



Organs-on-Chips for Disease Modeling and Drug Development: Engineering, Validation and Medical Translation

Órganos en chip para el modelado de enfermedades y el desarrollo de fármacos: ingeniería, validación y traslación a la medicina

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ABSTRACT

Introduction: about nine in ten drug candidates that enter clinical development fail, partly because preclinical models, including animal models, predict human responses poorly. Organs-on-chips (OoCs), microfluidic devices lined with living human cells under fluid flow, have emerged as engineered alternatives that reproduce organ-level physiology. **Objective:** to critically describe the engineering principles of OoCs, the evidence on their predictive value in toxicology and pharmacology, their use in disease modeling and personalized medicine, and the regulatory and technical barriers to their adoption. **Development:** a human Liver-Chip evaluated with a blinded set of 27 drugs reached a reported sensitivity of 87% and specificity of 100% for drug-induced liver injury, and an airway chip identified antiviral candidates that cell lines under static conditions missed. Patient-derived organoids integrated into chips are being explored for personalized drug screening. Regulatory frameworks have begun to accept non-animal methods, but unresolved issues include small-molecule absorption by device materials, limited throughput, scarce standardization and the lack of prospective clinical validation. **Conclusions:** OoCs are a promising complement to conventional preclinical models rather than a proven replacement; their clinical value will depend on independent validation, standardization and clearly defined contexts of use.

Keywords: lab-on-a-chip devices; drug evaluation, preclinical; precision medicine; toxicity tests.

RESUMEN

Introducción: alrededor de nueve de cada diez candidatos a fármaco que ingresan al desarrollo clínico fracasan, en parte porque los modelos preclínicos, incluidos los animales, predicen mal la respuesta humana. Los órganos en chip (OoC), dispositivos microfluídicos revestidos de células humanas vivas bajo flujo, han surgido como alternativas de ingeniería que reproducen la fisiología a nivel de órgano. **Objetivo:** describir críticamente los principios de ingeniería de los OoC, la evidencia sobre su valor predictivo en toxicología y farmacología, su uso en el modelado de enfermedades y la medicina personalizada, y las barreras regulatorias y técnicas para su adopción. **Desarrollo:** un Liver-Chip humano evaluado con un conjunto ciego de 27 fármacos alcanzó una sensibilidad reportada de 87% y una especificidad de 100% para la lesión hepática inducida por fármacos, y un chip de vía aérea identificó candidatos antivirales que las líneas celulares en condiciones estáticas no detectaron. Los organoides derivados de pacientes integrados en chips se exploran para el cribado personalizado de fármacos. Los marcos regulatorios han comenzado a aceptar métodos no animales, pero persisten la absorción de moléculas pequeñas por los materiales del dispositivo, el bajo rendimiento, la escasa estandarización y la falta de validación clínica prospectiva. **Conclusiones:** los OoC son un complemento prometedor de los modelos preclínicos convencionales y no un reemplazo demostrado; su valor clínico dependerá de la validación independiente, la estandarización y la definición clara de contextos de uso.

Palabras clave: dispositivos laboratorio en un chip; evaluación preclínica de medicamentos; medicina de precisión; pruebas de toxicidad.

INTRODUCTION

Drug development remains a lengthy and costly process with a very high failure rate: approximately 90% of candidates entering clinical development do not reach approval because of lack of clinical efficacy (40% to 50%), unmanageable toxicity (around 30%), poor pharmacological properties (10% to 15%), or commercial and planning reasons (around 10%).⁽¹⁾

Part of this failure is attributed to the limited predictive capacity of preclinical models. An umbrella review concluded that only about 5% of therapeutic interventions tested in animals eventually obtain regulatory approval for human use,⁽²⁾ and another narrative review places the failure rate for translating drugs from animal experimentation into treatments in people above 92%.⁽³⁾

Organs-on-chips (OoC), also called microphysiological systems or tissue chips, are microfluidic devices lined with living human cells cultured under flow, which reproduce organ-level physiology and pathophysiology with high fidelity.^(4,5) They are credited with utility in multiple stages of drug discovery and development, both for understanding normal organ function and disease pathophysiology and for more accurately predicting the safety and efficacy of investigational drugs.⁽⁵⁾

Regulatory interest has also grown. At the end of 2022, the FDA Modernization Act 2.0 authorized the use of alternatives to animal experimentation, such as cell-based assays and computational models, to support drug applications,⁽⁶⁾ and in April 2025, the FDA published a roadmap to reduce animal testing in preclinical safety studies through new approach methodologies, including organ-on-a-chip systems.⁽⁷⁾

For physicians, this transition is relevant because it changes the nature of the preclinical evidence on which the safety of the drugs they prescribe is based, and because it opens the possibility of patient-specific models. This review aims to critically describe the engineering principles of OoCs, the evidence on their predictive value in toxicology and pharmacology, their application to disease modeling and personalized medicine, and the regulatory and technical barriers that affect their adoption.

