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A review on integrating organ-on-chip microphysiological systems into early phase clinical trials for accelerated drug development

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ABSTRACT

Organ-on-chip (OOC) microphysiological systems have emerged as a promising alternative to traditional in vitro and animal models for drug development. These advanced platforms recreate the complex microenvironment and physiological functions of human organs, enabling more accurate predictions of drug efficacy and toxicity. The complex tissue-tissue interfaces, biochemical gradients, and mechanical cues found in vivo can be simulated effectively by OOC systems providing a powerful way for preclinical drug screening and testing. The integration of OOC systems into early phase clinical trials has the potential to revolutionize drug development by bridging the gap between preclinical studies and human clinical outcomes. This approach allows for the evaluation of drug candidates in a more physiologically relevant context, taking into account factors such as organ-specific responses, inter-individual variability, and disease-specific conditions. The incorporation of patient-derived cells and the development of multi-organ platforms further enhance the predictive power of OOC systems, enabling personalized medicine approaches and the assessment of systemic effects. However, challenges such as standardization, validation, scalability, and regulatory acceptance need to be addressed to fully realize the potential

of OOC systems in clinical settings. As the knowledge on OOC systems advances, their integration into early phase clinical trials is expected to streamline the drug development process, reduce the reliance on animal testing, and accelerate the translation of basic research into safe and effective therapies for patients.

Keywords: *Organ-on-chip, microphysiological systems, drug development, Early phase clinical trials, in vitro models.*

1. INTRODUCTION

The process of developing new therapeutic drugs is extremely complex, time-consuming, and resource intensive. It is estimated that bringing a new drug to market requires 10-15 years of research and development efforts at a cost exceeding $2.5 billion [1,2]. However, despite massive investments, the number of new molecular entities and therapeutic biologics achieving regulatory approval remains frustratingly low. A key contributor to high attrition rates in drug development is the poor predictive value of preclinical studies for clinical efficacy and safety outcomes in humans [3,4]. Conventional *in vitro* models utilizing immortalized cell lines lack the physiological complexity to adequately represent human biology, while animal models often fail to recapitulate human-specific drug responses due to interspecies differences [5]. To address these limitations, the emerging field of organ-on-chip microphysiological systems offers a promising new paradigm for drug screening and testing. Organ-on-chip (OOC) devices are microfluidic cell culture systems created with microengineering technologies that contain continuously perfused chambers inhabited by living human cells arranged to simulate tissue- and organ-level physiology [6]. OOC platforms provide a more accurate representation of the in vivo microenvironment compared to traditional cell culture and animal models by recreating key features of the human body *in vitro*. Advantages include tissue- and organ-specific cell types, 3D architectures, controlled biochemical and mechanical cues, and tissue-tissue interfaces facilitating intercellular crosstalk [3,7]. OOC systems have been developed to model a variety of major organs including the gut, liver, kidney, lung, heart, brain, and skeletal muscle amongst others [8]. A growing body of research demonstrates the utility of individual organ models for applications from basic research to applied drug development and toxicology studies. Moreover, recent advances have enabled the integration of multiple OOC models through microfluidic channels to create interconnected multi-organ systems capable of reproducing systemic human physiology [9].

The goal of this review article is to explore the tremendous yet underutilized potential of OOC platforms, particularly multi-organ systems, to accelerate drug development by enabling more efficient and predictive compound screening in the preclinical space. We assess the growing evidence that OOC models can improve prediction of clinical drug responses compared to conventional *in vitro* and animal models in the published literature. Furthermore, we propose and examine strategies for the incorporation of OOC systems into early phase clinical trials to provide human clinical data earlier in the pipeline. This approach could transform the drug development process by allowing for definitive human proof-of-concept studies to prioritize compounds and streamline go/no-go decisions ahead of costly late-stage clinical trials.

