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Organ-On-A-Chip Technology for Drug Development and Personalized Medicine

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ABSTRACT

Organ-on-a-chip (OoC) technology is an emerging microfluidic-based approach that has gained significant attention in pharmaceutical research and biomedical applications. Conventional drug development methods, including two-dimensional (2D) and three-dimensional (3D) cell culture models and animal testing, have several limitations in accurately predicting human physiological responses and drug toxicity. To overcome these challenges, OoC technology has been developed to reproduce the structural and functional characteristics of human organs under controlled in vitro conditions. These microfluidic platforms contain living human cells, fluid channels, and mechanical stimuli that help mimic the natural microenvironment of different organs. This review highlights the design, fabrication, and applications of single-organ and multi-organ-on-a-chip systems, including heart, liver, lung, kidney, brain, and gut models. These platforms provide valuable opportunities for drug discovery, preclinical drug evaluation, drug screening, toxicity assessment, and absorption, distribution, metabolism, excretion, and toxicity (ADMET) studies. Furthermore, the integration of patient-derived cells and organoids into OoC platforms offers new possibilities for personalized medicine by evaluating individual patient responses to different drug treatments. Despite their promising applications, challenges related to chip standardization, stability, reproducibility, and integration of multiple organ systems remain. Future advancements in microfluidics, 3D printing, biosensors, and artificial intelligence may further improve the reliability and practical applications on this technology. Overall, organ-on-a-chip technology represents a promising research platform for improving drug development and supporting the advancement of personalized medicine.

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INTRODUCTION

The development of a new medicine is a lengthy and costly process. Candidate compounds are commonly evaluated using in vitro cell models and animal studies before progressing to clinical trials. Although these approaches have contributed substantially to biomedical research, their ability to predict human responses is limited. Conventional static cultures may lack vascular components, dynamic mechanical cues, and interactions among multiple cell types. Animal models can also differ from humans in physiology, metabolism, and disease mechanisms, making direct translation of some findings difficult [1,2].

Drug development may take approximately 10–15 years and incur costs estimated in the billions of dollars, while many candidates that pass preclinical evaluation do not ultimately succeed in clinical development [3]. These challenges have encouraged the development of experimental systems that preserve the control of in vitro studies while reproducing selected features of the human in vivo environment.

Organ-on-a-chip (OoC) technology uses microfluidic devices to culture living cells under controlled conditions. Fluid movement through small channels can provide continuous nutrient delivery and waste removal, while flow-induced shear stress and mechanical deformation can reproduce selected physiological stimuli. Depending on the design, different cell types may be cultured in adjacent channels or on opposite sides of a porous membrane. Such arrangements allow investigators to examine cell –cell interactions, barrier function, tissue responses, and drug effects in a controlled environment [4–6].

OoC platforms have been developed for several organ systems and are increasingly explored for pharmacological and toxicological applications. They may provide information relevant to pharmacokinetics (PK), pharmacodynamics (PD), metabolism, and organ-specific toxicity. Integration of patient-derived cells or organoids also creates opportunities to investigate inter-individual variation in drug responses [7,8]. Multi-organ systems seek to model interactions between tissues and the movement of compounds or metabolites between organ modules [9,10].

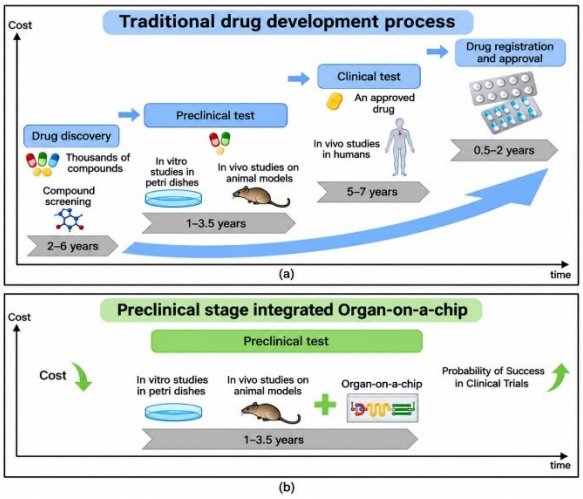

Figure 1: Schematic Comparison of Conventional Drug Development Methods and Organ-On-A-Chip (OoC) Technology.