METHODS

A descriptive narrative literature review was conducted to synthesize the evidence on the engineering foundations of organs-on-a-chip, their predictive value, their medical applications, and the barriers to their adoption.

Search strategy and information sources

The search targeted literature indexed in PubMed/MEDLINE, including PubMed Central, and was complemented by consulting journal websites, open-access institutional repositories, legislative portals, and official websites of regulatory agencies. MeSH/DeCS terms and free-text terms were used and combined with Boolean operators (AND, OR):

- ("Lab-On-A-Chip Devices" OR "organ-on-a-chip" OR "microphysiological systems") AND ("Drug Evaluation, Preclinical" OR "toxicity" OR "drug development")
- ("organ-on-a-chip" OR "organoids-on-a-chip") AND ("precision medicine" OR "personalized medicine" OR "disease modeling")
- ("organ-on-a-chip") AND ("standardization" OR "validation" OR "regulatory" OR "FDA")

Inclusion and exclusion criteria

- Inclusion criteria:
 1. Narrative and systematic reviews, perspective articles, experimental studies with predictive validation or disease modeling data, and official legislative or regulatory documents.
 2. Documents written in Spanish or English.
 3. Works focused on medical or pharmacological applications in humans and on the engineering, validation, and regulatory challenges of the devices.
- Exclusion criteria:
 1. Press releases and commercial material without primary data, and conference abstracts without full text.
 2. Works focused exclusively on non-biomedical applications of microfluidic devices.
 3. Duplicate documents or those without a described methodology.

Selection of studies and analysis of information

The selection was based on the clinical relevance and apparent methodological quality of each document, prioritizing reviews and studies with quantitative performance evaluation. No systematic screening process was applied, and risk of bias was not formally assessed. The information was synthesized qualitatively and thematically along the following axes: engineering foundations, toxicity and drug response prediction, disease modeling, personalized medicine, regulatory framework, and technical barriers. As a limitation inherent to the narrative design, the possibility of selection bias in the retrieved literature and the impossibility of generating combined statistical estimates are acknowledged.

DEVELOPMENT

Engineering Fundamentals of Organs-on-Chips

An OoC integrates microfabrication, microfluidics, tissue engineering, and cell biology. Its principle involves culturing human cells in chambers of micrometer dimensions under continuous perfusion, so that tissue interfaces, vascular perfusion, and the mechanical signals characteristic of the organ are reproduced.^(4,5) An example is the bronchial airway chip, which features highly differentiated human bronchial epithelium and pulmonary endothelium arranged in two parallel channels separated by a porous membrane, allowing the modeling of viral infection, strain-dependent virulence, cytokine production, and the recruitment of circulating immune cells.⁽⁸⁾

The device material affects the validity of pharmacological results. Polydimethylsiloxane (PDMS) is widely used, although other plastics are also employed, and the absorption of small molecules is not uniformly addressed by developers, so its characterization is among the identified standardization needs.⁽⁹⁾

Another axis of engineering is cellular complexity and, in particular, vascularization. Quintard et al. developed a platform that generates perfusable endothelial networks around spheroids and vascular organoids derived from pluripotent cells and cultured for up to 30 days in the chip, and observed that the growth, maturation, and function of the organoids improved when cultured using this vascularization method.⁽¹⁰⁾

Finally, the first devices relied on endpoint analysis, which limited the understanding of dynamic processes. The integration of mechanical, electrical resistance, microbead-based, and oxygen- and metabolite-specific sensors enables real-time monitoring of the cellular response.⁽¹¹⁾

Prediction of toxicity and drug response

Quantitative assessment of predictive value is the central requirement for OoCs to be accepted as decision tools. In a study with 870 human Liver-Chips and a blinded set of 27 drugs with known or absent hepatotoxicity, the device met the IQ MPS consortium's qualification guidelines, with a sensitivity of 87% and a specificity of 100% for drug-induced liver injury. The authors further estimated, using an economic model, that such performance could generate more than \$3 billion annually in small molecule research and development productivity.⁽¹²⁾

These results derive from a single study conducted by the company that markets the device, and the economic figure is an estimate derived from a model rather than a measurement. Before generalizing, independent replications and evaluations in other organs are required.

In pharmacology, the airway chip showed that coadministration of nafamostat with oseltamivir doubled the therapeutic window of oseltamivir in influenza A infection. Furthermore, clinically relevant doses of amodiaquine inhibited infection by pseudotyped SARS-CoV-2, whereas clinical doses of hydroxychloroquine and other antivirals that block virus entry in cell lines under static conditions did not; amodiaquine also showed prophylactic and therapeutic activity in hamsters.⁽⁸⁾ The contrast with static cell lines illustrates the central argument in favor of these models, although a preclinical result alone does not equate to clinical efficacy.