2. CURRENT CHALLENGES IN DRUG DEVELOPMENT

The traditional drug development pipeline is beset by major challenges that contribute to the high costs, prolonged timelines, and poor success rates associated with bringing new drugs to market. Key issues relate to the imperfect nature of preclinical tools for predicting efficacy and safety in human patients. A primary limitation of standard preclinical approaches is the continued reliance on simplistic *in vitro* models based on immortalized cell lines and primary cells grown in 2D cultures [10]. While easy to use and amenable to high-throughput screening, these models lack critical features of human physiology that influence drug responses. Absent are realistic cellular microenvironments with 3D tissue architecture, biochemical gradients, mechanical forces, and multicellular complexity [11]. Additionally, interindividual variations in genetics, gene expression, and metabolic capacity that produce heterogeneous drug responses in the human population are not adequately modelled with clonal cell lines. Outcomes in such reductionist systems thus frequently fail to translate to more complex human biology.

Animal models, though whole living systems, also have substantial shortcomings for predicting human drug effects and toxicities [12]. Interspecies differences in genetics, molecular targets, signalling pathways, metabolism, and physiology produce discordances in drug absorption, distribution, metabolism, and elimination. Studies estimate concordance rates between animals and humans as low as 43% for toxicity and 8% for efficacious target identification, with issues particularly prevalent for immunotherapies and oncology candidates [13,14]. Failures of animal models to predict life-threatening adverse effects underlie the high clinical attrition rates. The reliance on preclinical tools with low human translatability propagates upstream to negatively impact later stage drug development. Candidate selection is impaired, increasing the likelihood of failure. Pivotal trials become larger and lengthier to provide statistical confidence, raising costs. Approved drugs occasionally still elicit unanticipated toxicities in the patient population. There is consequently an urgent need to incorporate testing platforms with higher human relevance earlier in the pipeline.

Additional challenges in drug development involve recruitment for clinical trials. The growth in targeted therapies increases the need to identify patients with specific molecular biomarkers and phenotypic characteristics, slowing enrolment. Competing trials at major medical centres thin out available participants, while remote sites lack infrastructure and personnel for cutting-edge studies [15]. The inclusion of special populations such as children and the elderly are frequently inadequate to understand drug effects on these groups. High costs and little chance of receiving the experimental drug over standard-of-care also deter patient participation

3. AN OVERVIEW ON OOC MICROPHYSIOLOGICAL SYSTEMS

Organ-on-chip (OOC) devices are microengineered biomimetic systems created to model essential features of human organ physiology *in vitro* for applications from fundamental research to applied pharmaceutical studies [4,16]. These miniaturized systems leverage expertise from microfluidics, tissue engineering, microfabrication, and microelectronics to construct microscale tissue and organ proxies on plastic or glass chips. A key feature of OOC systems is the use of microfluidic channels to continuously perfuse culture media, nutrients, chemical stimuli, and other cells through tissue compartments inhabited by living cellular constructs [17]. This recapitulates the dynamic microenvironments in the body absent in static well plate cultures. Tissue compartments are created via approaches including seeding cells in extracellular matrix gels or on porous membranes to enable 3D architectures. Microfluidic barriers, such as membranes or micropillars, can also be integrated to segregate adjacent tissue regions while allowing biochemical crosstalk. Furthermore, OOC devices incorporate embedded sensors and actuators to enable precise control of biophysical and biomechanical cues like fluid shear stress and cyclic stretching to mimic physiological movements [6,18].

3.1 Advantages over traditional in vitro and animal models

Emulating human organ-level complexity is impossible in conventional platforms, OOC systems offer multiple advantages as superior preclinical models for pharmaceutical applications. Clear benefits compared to simplistic immortalized cell line cultures include the use of primary human cells, 3D heterotypic cultures, tissue-tissue interfaces, and dynamic media flow [7,19]. These features better recapitulate the multicellular architectures, biochemical gradients, mechanical microenvironments, and cellular interactions within living organs. OOC models also permit incorporation of patient-derived cells, disease pathology, and interindividual variation to create personalized platforms for specialized drug screening and precision medicine [20]. Relative to animal models, OOC systems provide a more precise representation of human physiology at cellular and tissue levels along with greater flexibility for manipulations [9,21]. Human-specific cell types and responses are inherently modeled rather than approximated across species. Experimental conditions can be strictly controlled and replicated, overcoming intrinsic variability with animal studies. OOC platforms also facilitate high-throughput experiments and consistent multiday live-cell imaging not feasible in animals. Their small scale enables extensive parallelization with different conditions, cell types, and drug candidates tested simultaneously on a single chip. Table 1 provides a comparative review of OOC platforms and traditional preclinical models.

