Invited Editorial

Human-on-Chip Technology: Current State and Future Challenges

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"Human-on-chip" (HoC) [1] is a revolutionary concept, representing a miniature functional version of the human body within a microfluidic device that provides researchers with an unprecedented opportunity to study diseases, test drugs, and develop personalized treatments [1-8]. HOC is an advanced version of organ-on-a-chip technology. At the same time, organ-on-chip is limited to studying individual organs or tissues; HoC integrates multiple organ-on-a-chip systems into a single platform, representing different organs or tissues connected by a circulatory system [7,9]. These systems simulate the complex interactions between organs in response to drugs, diseases, and other stimuli, which provide a more comprehensive understanding of human physiology and drug responses [7,10,11]. HoC, often referred to as 'Body-on-a-chip,' [10] offers a more ethical, accurate, and reliable platform for experimentation than traditional cell cultures and animal testing. In this editorial, we delve into the exciting realm of HoC technology, exploring its current state and future challenges [10, 12].

It was first developed in the mid-2010s. One of the pioneering works in this field was a lung-on-a-chip that mimicked a human lung's mechanical and biochemical functions [13]; since then, many single and multi-organ-on chips devices have been created, such as tooth-on-a-chip [14], on-chip small intestine-liver coupled model [15], EVATAR (appear or act for a dynamic recently developed in *vitro* device that permits organ-organ coalescing of hormonal signaling as a phenocopy of women periodical cycle and similar to an expectant endocrine circuit and has an appreciable perspective to be utilized for invention of new medicine and overall pharmacological researches) [16], bone-marrow-on-a-chip etc. [17].

HoC devices utilize microfluidics to transport nutrients, gases, and metabolites, mimicking blood flow in the human body. Multiple organ chambers are connected via microchannels, allowing communication between them. Microchannel geometry is adjusted to maintain physiological flow rates and balance hydraulic resistances. Fluid recirculation is achieved using external pumps, microfabricated on-board pumps, or gravity-driven flow. Gravity-driven systems, often bidirectional, can maintain physiological flow rates and compact designs. Flow rectifiers can create unidirectional flow, which is crucial for tissues like endothelium. Integrated sensors are vital for assessing tissue health in such microdevices. Aptamer-based electrochemical

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sensors, luminescence, enzyme-based sensors, microelectrode arrays, and transmembrane electrical resistance electrodes monitor various physiological parameters like protein levels, oxygen, glucose, and electrical activity [18]. Maintaining cell viability and considering flow rates, fluid residence times, and oxygen supply in each organ compartment is essential to replicate in vivo drug metabolism rates. Also, it is crucial to connect organ chambers physiologically relevantly. Three critical design elements must be considered to achieve these standards for copying functions of in vivo organs-scaling Factor, fluid Volume, and fluid-to-cell ratio in tissues.

The implications of HoC technology are vast and transformative. It provides holistic understanding and is invaluable in developing targeted therapies for complex and multifaceted diseases like cancer, diabetes, and neurodegenerative disorders with greater efficiency and precision. Here are some of the critical implications of this innovative technology.

Drug Discovery and Development

In Drug Discovery and Development, HoC models signify a ground-breaking advancement, facilitating precise and efficient testing of novel pharmaceuticals. These cutting-edge systems empower pharmaceutical companies to assess drug efficacy, toxicity, and potential side effects directly on human cells and tissues. HoC devices offer a streamlined and ethically responsible approach, diverging significantly from conventional laboratory setups and animal testing methods. These systems are inherently compact, requiring fewer resources than traditional methods. This efficiency translates into substantial cost savings for research and drug development endeavors, concurrently enhancing the ethical integrity of the drug discovery process. Significantly, HoC technology substantially improves the early stages of drug development. By providing more accurate and predictive data in these pivotal phases, HoC models hold the potential to mitigate the costs typically associated with unsuccessful clinical trials. This precision augments the efficiency of the entire drug development pipeline.

Furthermore, HoC technology's impact is significantly expediting the drug development timeline. This acceleration is especially critical when timely access to life-saving medications is imperative. Moreover, HoC systems offer automation capabilities and can be employed for high-throughput screening of drugs and compounds. Researchers can simultaneously assess many substances, significantly expediting drug discovery [19].

Personalized Medicine

HoC technology offers a transformative approach to healthcare. By utilizing patient-specific cells, HoC models provide a unique opportunity to delve into the intricate interplay between drugs, treatments, and individual genetic backgrounds. This precision allows researchers to tailor treatments with unprecedented accuracy, ensuring a bespoke approach to each patient's genetic makeup. HoC technology enables the development of highly customized treatment plans, optimizing therapeutic interventions for various diseases and conditions. By mimicking human physiology in vitro, these models offer a comprehensive understanding of how specific drugs affect individual patients, paving the way for personalized therapies. HoC's ability to replicate disease pathology further amplifies its impact, facilitating in-depth disease progression studies and identifying targeted therapeutic strategies. In essence, technology epitomizes the future of personalized medicine, promising enhanced efficacy, minimized side effects, and improved patient outcomes [7].