Disease modeling

Beyond toxicology, OoCs have been used to model complex diseases and rare genetic disorders, study the interaction between the host and the microbiome, reproduce inter-organ physiology, and recapitulate human clinical responses to drugs, radiation, toxins, and infectious pathogens.⁽⁴⁾ Intestinal chips illustrate this versatility: they are used to study intestinal infections, colorectal cancer, and Crohn's disease.⁽¹³⁾ Table 1 summarizes some medical applications, along with their representative evidence and limitations.

Table 1. Medical applications of organ-on-a-chip: representative evidence and limitations.

Application	Representative evidence	Scope and limitations
Drug-induced hepatotoxicity	Liver-Chip: 870 devices and 27 drugs; sensitivity 87% and specificity 100%.(12)	A single study from the company that markets the device; independent replication is required.
Antiviral repurposing	Airway chip: amodiaquine inhibited pseudotyped SARS-CoV-2; hydroxychloroquine did not.(8)	Preclinical evidence; confirmation in hamsters, without clinical efficacy data.
Intestinal disease	Intestinal chips for infections, colorectal cancer, and Crohn's disease.(13)	Review of mostly preclinical models.
Personalized oncology	Patient-derived organoids-on-chip for drug screening.(14)	Advantages over conventional organoids; improvement in clinical outcomes remains to be demonstrated.
Vascularized tissues	Perfusable endothelial networks in organoids, cultured for up to 30 days.(10)	Experimental model under development.

OoC: organ-on-a-chip.

Personalized medicine

The possibility of using OoC as “living avatars” of patients, instead of animal models, for drug development and personalized medicine is presented as an increasingly imminent prospect.(4) Intestinal chips, for example, enable the representation of diverse human populations and are considered promising for personalized medicine.(13)

In oncology, patient-derived organoids preserve the heterogeneity of the original tumor, but conventional organoids exhibit poor stability, a simple tumor microenvironment, and low yield, limitations that microfluidics-based organoids-on-a-chip aim to overcome for personalized drug screening.(14)

It should be emphasized that the reviewed evidence derives mainly from preclinical studies and reviews; no studies were retrieved that prospectively demonstrate that guiding the treatment of 1 patient with a chip derived from their own cells improves their clinical outcomes. Therefore, OoC-based personalized medicine should be considered a hypothesis under evaluation.

Regulatory framework

The FDA Modernization Act 2.0 allows safety and efficacy studies to include animal testing or non-animal methods, such as cell assays and computational models, and eliminates the requirement for animal studies for licensure of a biosimilar or interchangeable biological product.(6)The law therefore expands the types of acceptable tests without prohibiting animal studies.

The FDA's April 2025 roadmap proposes a gradual approach that begins with monoclonal antibodies, for which current requirements include repeat-dose toxicity studies in non-human primates. As an example of the limitations of animal prediction, the document recalls the TGN1412 case, which caused a potentially life-threatening cytokine release syndrome in volunteers despite appearing safe in primate studies.(7)In April 2026, the agency published an annual progress report assessing compliance with the goals of that roadmap.(15)

For OoCs to be accepted as credible alternatives to animal experimentation, they must undergo an extensive qualification process, and standardization can contribute to characterizing each device, comparing it with reference elements, and facilitating communication among stakeholders.(9)

Technical and standardization barriers

Alver et al. point out that OoCs face technical and regulatory barriers that may complicate their industrial adoption and their use in preclinical trials, and that certain design and process characteristics could hinder their widespread dissemination.(16)Additionally, there is limited uniformity in the treatment of small-molecule absorption by the device materials,(9)and the low performance of conventional organoids.(14)

Meneses et al. propose that a balance exists between integrating advanced technologies, which increase complexity and physiological realism, and standardizing, which favors reproducibility and validation; they maintain that standardization should be considered from the outset when incorporating new technologies.(17)The failure to resolve this balance is among the main obstacles to their translation.

Implications for medical practice and research

From a clinical perspective, it is advisable to distinguish between preclinical predictive validity and clinical efficacy: an OoC with high sensitivity for detecting hepatic toxicity does not, by itself, demonstrate patient benefit. Clinicians can contribute by defining clinically relevant contexts of use, participating in the design of outcomes comparable to real-world practice, and critically evaluating commercial claims.

In resource-limited settings, adoption will depend on microfabrication and cell culture infrastructure, as well as the availability of shared standards. These considerations are an interpretation by the author based on the reviewed literature and not a finding of the cited studies.

CONCLUSIONS

Organs-on-chips combine microfluidic engineering and human cells to reproduce organ functions with greater fidelity than conventional cultures, and there are encouraging quantitative data on their ability to predict liver toxicity and identify antiviral candidates. However, the available evidence comes mainly from preclinical studies and a small number of evaluations, some conducted by the manufacturers themselves. Problems persist with molecule absorption by materials, low throughput, lack of standardization, and absence of prospective clinical validation of their use in personalized medicine. Regulatory frameworks have begun to create space for these methods, but OoCs should be considered a promising complement to conventional preclinical models and not a proven replacement. Their value for medicine will depend on independent validation, early standardization, and clear definition of their contexts of use.

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CONFLICT OF INTEREST

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