Table 1: Comparison of key features and capabilities between organ-on-chip platforms and traditional preclinical models

Features	2D Cell Cultures	Animal Models	Organ-on-Chip Models
Human cell types	Immortalized cell lines	Different species	Primary human cells
Architecture	2D monolayers	3D whole organism	3D tissue constructs
Vascular perfusion	Static cultures	Native vasculature	Microfluidic channels
Biochemical microenvironment	Simplistic	Physiological	Tissue-specific gradients
Mechanical microenvironment	Stiff plastic/glass	Dynamic motions	Physiologic biomechanics
Multiple cell types	Typically monocultures	All native cells	Cocultures of multiple cell types
Throughput for screening	High	Low	Medium to high
Genetic diversity	Clonal lines	Inbred strains	Patient-derived cells
Cost per experiment	Low	High	Medium to low
Clinical predictive value	Low	Moderate	Potentially high

3.2 Key organ-on-chip platforms and their applications

A range of OOC models have been developed to recapitulate functions of major human tissues and organs, including the heart, liver, kidney, lung, gut, brain, bone, muscle, skin, reproductive system, vascular network, and immune system [10,22]. Connected multi-organ platforms are also emerging to evaluate integrated systemic pharmacology and toxicology. OOC systems are enabling diverse pharmaceutical applications from fundamental investigation of human biology and disease to applied drug toxicity screening, efficacy testing, ADME profiling, and personalized medicine [11]. Notable examples include liver chips integrating primary hepatocytes, stromal cells, and perfusion to predict drug metabolism and hepatotoxicity with higher accuracy than animal models [12,13]. Lung OOC platforms combining epithelium, endothelium, and cyclic mechanical strain can emulate pulmonary absorption, inflammation, and toxicity for inhaled drugs [14,23]. Gut chips

containing villus epithelium, secretory crypts, microbiome, and peristalsis mimic intestinal physiology and drug processing [15]. Linked gut-liver systems model first-pass metabolism following oral drug administration. These represent just a sampling of the expanding repertoire of OOC systems providing advanced *in vitro* models for pharmaceutical research. A summary of major OOC systems used in the clinical research is provided in Table 2.

Table 2: Summary of major organ-on-chip systems and their applications in pharmaceutical research

Organ Model	Key Components	Applications
Gut	Villi epithelium, crypts, mucus, microbes	Drug absorption, inflammation, microbiome effects
Liver	Hepatocytes, Kupffer cells, endothelium	Metabolism, hepatotoxicity, virology
Kidney	Proximal tubule, podocytes, endothelium	Nephrotoxicity, renal clearance
Lung	Alveolar, airway epithelium	Pulmonary toxicity, drug delivery
Blood-brain barrier	Brain endothelium, astrocytes, pericytes	Neurotoxicity, CNS permeability
Heart	Cardiomyocytes, fibroblasts	Cardiotoxicity, arrhythmias
Bone	Osteoblasts, osteoclasts	Bone density, metastases
Skin	Keratinocytes, fibroblasts, melanocytes	Dermatitis, transdermal delivery

4. INTEGRATING ORGAN-ON-CHIP SYSTEMS INTO EARLY PHASE CLINICAL TRIALS

While organ-on-chip (OOC) platforms have demonstrated tremendous potential for improving preclinical drug testing, their incorporation into human clinical trials has been exceptionally limited. However, integrating OOC systems into early phase clinical trials could provide transformative advances for accelerating drug development and approval [16,24]. Early phase clinical trials, encompassing Phase 1 and 2 studies, represent the first testing of an investigational drug in human subjects. They are designed to characterize pharmacokinetics, pharmacodynamics, preliminary efficacy indications, and adverse effects while also determining safe dosage levels [17,18]. Outcomes from early phase studies critically inform whether a drug candidate merits the major investments for expansive late phase efficacy trials. However, the limited predictive value from preclinical models leads to high Phase 2 failure rates, ranging from 50-80% [19-21]. Failed trials represent billions in squandered resources and delayed development timelines. Figure 1 shows how OOC systems can be used in various stages of clinical trials.

