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Exploring Organ-on-Chip Systems as Functional Bioassays for Drug Screening: Principles and Models

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Abstract. Organ-on-chip (OoC) systems are rapidly becoming an avant-garde tool for mimicking the organization and function of human organs in vitro. Through integration of microfluidic techniques and living human cells, they enable physiologically realistic conditions for drug testing, which simply can not be achieved using standard 2D cultures or animal models. This review provides a summary of the principles and constructions of liver-, heart-, lung-, and gut-on-chip systems, and discusses how each system recapitulates specific organ function. Special attention is given to their utilization as functional bioassays for drug discovery. By linking together organ chips to form fluidic circuits, researchers can emulate inter-organ pharmacokinetics and dynamic biological responses that are essential for drug metabolism, efficacy testing, and toxicity testing. While challenges still exist in ruggedizing, scaling up and cell sourcing, OoC technologies are moving towards predictive and personalized preclinical testing platforms. Such systems have great promise to increase the predictive and efficiency aspects of pharmacology and improve the relevance of pharmacological evaluations to the human condition.

Keywords: organ-on-chip, Liver, Heart, Gut, Lung, Bioassay

1. Introduction

On-chip organ technologies have now been recognized as a disruptive tool in drug screening and biomedicine. The microengineered systems are designed to mimic the structure and function of human organs, providing a more physiologically relevant and dynamic platform than those of traditional 2D cell culture or animal models. Since OoCs incorporate living human cells in microfluidic devices, they can mimic tissue-tissue interfaces, mechanical loading and chemical gradients that are essential for replicating organ-level functionalities [1-2].

Limitations in currently available preclinical models led to the emergence of OoC systems. Although animal models are frequently used, they have limited ability to predict human-specific responses due to interspecies variability, leading to high clinical trial failure rates. Classic in vitro methods, although appropriate for high-throughput screening, are limited to simulate human physiology and drug absorption, metabolism and toxicity. Therefore, the call for more predictive and human-based models resulted in a rapid development of OoC platforms [3-4].

We will start first by discussing the historical perspective and the basic principles and importance of organ-on-chip technology then we will do an extensive analysis of its use as bioassays for drug

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screening. Particularly, we investigate how OoC models (multiple, e.g. liver, lung and gut-on-chip) are designed, and how their biological mechanisms and elements contribute to predictive power enhancements in drug studies. This review want to consider the potential of OoCs as a new type of drug test device by summarizing the latest progress in various chip types [5].

2. The different types of organ on chips

2.1. Liver organ on chip

Liver-on-a-chip (LoC) platforms are microfabricated systems for modelling the physiological architecture and key functionalities of the human liver. They are designed to mimic key hepatic functions—in particular metabolism, detoxification, and cell-cell communication—within a controllable and scaled-down microfluidic workspace [6-8].

In general, LoCs encompass an array of interconnected microchannels that are coated with human liver cells, such as primary hepatocytes and supporting non-parenchymal cells (e.g., liver sinusoidal endothelial cells, Kupffer cells, or hepatic stellate cells). These cells are suspended in a 3D extracellular matrix and continuously perfused with culture medium to model blood flow. This enriched microenvironment provides an optimal milieu for liver-specific functions such as oxygen and nutrient exchange, and waste removal [6,9].

Of particular interest in LoC design is the capability to produce physiological gradients (eg., of O2 or metabolite contents) that are essential for replicating liver zonation and region-specific metabolism. In more sophisticated designs, multiple chambers or compartments can be created in which cells are spatially separated but can interact through porous membranes.

Biosensors, mechanical stimulation, and induced pluripotent stem cell-derived dendritic cells-like cells could also be integrated to promote physiological relevance and the patient-specific functionalities in next-generation liver chips. Together, these design features enable LoC systems to sustain hepatic function and closely mimic the in vivo liver microenvironment [5-6].

2.2. Heart organ on chip

Heart-on-a-chip (HoC) technologies are fabricated platforms that mimic the structural and functional features of heart tissue in vitro. Such systems are designed to mimic major features of the heart, i.e., rhythmic contraction, electrical contraction, and mechanical compliance [10].

The common denominator of most HoC designs is the application of human cardiomyocytes (usually from human-induced pluripotent stem cells [hiPSCs]) on flexible or micropatterned substrates. This orientation leads to cellular alignment and coordinated contractions, which closely resemble the anisotropic structure observed in native heart wall assembly and the ability to produce directional force.

For electromechanical activity, most systems also have electrical stimulating components and mechanical stretcher-functions. These components enable control over contraction frequency, simulating both normal and pathological heart rhythms. Real-time monitoring is frequently conducted with embedded strain sensors or cantilevering systems to accurately detect contraction forces [10].

Moreover, microfluidic perfusion systems are incorporated into the device to provide nutritions, oxygen, and to maintain the culture environment, thereby closely mimicking the vascularized niche of the myocardium. Several other chips are based on multistacked design and soft scaffolds, with a focus on not only mechanical integrity but also electrophysiological measurement.

