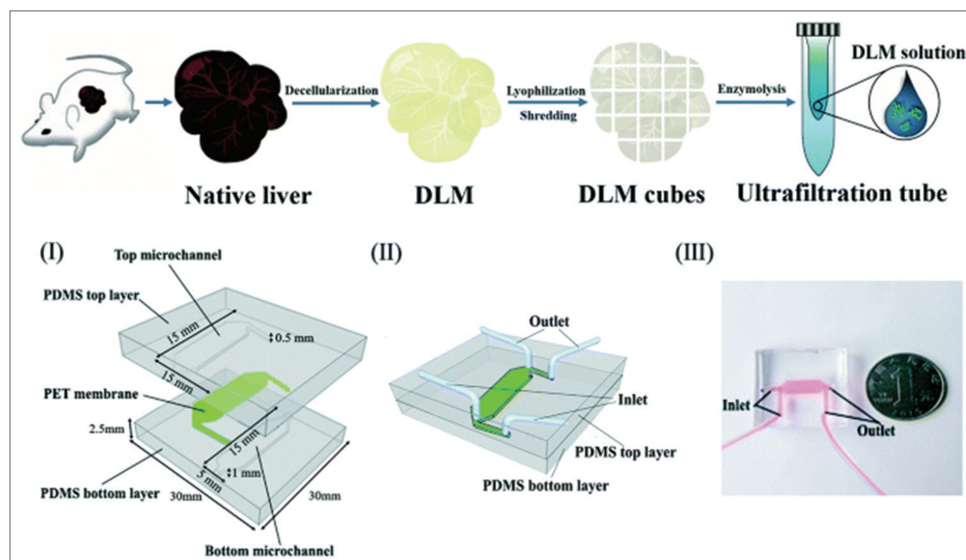

Figure 3: Liver organ on a chip model is given as an example

hepatic spheroids, the group developed a biomimetic platform.[37] In order to learn how hepatocytes influence other cell types, they developed models. To determine the toxicity of drugs to liver cells, high-throughput tests were created.[38] As a means of detecting the biomarkers manifested during hepatotoxicity[39], they developed microfluidic electrochemical chip immunosensors. Using measurements of metabolite synthesis and antigen presentation cell activity, they developed assays to track drug-induced skin sensitization.[40] To find substances that cause systemic skin reactions, this approach can be useful as a drug screening platform. To simulate the complex 3D tumor microenvironment[41], they created biomimetic liver tumors by combining decellularized liver matrices with gelatin methacryloyl. With this setup, researchers may better study the effects of potential anti-cancer drugs in a disease model. In addition, several disease and injury conditions were evaluated. They applied this method to studying hepatitis B virus replication.[42] A method for simulating the effects of alcohol on the body was created. The functional outcome of these studies can be enhanced by further characterization of cultured cytoplasm in metabolomics, proteomics, genomics, and epigenomic analysis.[43]

APPLICATIONS

The vast majority of proofs of concept are created for a specific function. In this part, we outline the many strengths of existing organs-on-chips (OoCs), which can be put to use by commercial enterprises interested in testing and predicting compound efficacy and side effects, as well as by biological researchers who want to employ OoCs to simulate the complexity of normal or diseased human states. When still in the research and development phase before commercialization, most OoC prototypes struggle to meet the needs of both multiplexing and biological complexity. OoCs are an *in vitro* system; therefore, they cannot mimic every aspect of an organ's or body's physiology. Tissue functions and read-outs that are crucial for the desired application frequently guide the final marketed form factor of an OoC device. Therefore, it is important to differentiate between features that are required and those that are only preferable at various points during the translation of an OoC device. This is best done after gathering input from the final consumers.