Reduction in Animal Testing

HoC models present a compassionate and ethical alternative to conventional animal testing in biomedical research. They facilitate the in-depth exploration of human physiology and diseases, preventing the reliance on animal models. Compared to traditional drug testing methodologies, which predominantly hinge on animal models or static cell cultures, HoC models offer a more precise avenue for assessing how drugs interact within the human body. The discordance between animal-based predictions and human responses has been a source of substantial setbacks and financial burdens in drug development, often delaying the availability of life-saving treatments. Researchers gain a more comprehensive understanding of drug efficacy and toxicity by meticulously simulating the intricate interplay of human organs and tissues. This breakthrough diminishes the necessity for animal testing, expediting drug development and potentially expediting the approval of novel therapies. While animal models still hold their place in chronic exposure tests, this Micro-physiological System technology is progressively evolving to replace

animal-based investigations [20].

Biological Research Advancements

HoC technology not only benefits drug development but also contributes to advancing our understanding of basic biology, disease mechanisms, and organ interactions. HoC devices can mimic the complex interactions between different organs and tissues in the human body. This interconnectedness is crucial for holistically understanding diseases and drug responses. It is also possible to monitor microenvironmental parameters like pH, O2 levels, and temperature by incorporating electrochemical immune biosensors to measure soluble biomarkers and miniature microscopes for observing organoid morphologies [21]. HoC models can test the compatibility and efficacy of medical devices, such as implants and prosthetics, in a more physiologically relevant environment.

Disease Modelling

Scientists can create disease-specific organoids on chips to study complex diseases such as cancer [22-24], diabetes [25], cardiovascular diseases [26], Parkinson's disease [27], etc. These models offer insights into disease mechanisms and potential treatments, paving the way for targeted therapies. HoC technology allows researchers to mimic the interactions between different organs and tissues. Moreover, due to their rarity, this technology enables researchers to study rare diseases that are challenging to learn in clinical settings or clinical trials [28].

Safety Testing

HoC models enable the assessment of drug-induced toxicity in various organs simultaneously and more effectively. This capability is crucial for identifying potential adverse effects early in the drug development. Also, it enables researchers to study chronic drug-induced effects. Zhang YS *et al*. developed automated and functional human heart-and-liver-on-chips and human heart-and-liver-cancer-on-chips to demonstrate long-term monitoring of chronic drug responses and short-term evaluation of acute toxicity, respectively [21]. HoC models can be used to study the effects of environmental toxins and chemicals on human organs. This information is valuable for assessing ecological hazards, understanding public health issues, and developing safety regulations. Moreover, these systems provide an opportunity to test a new drug in conditions where it is not ethical or safe to do so, such as placenta-on-chip can be used to study the concentration of drug reaching embryo when administered in a pregnant woman [29].

Challenges and Future Directions

While HoC technology holds immense promise, it is not without its challenges. The complexity of recreating human biology at a microscale, ensuring the long-term stability of the devices, and integrating data from multiple sources are just a few of the technical hurdles' researchers must overcome [30]. It is difficult to recapitulate the full biological functions in these microdevices, such as incorporating the immune system and innervation, which is particularly important in studying viral diseases [19]. Incorporating biosensors into Organ-on-Chips (OoCs) for the continuous and extended real-time tracking of biomarkers in cell media is a challenging objective. Currently, this goal faces several obstacles, including i) the need to prevent biofouling for long-term monitoring by passivating biosensor surfaces, ii) reaching saturation on biosensor surfaces due to inherent thermodynamic and kinetic limitations of receptors, and iii) the necessity for labels and reagents to detect most analytes [31]. The advancement in artificial intelligence (AI) would improve the design and data processing of OoCs [32]. Also, the material used in fabricating such microdevices should be inert, as the results might be affected if the tested drug interacts with the materials used in fabrication [21]. Additionally, regulatory agencies must establish clear guidelines for using HoC technology in drug development and clinical trials. Standardization and validation processes are essential to ensure the reliability and reproducibility of results.

In conclusion, HoC technology represents a beacon of hope in medical research. By faithfully replicating the human body's intricate workings, HoC platforms can accelerate drug development, enhance our understanding of diseases, and usher in a new era of personalized medicine. As research in this field progresses, we can anticipate a future where diseases are entirely understood and treatments are as unique as the individuals they aim to heal. While HoC technology holds significant promise, it's important to note that it is still a developing field, and ongoing research is essential to fully realize its potential in revolutionizing healthcare and drug discovery. As this technology evolves, collaboration between researchers, healthcare professionals, and regulatory

bodies will be crucial to harness its full potential. The era of HoC technology is upon us, heralding a new age of precision, compassion, and efficacy in healthcare.

Consent for Publication

The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work, including any accuracy or integrity issues.

Disclosure

The author declares that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly with the subject matter or materials presented in this editorial. This includes honoraria, expert testimony, employment, ownership of stocks or options, patents, or grants received or pending royalties.

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Information is taken from freely available sources for this editorial.

Authorship Contribution

All authors contributed significantly to the work, whether in the conception, design, utilization, collection, analysis, and interpretation of data or all these areas. They also participated in the paper's drafting, revision, or critical review, gave their final approval for the version that would be published, decided on the journal to which the article would be submitted, and made the responsible decision to be held accountable for all aspects of the work.

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