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Three-dimensional microtissue constructs, including cardiomyocytes mixed with other cell types (e.g., fibroblasts, endothelial cells) in hydrogels, are also included in many HoC models. These constructs can be made in the form of rings, rods or chambers to mimic heart muscle geometry and kinetics. In general, HoC systems present a more physiological approach to study the heart in a high-controlled environment [10].

2.3. Lung organ on chip

The human lung is a structurally complex system with dynamic functions in which gas exchange takes place, primarily at the alveolar–capillary interface. Accordingly, lung-on-a-chip (LoC) devices have been engineered to emulate this complex system. These models intend to recapitulate several key physiological aspects, including breathing motions, barrier resistance and immune cell trafficking [11-12].

Typical lung chips include a pair of fluidic microchannels separated by a thin, flexible porous membrane. Human alveolar epithelial cells are placed on one side of the membrane, representing the airway surface, and pulmonary microvascular endothelial cells are seeded on the opposite side, representing the vascular compartment.

To mimic breathing, alternating vacuum is applied to the side chambers of the device, thereby periodically stretching the membrane and entrained cells. This mechanical actuation mimics the stretch and relaxation of lungs during breathing and is also important for maintaining normal cell function and shape.

The epithelial surface is typically cultured at an air-liquid interface, and the blood side is perfused with culture medium to mimic the flow of blood. This setup allows process-related modeling, such as aerosol drug delivery, immunological responses, and gas exchange, under near-physiological conditions [11-12].

More sophisticated models can also incorporate immune components such as macrophages or neutrophils to model inflammatory responses or infection dynamics. Surface modifications, ECM coatings, or hydrogel layers are widely applied to enhance cell adhesion and mimic the extracellular environment. By combining mechanical, biological, and fluidic constituents, the lung-on-a-chip offers a tractable, physiologically accurate mimic of the alveolar interface, as well as a repeatable in vitro system for toxicological studies.

2.4. Gut organ on chip

Gut-on-a-chip devices are microfluidic-based systems designed to replicate the structure and functions of the human GI tract. Such systems aim to reproduce the dynamic microenvironment of the intestine, featuring characteristics such as peristalsis-like motion, nutrient uptake, barrier integrity, and host–microbiome crosstalk, within a controllable in vitro environment [13-15].

The device generally comprises two microchannels divided by a permeable and flexible membrane. Human intestinal epithelial cells are grown on the upper surface of the membrane and become confluent as a monolayer modeling the intestinal mucosa. The bottom channel may be coated with endothelial cells to mimic the underlying vasculature, and nutrient transport and intercellular signaling across the gut–blood barrier may be investigated.

To mimic the mechanical forces experienced in the digestive system, the majority of gut chips have vacuum-driven side chambers that cyclically deform the membrane to reproduce the peristaltic-like motion. This mechanical stretch induces epithelial differentiation, villus-like structure formation, and tight junction formation, providing a more physiological model.

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Both channels are subjected to flow as well as mechanical stimulation. The upper (luminal) channel can be exposed to nutrient-rich medium (and microbiota) to mimic the gut lumen, whereas the lower (vascular) side can be perfused to offer metabolic supply and waste clearance. With this setup, it is possible to retain polarity of epithelial cells and thus, to better mimic nutrient absorption kinetics [13,15].

A few more advanced designs also facilitate co-culture with commensal or pathogenic bacteria under air–liquid interface conditions, offering platforms for controlled studies on the microbial impact on gut health and disease. As a support for these cultures, extracellular matrix coatings and hydrogel scaffolds are commonly employed to offer mechanical support and biochemical signals to the cells.

Overall, gut-on-a-chip systems provide a flexible and modular platform to explore gut physiology. Their structure enables fine tuning of the physical, chemical and biological parameters and is essential to mimic the extremely dynamic environment of the human GI tract [14-15].

3. Applications of organ-on-chip systems as bioassays in drug screening

Organ-on-a-chip technologies are a type of bioassay that may be used not only to mimic discrete organ functions, but also to replicate the inter-organ interactions that are critical for drug screens. Although single-organ chips (liver-, heart-, lung-, gut-on-chip) are useful for organ-specific toxicity and drug metabolism investigations, the major potential lies in extending and combining multiple organ models as an integrated system to better mimic human physiological responses to drugs [1,4].

In the human body, the impact from a drug is likely to be the result of how it is metabolized over time or concurrently by multiple organs. For example, a substance may be metabolised in the liver, travel through the bloodstream, then affect the heart, or be excreted via the intestine. Such complexity of physiology cannot be replicated using conventional (non-monolithic) assays, but in integrated organ-on-chip systems, researchers can simulate these multi-step processes within a microfluidic environment [3-4].

By connecting liver chips to heart or gut chips through fluidic circuits, scientists can observe how the metabolic byproducts affect downstream tissues. For instance, the liver-heart chip configuration is a renowned example where hepatic metabolism of some drugs produces harmful metabolites that cause cardiac dysfunction. This platform is capable of identifying metabolism-mediated cardiotoxicity, which is a common cause of late stage drug attrition that may be overlooked when using standard, isolated cell-based assays [1,4,10].