(a)In conventional drug development, the overall costs tend to increase progressively throughout the development process. (b) The application of organ-on-a-chip (OoC) technology is expected to reduce drug development expenses and potentially improve the success rate of clinical trials

This review aims to provide a framework for supporting the development of new OoC systems and exploring their applications as alternative platforms for pharmacological, pharmacokinetic, and toxicological studies. The ultimate objective is to improve the accuracy, reliability, and practical application of these systems as research tools in drug development.

Principles and Fabrication of OoC Systems

Basic concept

An OoC device is a microengineered culture platform designed to reproduce selected structural, cellular, and functional features of an organ. The device generally contains microchannels or chambers in which organ-specific cells are maintained under defined culture conditions. A porous membrane, extracellular matrix (ECM), hydrogel, or other supporting material may be incorporated to support tissue organization and communication between cell populations. Depending on the organ model, the platform may include perfusion, mechanical actuation, electrical stimulation, or integrated sensors [12,13].

Physiologically relevant parameters may include flow rate, pressure, shear stress, pH, osmotic conditions, nutrient availability, and exposure to drugs or toxins. The parameters selected should reflect the biological question and the functional unit being modelled. OoC devices are not complete miniature organs; rather, they reproduce selected features that are relevant to a defined experimental purpose.

Design and fabrication workflow

The design process begins by identifying the organ function or disease feature to be represented. Cell source, culture medium, geometry, fluid flow, mechanical cues, and analytical endpoints are then selected. Computer-aided design (CAD) tools can be used to define channel and chamber geometry before fabrication. Photolithography, soft lithography, stereolithography, and other microfabrication or additive-manufacturing approaches may be used according to the required resolution, material, and device architecture [13,14].

After fabrication, the device is assembled and prepared for cell seeding. Cells are introduced into the appropriate compartments and cultured until the required tissue organization or barrier formation is achieved. The model is then assessed using biochemical, imaging, and biophysical measurements. Figure captions in the source manuscript describe this general sequence as device design, microfabrication, tissue culture, and biological assays.

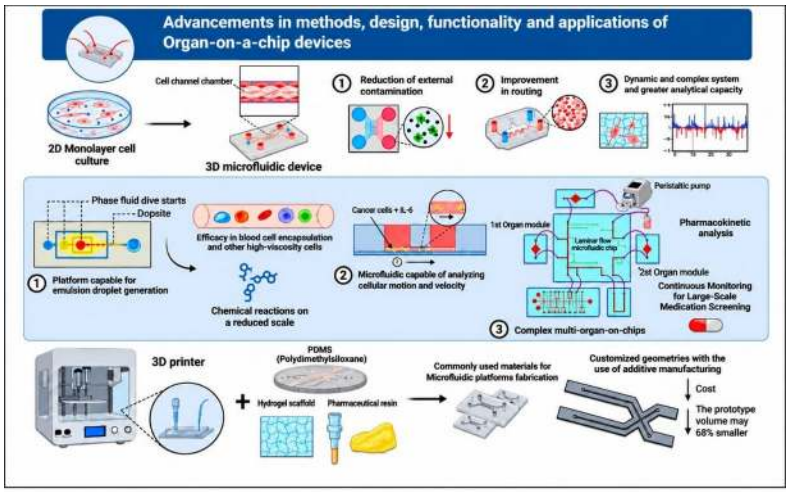

Figure 2: Schematic Representation of Organ-On-A-Chip (OoC) Technology.