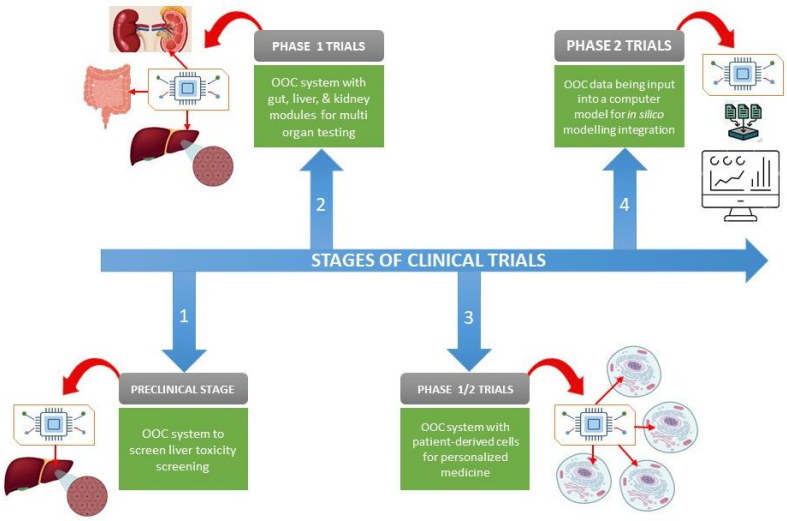

Figure 1: Schematic overview of strategies for integrating organ-on-chip testing into early phase clinical trials

4.1 Strategies for effective integration

Strategic incorporation of OOC platforms into early phase trials could significantly de-risk clinical programs by generating human data earlier to prioritize compounds, determine effective doses, and establish preliminary clinical proof-of-concept to

justify Phase 3 trials [22]. OOC systems provide a testing bridge from preclinical to clinical spaces. Promising integration strategies include:

- Parallel testing: Comparing OOC and animal model results versus human outcomes to assess concordance and refine systems.
- Patient-derived OOC: Incorporating cells or biofluids from trial participants into personalized OOC platforms to predict individual responses.
- Dose-response: Evaluating human OOC dose-responses to establish safe starting doses and minimally effective doses for trials.
- Toxicity screening: Using OOC systems to assess human organ toxicities earlier before trials commence.
- Clinical proof-of-concept: Demonstrating efficacy signals in OOC models before conducting large-scale human studies.
- Compound prioritization: Testing lead candidates against OOC systems modeling disease pathways to rank for trials.
- Response stratification: Applying OOC systems with trial participants' cells to stratify responders from non-responders.
- Off-target effects: Screening for off-target organ impacts in OOC models during trials.
- Post-market monitoring: Continually testing drugs on chip systems to identify rare adverse events.

Effective integration will require close collaborations between regulators, pharmaceutical companies, and OOC technology developers to design appropriate validation frameworks and paradigms for incorporating OOC data into approval packages [23,25]. Additionally, innovative trial designs that seamlessly integrate OOC testing with clinical studies will need to be developed, leveraging computational pharmacology modelling to bridge across platforms [24].

4.2 Patient-derived cells and personalized medicine

A major advantage of organ-on-chip (OOC) systems is the ability to incorporate patient-derived cells to create personalized platforms that account for individual genetic and cellular variability in drug responses [25]. This enables precision medicine approaches where clinical treatments are tailored to subgroups of patients based on predictive outcomes from their own cells tested on chip. Patient-derived OOC models can be created by acquiring tissue biopsies or biofluid samples like blood during clinical trials to isolate primary cell types which are then cultured in the OOC system. For example, colorectal cancer organoids derived from patient biopsies have been integrated into a gut OOC system to screen drug sensitivities for precision oncology [26]. Hepatocytes derived from blood cell reprogramming have been used in a liver OOC platform to predict personalized drug metabolism rates and susceptibilities[33]. Additionally, the integration of induced pluripotent stem cells (iPSCs) into OOC devices offers transformative opportunities for personalized medicine [27]. iPSCs generated from trial participants can be differentiated into any tissue cell type to model patient-specific responses on chip. Furthermore, gene editing of iPSCs can introduce specific disease mutations to evaluate genotype-specific drug effects relevant to genetic subpopulations. Determination of individual variabilities in drug efficacy, toxicity thresholds, and off-target effects using OOC systems containing cells derived from clinical trial volunteers, more effective patient stratification and treatment optimization can be achieved. Patient-derived OOC approaches also facilitate the expansion of targeted therapy development for rare diseases or genetically-defined patient subgroups where clinical trial recruitment is challenging