ORGAN/DISEASE MODELLING

Analysis of organ structure and function, in-depth etiology of disease, development of reliable diagnostics, and effective and well-tolerated treatment drugs are only a few of the many possible uses of *in vitro* modeling of disease pathways connected with many organs and organ systems.[44,45]

PHARMACOLOGY

A drug's development process starts with its discovery in the lab and finishes with its release to the market and subsequent marketing and surveillance. To put it simply, there are five main phases: (i) drug discovery and development; (ii) preclinical research; (iii) clinical development; (iv) food and drug administration review and approval; and (v) safety monitoring post-release. Count on spending a minimum of 10–15 's on this project. Companies in the pharmaceutical and biotechnology industries stand to lose a lot of money if the drug under study turns out to be ineffective, incompatible with human metabolism, or causes severe or fatal side effects. OOAC models provide for precise and timely assessment of medication efficacy and the effect of new therapies on target locations and related organs.[46,47]

PERSONALIZED MEDICINE

Multiple patients may share the same drug class prescription, albeit the specifics will vary per condition. The clinical context can produce large inter-individual differences in medication response and safety.[48]

When it comes to precision medicine, we have only just begun to scratch the surface. Because of genomic sequencing of solid tumors and the identification of critical molecular targets, primary and metastatic cancers have shifted from being fatal diseases to chronic, treatable ailments. Care for people

with HIV/AIDS, hepatitis B, and other long-term illnesses will be completely transformed if precision medicine is applied to these diseases. Based on a person's unique medical history and DNA, precision medicine will enable the creation of highly effective and individualized treatment plans.[49] OOAC can be tailored to each individual by analyzing health records and using samples from actual patients.

IN DENTISTRY

The tooth's specific biological structure is crucial to the diagnosis and treatment of illness. The dentin matrix and the many dentinal tubules of 2 m in diameter generate a calcified permeable barrier that allows cells in the dental pulp to indirectly associate with one another. *In vitro* studies that recreate the dentin-pulp interface are needed to better understand the morphologic, metabolic, and functional activity of biomaterials on living dental pulp cells, even though the cytotoxic response of the dental pulp to biomaterials has been extensively investigated. Cristaine *et al*. built an organ-on-a-chip model system to study this problem.[49] The technology connects cells cultivated on a dentin wall inside a microfluidic device that mimics the shape and function of the dentin-pulp interface. The dentin fragment is located between two chambers in the PDMS tooth-on-a-chip. Apical papilla stem cells were grown in odontogenic media, seeded onto the dentin surface, and examined live-cell microscopically to capture pulp cell responses to dental materials on-chip. Clinically utilized, standard dental materials were examined for cytotoxicity, cell morphology, and metabolic activity on-chip and compared to controls grown in the same conditions but outside of the microfluidic device.[50] In conclusion, the tooth-on-a-chip is a platform that permits live-cell imaging to investigate dental pulp cell responses to biomaterials by simulating the physiologic circumstances of the pulp-dentin interface.

CONCLUSION

Recent developments in OOAC technology have been discussed. Microfluidic chips are a promising tool for OOAC research and development. Great scientific progress has been made thanks to the extensive attention given to its development all around the world. Numerous OOACs have been planned and developed. Researchers have looked at a variety of human body parts. The long-term objective of OOAC is to create a model of a "Human-on-a-chip" by integrating a variety of functional organs onto a single silicon substrate. Although OOAC technology has advanced rapidly, the concept of a "human-on-a-chip" is still rather far off. The primary disadvantage of the most commonly used substance, PDMS, is that the resulting film is thicker than the *in vivo* shape. Reduced solvent efficacy and toxicity are associated with a decrease in the absorbance of tiny hydrophobic compounds. As a result, it is important to find suitable alternatives. Components must be low-cost and easy to dispose of because the current cost of manufacture and experimental implementation is not conducive to the broad usage of organ chips. It is important to recycle the more expensive parts. Media volume and connector size are two aspects of integrated systems that need to be lowered for widespread application. The concentration of different metabolites may alter if samples are collected on the chip, which could affect its functionality. This necessitates the development of better sensors. It is also necessary to develop universal cell culture mediums applicable to all body systems. Crucially, as the number of organs on the chip grows, so does the complexity of its activity, and the resulting data carries with it artefactual and non-translatable dangers. There is not a way to fix this right now. Long-term, repeated dosages or on-chip experiments raise the possibility that *in vitro* biomarkers do not accurately represent their *in vivo* counterparts.

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