Materials and engineering considerations

Common device materials include glass, silicon, polydimethylsiloxane (PDMS), polymethyl methacrylate (PMMA), cyclic olefin copolymers, films, and hydrogels. Glass and silicon can support precise fabrication, although silicon has limited optical transparency. PDMS is widely used because it is transparent, flexible, and relatively easy to process; however, its capacity to absorb some small molecules can complicate drug-exposure studies. PMMA offers optical transparency and mechanical strength. Material selection should therefore consider optical access, chemical compatibility, cell compatibility, fabrication requirements, and possible interactions with test compounds [16,21].

Fluidic design is central to model performance. Flow rate and shear stress need to be controlled in a manner appropriate to the tissue under study. Pumps, tubing, reservoirs, and connectors can influence the delivered exposure and the stability of the culture environment. Validation should include repeatability testing and comparison with relevant biological or pharmacokinetic expectations.

Single-Organ-on-a-Chip Model

OoC platforms are commonly grouped into single-organ and multi-organ systems. Single-organ devices focus on a particular tissue or organ function and are useful for studying organ-specific physiology, disease mechanisms, and responses to drug exposure. Multi-organ platforms connect two or more modules to investigate inter-organ communication and the effects of metabolism or distribution across tissues [15,18].

Heart-on-a-chip

Heart-on-a-chip systems aim to reproduce selected structural and functional properties of cardiac tissue. Models may include cardiomyocytes, cardiac fibroblasts, and other relevant cell populations, arranged in two-dimensional or three-dimensional configurations. Electrical and mechanical stimulation can be incorporated to support contractile activity and to examine how cardiac tissue responds to external cues [19,20].

These platforms have been investigated for cardiac disease modelling, including ischaemia and fibrosis, and for evaluating drug-induced cardiotoxicity. Measurements of contraction, electrical activity, cell viability, and other tissue-specific endpoints can provide information about pharmacological effects. Device materials and their interactions with test compounds are important considerations; in particular, absorption of small molecules by PDMS may affect the effective drug concentration [21].

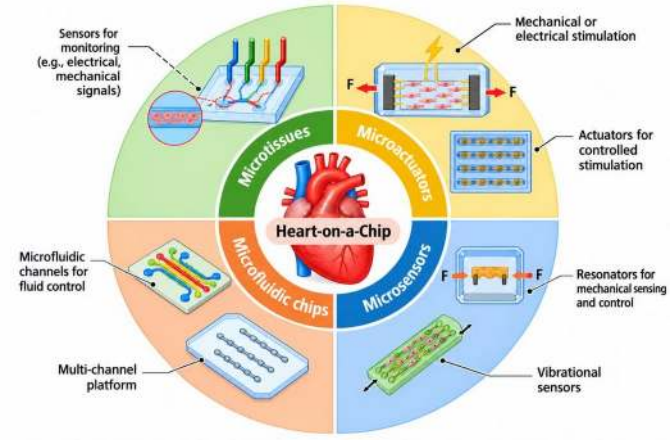

Figure 3: Structural Components of a Heart-On-A-Chip System.

Liver-on-a-chip

The liver plays a central role in drug metabolism and is a major site of drug-induced toxicity. Liver-on-a-chip systems seek to maintain liver-specific cells under controlled perfusion and to reproduce aspects of the hepatic microenvironment. Cell populations discussed in the source include hepatocytes, liver sinusoidal endothelial cells, and hepatic stellate cells. Their organization within microchannels can support investigation of cell interactions, metabolic activity, and responses to potentially hepatotoxic compounds [22,23]

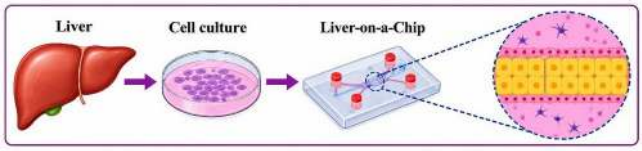

Figure 4: Preparation Process and Internal Structure of a Liver-On-A-Chip System.