4.3 Multi-organ platforms for systemic effects

A key milestone in the progression of OOC technology has been the interconnection of individual tissue and organ models to create integrated multi-organ systems capable of emulating whole-body physiology [28]. These advanced platforms allow for evaluation of complex systemic pharmacology responses and toxicities that manifest across multiple organs in the body. Multi-organ OOC systems combine arrays of tissue/organ modules like liver, heart, lung, gut, kidney, and neurovascular units linked by circulating microfluidic channels to model interactions through pharmacokinetic and pharmacodynamic factors [29]. This enables assessment of absorption, distribution, metabolism and excretion (ADME) profiles following oral or intravenous drug administration. Additionally, multi-organ OOCs can examine systemic toxicities and efficacy pathways that emerge at higher levels of integration. For instance, a ten-organ platform revealed gut microbiome-mediated effects of NSAIDs on renal toxicity that were absent in the kidney model alone [30]. The capability to recapitulate network-level human physiology is critical to accurately evaluate many drug classes, particularly immunotherapies like checkpoint inhibitors with complex systemic mechanisms [31]. Integration of multi-organ OOC testing into early phase trials, human data on systemic on- and off-target drug effects can greatly assist go/no-go decisions and optimization of dosing regimens to maximize efficacy and minimize toxicity

4.4 In silico modelling and computational approaches

The effective integration of organ-on-chip (OOC) systems into drug development pipelines will require synergistic use of computational modelling approaches to bridge across platforms. In silico physiologically-based pharmacokinetic (PBPK) models can help translate insights from OOC models into anticipated clinical outcomes in patients.

PBPK modelling is a powerful technique that leverages computational simulations of ADME processes and drug-system interactions to predict pharmacokinetics and drug concentrations in virtual patient populations [32]. These models incorporate extensive physiological and drug parameters along with demographics to account for interindividual variations. Linking PBPK models with pharmacodynamic models of drug effects further allows prediction of efficacy and toxicity. Several strategies can integrate in silico modelling with OOC platforms. PBPK models can help extrapolate the limited functional capacity of OOC systems to full human physiology. For instance, pharmacokinetic measurements from a liver OOC can inform a PBPK model to then simulate systemic circulation and metabolism. In addition, PBPK models can identify parameters needing evaluation in OOC systems to enhance clinical translation. Iterative experiments can then refine the models. Moreover, combining multivariate OOC data with PBPK models and machine learning algorithms can strengthen cross-platform predictions. For example, OOC pharmacokinetics, biomarker readouts, and toxicity thresholds can train neural networks to predict clinical outcomes tailored to individual patient factors simulated in PBPK models [33]. This personalized *in vitro-in silico* approach could provide powerful decision support for precision medicine applications.

5. CHALLENGES AND LIMITATIONS

While organ-on-chip (OOC) systems hold enormous potential to transform drug development, there remain significant challenges and limitations that must be addressed to enable widespread adoption and regulatory acceptance of these platforms. A foremost hurdle is demonstrating definitive correlation of OOC model outcomes with clinical responses in humans through rigorous validation. While individual systems have shown good predictive capacity in limited cases, validation efforts across broad applications, systems, and drug classes are still lacking. Demonstrating reproducibility and standardization of system fabrication and performance is critical for validation [34,35].