Analogously, combinations of gut-liver-lung chips have been created to model the oral administration and first-pass metabolism of inhaled or orally consumed drugs. Once the compound passes through an intestinal chip to simulate absorption, it will then pass through a liver chip to evaluate metabolism, and finally pass into a lung chip for pulmonary toxicity testing. These multi-organ platforms are especially suited for the investigation of complex pharmacokinetics and tissue-specific drug effects [4,11,13].

Most importantly, these systems also facilitate real-time sampling or continuous monitoring, thus allowing for visualization of in situ alterations of barrier integrity, enzymatic function or electrophysiological features in various organs. In conjunction with biosensors, they are sensitive, automated bioassays for measurement of quantifiable time-dependent biological responses [5,10,16].

Such organ numbers, organ gradients, and combinations can be modified based on the drug class or target, which is another key feature. For instance, liver-gut systems have been developed to investigate oral drug absorption and hepatic metabolism, and liver-kidney or liver–lung pairs are

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employed to evaluate the clearance and systemic toxicity. This modular structure enables the use of organ-on-chip systems for different types of drugs and various kinds of screenings [1-3].

In summary, by combining several organ-on-chip models into integrated bioassay platforms, a more comprehensive and predictive drug screening process would be provided. However, they offer a dynamic, physiologically relevant approach to drug behavior across organ systems thus reducing dependence on animal models and improving the safety and efficiency of preclinical testing [1,4-5].

4. Discussion

Despite the great potential of organ-on-a-chip technologies as advanced bioassay systems, several hurdles remain to the universal adoption of such platforms for drug development. Standardization is one of the most crucial challenges. Traditional devices are fabricated in academic or research environments with proprietary materials, frameworks, and protocols. This variability introduces an impediment to reproducibility and it interferes with the comparison of results between laboratories and between studies [2-3].

Also, a drawback is that scalability and throughput are insufficient. Organ-on-chip devices are of substantially less throughput than traditional cell-based assay or HTP platforms. Due to their complexity and dependence on manual manipulation, only few compounds can be tested in parallel. In the case of pharmaceutical industry applications, in particular for early-stage compound screening, higher level of automation and parallelization are necessary to compete with established approaches [4,16].

In addition, a number of existing models continue to depend either on use of cell lines or partially-differentiated stem cell-derived tissues, which may not fully recapitulate the behavior of primary human tissues. For example, inconsistency in sourcing of cells, immaturity and lack of long-term function may affect consistency of the assay. It also remains to be developed how to integrate supporting cells such as immune cells, stromal cells, or innervation. Additionally, fully recapitulating tissue complexity in vivo has been challenging [5,9]. With regard to integration, while multi-organ systems have been shown, achieving highly integrated and physiologic temporal coupling between more than 2-3 organ types is currently technically demanding. Realistic circulation, feedback control and dose distribution among connected chips await further development [4,11].

In the future, a number of promising directions suggest that interest in and development of such systems will grow. A major realm is personalized medicine, such as using patient-specific iPSC-derived tissues of organs to recapitulate the genetics for personalized drug testing. Drug responses and toxicities would then be testable on a person-by-person basis, bringing a new paradigm in the choice of treatment drugs [5-6]. Also of interest is the emergence of biosensors and real-time analytics on chip platforms. Incorporated sensors for pH, oxygen, metabolites, or electrophysiological signals provide continuous, non-invasive monitoring of cell functionality and drug response. In combination with automated fluidics and data acquisition this could allow all steps of a drug screening procedure to be conducted by a single stand alone benchtop unit [10,16]. Additionally, the development of commercial platforms and regulatory involvement, including the FDA's interest in organ-on-chip data for preclinical safety assessment, suggests an increasing institutional validation of such devices. Combined efforts between academia, industry, regulators and policy makers will be crucial to move organ-on-chip from a research based technology to the validated and widely used bioassay platforms [1,3].

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5. Conclusion

This review explores organ-on-chip (OoC) technologies, focusing on their design principles, key types (liver, heart, lung, gut), and applications in drug screening. It highlights how OoCs, by mimicking organ structures, dynamic microenvironments, and inter-organ interactions, offer more physiologically relevant platforms than traditional 2D cultures or animal models, enhancing predictive power in drug metabolism, toxicity, and pharmacokinetics studies. Despite their potential, OoCs face challenges: lack of standardization, limited scalability/throughput, incomplete tissue complexity, and technical barriers in multi-organ integration. Future advancements should prioritize standardization, improved automation, integration of diverse cell types, and enhanced multi-organ coupling. Collaborations between academia, industry, and regulators, alongside innovations in biosensors and personalized medicine, will be pivotal to translating OoCs into widely validated tools for preclinical drug development. With continued innovation in cell biology, microengineering, and automation, these platforms may redefine the future of bioassays by offering more predictive, human-relevant, and ethically responsible alternatives to traditional methods.

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