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The development of a liver-on-a-chip platform involves three main steps. Initially, the required target cells are isolated and cultured under suitable

conditions. Next, the main microfluidic chip structure is fabricated. Finally, the cultured cells, microfluidic components, and supporting control systems are integrated to develop the complete liver-on-a-chip platform.

Liver-chip models have also been used to examine disease-related changes. The source manuscript describes models of non-alcoholic fatty liver disease (NAFLD) in which free-fatty-acid exposure is associated with intracellular lipid accumulation and changes in genes related to lipid metabolism. Biomimetic liver-lobule chips have been proposed to investigate the distribution of lipid within hepatic tissue-like structures. Such models may help evaluate disease mechanisms and drug responses in vitro [23]

Brain-on-a-chip

Brain-on-a-chip (BoC) platforms aim to model selected cellular structures and interactions within the nervous system. The brain is highly complex, and a chip model generally focuses on specific barriers, neural cell populations, or tissue interfaces rather than reproducing the entire organ. These systems may be used to study the movement of drug molecules or nanocarriers across tissue barriers, interactions among cellular compartments, and disease-related responses. Integration of biosensors may support monitoring over time [24,25].

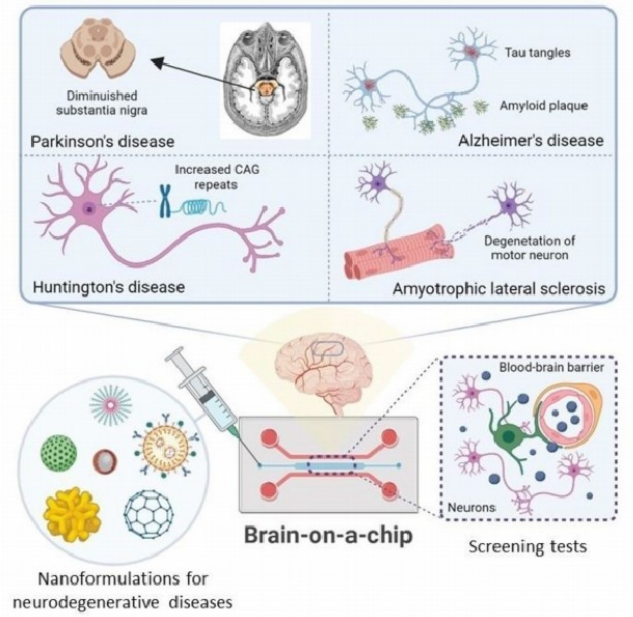

Figure 5: Schematic Representation of a Brain-On-A-Chip Platform.

Brain-on-a-chip technology is designed to reproduce the pathological and physiological characteristics of neurodegenerative diseases. It also serves as a preclinical screening platform for evaluating novel theranostic nanoformulations. The development of relevant brain models is increasingly required by clinical researchers because most brain-related studies are conducted using animal models. However, animal models are not always suitable for studying genetically related human brain diseases.Throughout medical history, animal models have made significant contributions to understanding human diseases and continue to play an important role, particularly in vaccine development. However, recent studies have shown that findings obtained from animal research cannot always be directly applied to humans.[25]

Lung-on-a-chip

Lung-on-a-chip (LOC) models reproduce selected features of the alveolar–capillary barrier. A representative design contains two parallel microfluidic channels separated by a thin porous membrane. Alveolar epithelial cells and pulmonary microvascular endothelial cells are cultured on opposing surfaces. Air exposure can be established on the epithelial side, while culture medium is perfused through the vascular

channel. Some designs apply cyclic mechanical stretching to model breathing-associated movement.