5.1 Standardization and validation

A key priority is developing standardized operational procedures and benchmarks for the fabrication, validation, and use of OOC systems to ensure reproducibility within and across different models [36]. Microfluidic device material and geometries, cell types and culture conditions, user operation, and analytical methods must be controlled and consistent. Standards for design, characterization, and performance metrics of OOC models need to be established, similar to good laboratory/manufacturing practices. Extensive retrospective validation studies are also required to correlate OOC model outcomes with accumulated human clinical trial data on marketed drugs spanning different indications and mechanisms of action. Prospective longitudinal validation integrating OOC testing into clinical trials for new drug candidates through the entire pipeline is also invaluable. Partnering with pharmaceutical companies and regulators is critical to access the necessary data and samples for robust validation. Only through such rigorously validated side-by-side testing can OOC systems earn regulatory qualification for routine use in drug development. Close collaboration with agencies like the FDA and EMA to develop appropriate validation frameworks will smoothen adoption. OOC technology developers should be transparent by publishing validation data in the peer-reviewed literature for review.

5.2 Scalability and high-throughput screening

The ultra-miniaturized scale of organ-on-chip (OOC) systems provides both a key advantage and challenge. Their small footprint enables extensive multiplexing of conditions, cell types, and drug panels onto a single device for high-throughput experimentation not feasible with animals. However, scaling up fabrication and operation for widespread use poses difficulties. Current OOC systems are predominantly fabricated as custom one-off devices in research settings through techniques like soft lithography, limiting throughput and consistency [37]. Moving towards mass manufacturing platforms like injection moulding and thermoplastic bonding as well as development of standardized component libraries will be critical to achieve economies of scale. Automation for parallelized operation of multiple OOC devices will also be essential. Integration of onboard microfluidic pumps, valves, and multiplexing architectures can enable automated recirculation of media, delivery of compounds, and sampling for high-content analysis [38]. Standardized instrument formats must be developed to seamlessly run plates containing many OOC chips simultaneously. Machine vision systems could further automate OOC imaging, monitoring, and biomarker quantification. The capabilities for cryopreservation and long-term storage of OOC cultures will enhance scalability by enabling use of cell banks rather than continual cultures. While challenges remain in maintaining viability and phenotypic stability, advances in optimized freezing media and protocols specifically for OOC systems are being made [39]. Overcoming hurdles in scalability, automation, and storage will expand the practicality of OOC platforms for widespread pharmaceutical industry adoption [40].

5.3 Regulatory acceptance and guidelines

Gaining formal regulatory approval for integrating organ-on-chip platforms into drug development represents perhaps the most pivotal milestone for translation of OOC systems from academic research tools to industry-standard preclinical assays [31]. However, significant innovation in regulatory policies and paradigms will be needed to accommodate this disruptive technology. While industry guidance documents acknowledge the potential of OOC systems, concrete protocols for validation requirements, data standards, quantitative modelling integration, and complementary use with existing methods are still lacking from most regulatory agencies [41,42]. Close collaborative efforts between regulators, pharmaceutical companies, and OOC technology developers will be essential to establish appropriate frameworks for validation, application,

and review. Future regulatory guidelines tailored for OOC technologies should provide flexible, adaptive guidance given the rapid evolution of this field, rather than be overly narrow or prescriptive initially. Training programs to educate agency reviewers on assessing OOC platforms and data integration will also help support adoption. With prudent regulatory evolution, the pharmaceutical industry can confidently incorporate validated OOC systems as reliable tools to enhance the drug development process [43].

6. CONCLUSION

Organ-on-chip micro physiological systems present a disruptive technology with the potential to transform drug development by enabling more predictive preclinical testing and seamless integration with human clinical trials. OOC platforms provide more accurate human-specific models compared to conventional simplistic cell cultures and animal studies. The capability to recreate complex human physiology *in vitro* allows evaluation of drug efficacy, toxicity, pharmacokinetics, and pharmacodynamics in a physiologically relevant context. Connected multi-organ OOC systems further offer revolutionary capabilities to study integrated systemic responses. Strategic incorporation of OOC testing early during clinical trials could provide human data to prioritize lead candidates, establish clinical proof-of-concept, and reduce late-stage attrition. While hurdles related to validation, standardization, scalability, and regulation remain, continued technological innovation in partnership with pharmaceutical and regulatory stakeholders can help realize the paradigm-shifting potential of OOC platforms to accelerate drug development and delivery of new therapies to patients.

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