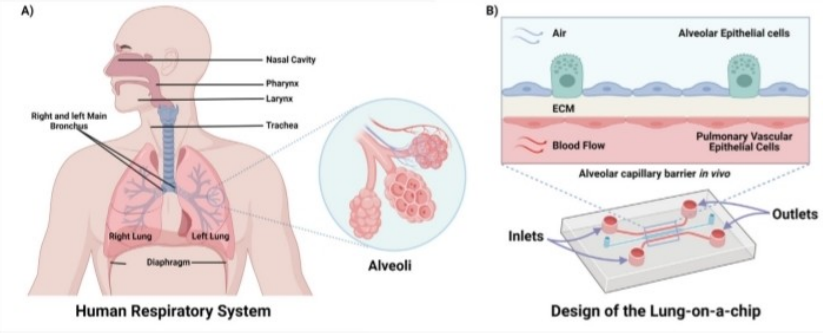

Figure 6: Reproduction of the Alveolar–Capillary Barrier Under in Vivo Conditions Using a Lung-On-A-Chip Model.

(a) In the human lungs, oxygen and carbon dioxide are exchanged through millions of small air sacs known as alveoli, which are surrounded by an extensive network of blood vessels.(b) The lung-on-a-chip platform is composed of two parallel microfluidic channels separated by a thin, porous membrane [10,26]

Patient-derived airway epithelial cells have been used to model respiratory disease features. The source manuscript describes an airway-on-a-chip model in which cells from patients with chronic obstructive pulmonary disease (COPD) displayed disease-associated characteristics, including goblet-cell changes, impaired ciliary function, inflammatory mediator secretion, and responses to cigarette-smoke exposure. Separate chips prepared from cells of the same patient may enable comparison of responses under different exposure conditions [27].

Kidney-on-a-chip

The kidney regulates filtration, electrolyte balance, and the reabsorption of essential substances. The nephron includes the glomerulus and renal tubules; the proximal tubule is particularly relevant to drug transport and nephrotoxicity. Kidney-on-a-chip models often focus on proximal tubular epithelium under perfusion, allowing investigators to examine cell viability, transport, barrier properties, and responses to nephrotoxic compounds [28].

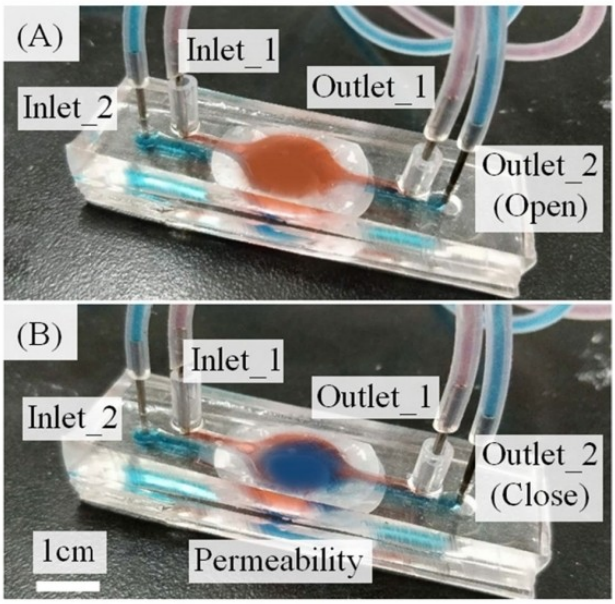

Figure 7: Evaluation of Permeability in a Microfluidic Kidney-On-A-Chip Model.

(A) Initially, the upper layer exhibited a red colour. (B) After perfusion, the colour of the upper layer gradually changed to blue, indicating that the culture medium passed through themembrane from the lower channel into the upper channel. Cell growth and apoptosis (programmed cell death) are essential parameters for assessing druginduced nephrotoxicity during drug screening. Live/dead staining demonstrated that cell death increased with rising drug concentrations, indicating that higher drug exposure caused greater cellular damage and an increased risk of nephrotoxicity. [29]

Gut-on-a-chip

The gut is involved in digestion, nutrient absorption, host–microbe interactions, and systemic homeostasis. Gut-on-a-chip (GoC) platforms provide controlled environments for studying intestinal epithelial function and selected interactions with microorganisms, nutrients, and drugs. Microfluidic perfusion and supporting matrices can help maintain intestinal cells and tissue-like structures [30].

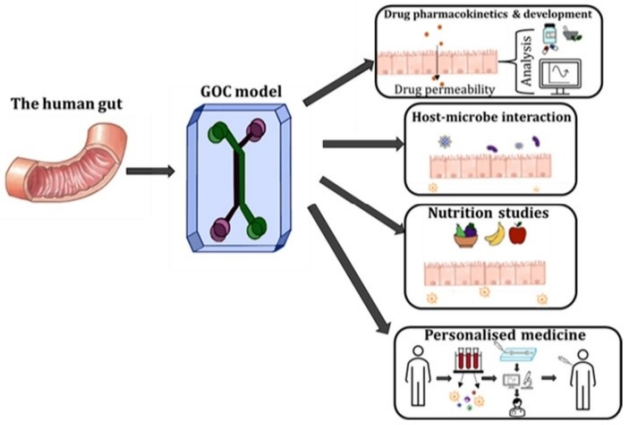

Figure 8: Schematic Representation of Gut-On-A-Chip (GoC) Models

Patient-biopsy-derived intestinal organoids are one source of primary intestinal cells. The source manuscript describes a platform in which cells derived from human intestinal organoids were seeded into a multilane device with an ECM-containing middle channel. Such models may support studies of intestinal physiology, inflammation, drug disposition, and patient-specific responses [31].

Muiti-Organ-on-a-Chip Systems

Multi-organ-on-a-chip (MOC) systems connect two or more tissue modules to investigate communication between organs. In one engineering approach, individually developed OoC units are connected through capillary tubing or a microfluidic interconnection platform. A modular design allows each tissue unit to be prepared and matured under organ-appropriate conditions before connection. Another approach uses a multi-organ plate in which several tissue compartments are integrated within a shared device [9,32].

Examples discussed in the source manuscript include intestinal–liver, liver–kidney, and intestinal–brain-axis configurations. These systems are intended to investigate the exchange of soluble signalling molecules, parent drugs, and metabolites between organ models. They may provide a more integrated view of drug absorption, metabolism, distribution, and organ-specific responses than an isolated single-organ model [32,33].

The development of a body-on-a-chip or human-on-a-chip platform requires careful consideration of the relative size and function of each tissue module, medium compatibility, fluidic connections, and the time scale of tissue responses. A shared circulation system can create practical challenges because different tissues may require different media and culture conditions. Flow distribution and the relative contribution of each organ module also influence interpretation of the results.

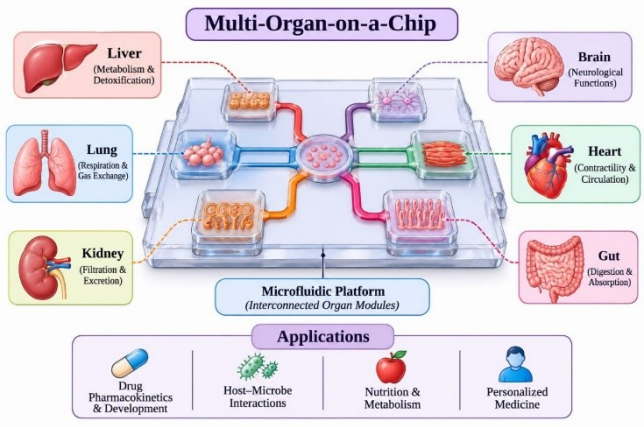

Figure 9: Schematic Representation of a Multi Organ on a Chip System

MOC platforms remain technically demanding. Their value depends on demonstrating that the connected system maintains functional tissues and produces interpretable, reproducible responses. Physiologically based pharmacokinetic and pharmacodynamic (PBPK –PD) concepts may help guide the design and interpretation of integrated systems [9,38].

Application in drug development

Preclinical drug evaluation

OoC technology is being investigated as an in vitro platform for preclinical drug evaluation. By providing controlled perfusion and selected organ-relevant features, these systems may help assess how candidate compounds affect human cells and tissue functions. Their potential applications include disease modelling, pharmacological testing, and the evaluation of direct and metabolite-mediated toxicity [34–36].

Toxicity is a major reason for attrition during drug development. The liver is particularly important because it metabolizes many compounds and can generate metabolites with biological activity or toxic potential. Liver chips may therefore contribute to hepatotoxicity studies, while heart, kidney, lung, and brain models can be used to investigate organ-specific effects. The value of each model depends on the cell source, functional maturity, exposure conditions, and validated endpoints [22,36,37].

ADME and pharmacokinetic studies

Absorption, distribution, metabolism, and excretion (ADME) are interconnected processes that influence drug exposure and response. Multi-organ systems may support investigation of selected aspects of these processes by linking tissues involved in uptake, metabolism, and clearance. The source manuscript discusses the use of multi-organ chips for pharmacokinetic evaluation and notes the emerging use of vascularized OoC models [38,39].

A connected platform can potentially reveal how a compound or its metabolites affect downstream tissues. However, an in vitro chip does not automatically reproduce whole-body pharmacokinetics. Device scaling, fluid volumes, tissue ratios, protein binding, and the representation of systemic clearance must be considered. Quantitative interpretation should be supported by appropriate experimental measurements and modelling.

Drug safety, efficacy and screening

OoC platforms may be used to compare candidate compounds, assess dose-dependent responses, and examine therapeutic effects alongside toxicity. Organ-specific chips are particularly relevant where a tissue is a known target of drug-induced injury. Multi-organ platforms may add information about indirect toxicity caused by metabolites formed in another tissue [40–42].

During lead optimization, in vitro findings are generally considered together with other preclinical evidence, including in vivo studies. OoC systems should therefore be viewed as complementary tools within a broader evidence framework rather than as universal replacements for existing methods. Their contribution will depend on reproducibility, predictive validity, and

acceptance of defined assays for particular applications [42,43].

Personalized Medicine

Personalized medicine seeks to tailor prevention or treatment to individual patient characteristics. Patient-derived OoC models offer a way to investigate disease-related cellular features and compare responses to candidate treatments under controlled in vitro conditions. Cells may be obtained directly from patient tissue or generated from induced pluripotent stem cells (iPSCs); organoids may also provide a source of patient-specific tissue structures [8,44,45].

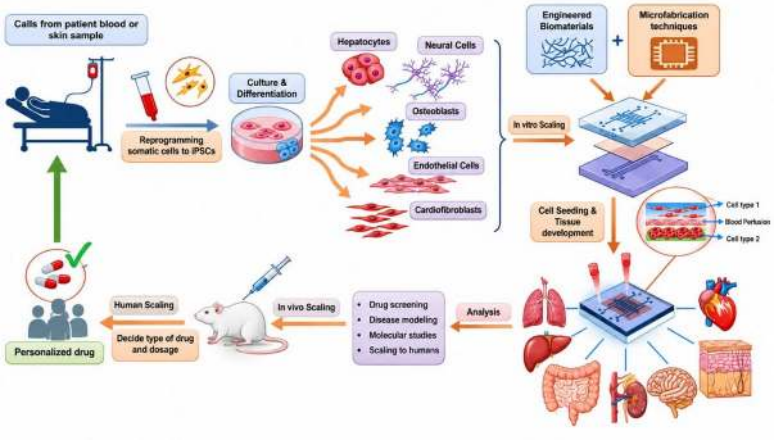

Figure 10: Personalized Drug Delivery System

A general workflow involves obtaining patient-derived cells, expanding or differentiating them, preparing the microfluidic device, seeding the cells, and allowing the tissue model to develop. Candidate drugs can then be tested using predefined endpoints such as cell viability, tissue function, inflammatory responses, or disease-associated markers. The results may inform research into patient-specific treatment responses, although clinical decisions require appropriate clinical validation and should not be based on an unvalidated chip assay alone [46–48].

The source manuscript describes patient-specific airway models in which cells from an individual were evaluated under different exposure conditions, illustrating how a patient's own cells can be used to study variable responses [27]. Patient-derived intestinal organoids and other primary-cell models may similarly help investigate individual differences in tissue behaviour. Such approaches could support the study of rare diseases, drug sensitivity, and treatment resistance.

Several challenges remain before personalized OoC testing can be routinely integrated into clinical care. These include the time and cost required to establish patient-derived cultures, variability in cell quality and maturity, limited sample availability, assay standardization, and the need to demonstrate that chip-based responses correlate with clinical outcomes. Ethical oversight, consent, and responsible handling of patient-derived biological material are also essential.

Challenges and Future Directions

Standardization and reproducibility

OoC platforms vary in device geometry, materials, cell sources, culture media, fluidic conditions, and analytical endpoints. This diversity can make results difficult to compare across laboratories. Standard operating procedures, reference materials, quality-control measures, and agreed criteria for tissue function are needed to improve reproducibility and support inter-laboratory validation [12,16,49].

Long-term stability and material limitations

Long-term culture requires stable tissue function, reliable perfusion, and materials that remain compatible with cells and test compounds. Absorption of hydrophobic small molecules by PDMS can alter the delivered dose, while tubing and device interfaces may introduce additional losses or variability. Material selection and compound-recovery studies should be

considered when designing drug-testing experiments [16,21].

Multi-organ integration and validation

Connecting several organ modules increases biological complexity but also introduces challenges in media compatibility, fluidic control, tissue scaling, and interpretation. A multi-organ system should demonstrate the function of each component and the validity of the inter-organ interactions being studied. PBPK–PD modelling can assist with experimental design and interpretation, but model assumptions and limitations must be stated [9,32,38].

Emerging technologies

Advances in microfabrication, 3D printing, bioprinting, hydrogels, and integrated biosensors may improve the structural complexity and monitoring capabilities of OoC devices. Automated fluid handling and real-time sensing could support higher-throughput experiments and more consistent operation. Artificial intelligence (AI) and computational models may help analyze complex datasets and connect experimental results with predictive models, provided that the underlying data are reliable and sufficiently diverse [5,15,37,51].

The future development of OoC platforms should prioritize fit-for-purpose validation. Rather than seeking a single universal chip, research should establish which model and endpoints are suitable for a specific drug-development question. Clear benchmarking against relevant human data, transparent reporting, and collaboration among engineers, biologists, clinicians, and pharmaceutical researchers will be important for wider adoption.

CONCLUSION

Organ-on-a-chip (OoC) technology has emerged as a promising and innovative approach in biomedical research, particularly in drug discovery, drug development, and personalized medicine. By combining microfluidic technology with human cells and tissue models, these platforms can reproduce important structural and physiological functions of human organs under controlled in vitro conditions. Different organ-on-a-chip models, including heart, liver, lung, kidney, brain, and gut chips, provide valuable opportunities for studying drug responses, toxicity, metabolism, and disease mechanisms. Furthermore, multi-organ-on-a-chip systems offer the possibility of investigating interactions between different organs and understanding the pharmacokinetic and pharmacodynamic behaviour of drug candidates.

One of the major advantages of this technology is its ability to use patient-derived cells to evaluate individual responses to different treatments, supporting the development of more effective and personalized therapeutic strategies. It may also help reduce dependence on animal testing, minimize drug development costs, and improve the prediction of human responses during preclinical drug evaluation. However, several challenges remain, including the complexity of device fabrication, limited long-term stability, difficulties in integrating multiple organs, and the lack of standardized protocols and validation methods.

Future research should focus on developing standardized, stable, and sensor-integrated OoC platforms with improved monitoring capabilities and reliable biological assessment methods. The integration of artificial intelligence, 3D bioprinting, patient-derived cells, and advanced microfluidic systems may further enhance their applications in pharmaceutical research. Overall, organ-on-a-chip technology has considerable potential to transform conventional drug development approaches and support the advancement of safer, more effective, and patientspecific treatments.

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