Adoption of organ-on-chip platforms by the pharmaceutical industry

Paul Vulto and Jos Joore

A key ambition of the organ-on-chip (OoC) field is to enable improved decision-making in drug discovery and development, based on leveraging the potential of OoC platforms to model human biology more effectively than traditional approaches, as reviewed by Low et al. (*Nat. Rev. Drug Discov.* **20**, 345–361 (2021))¹. This ambition has primed the establishment of multiple companies that have translated academic efforts into robust OoC platforms and made them commercially available on a service basis or as products over the past decade.

However, the extent to which these platforms are being adopted by the pharmaceutical industry and their impact on drug discovery is underexposed. With the aim of illuminating this area, here we highlight selected illustrative examples from publications where the application of commercial OoC platforms has been reported by researchers affiliated with pharmaceutical companies. A more comprehensive list of publications, together with the approach for identifying them, is described in Supplementary information.

Reported OoC applications in industry

Applications of OoCs in drug development and safety assessment are of high interest, given their ability to capture phenomena beyond the reach of standard cell culture models. Moreover, the human origin of OoCs can address issues with species-to-species translatability that may arise with animal experiments. Two of our examples illustrate the use of an OoC model to detect adverse effects observed in clinical studies that had not been detected in preclinical studies. In one study, Janssen, the Wyss Institute and Emulate applied a ‘blood vessel on a chip’ — a chip lined with human endothelial cells and perfused with human whole blood². The authors used this model to recapitulate pro-thrombotic effects of a monoclonal antibody against CD40L intended to treat autoimmune disorders, for which clinical development was terminated. In addition, the model provided mechanistic insight into this adverse effect and was used to optimize the drug candidate. In the second example, a team from AstraZeneca reproduced the kidney injury observed in a clinical trial with the antisense oligonucleotide SPC5001, using

a human proximal tubule model based on a triple-channel chip from Nortis³. In this study, an increase in cytotoxicity, as well as an increase in the clinically relevant biomarkers of kidney toxicity KIM-1, NGAL, clusterin, osteopontin and VEGF, were observed in chip perfusates during continuous 20-day exposure of chip-cultured human renal proximal tubule epithelial cells, but not in traditional 2D cultures.

Drug-induced liver injury (DILI) is a severe adverse effect for which models based on different species have produced discordant results in preclinical studies. Therefore, Emulate, AstraZeneca and Janssen assessed species-specific liver toxicity using chips comprised of primary hepatocytes, liver sinusoidal endothelial cells, Kupffer cells and hepatic stellate cells from rats, dogs or humans, cultured under fluid flow⁴. The inclusion of parenchymal and non-parenchymal cells enabled the capture of various aspects of liver toxicity, including hepatocellular injury, steatosis, cholestasis and fibrosis, and the chips recapitulated species-specific toxicities of acetaminophen, methotrexate, bosentan and TAK-875, as well as proprietary Janssen compounds.

Co-culturing cell types derived from multiple organs on a single chip enables analysis of drug effects involving interactions between organs. For example, scientists from Hesperos and AstraZeneca used a chip comprising hepatocytes and cardiomyocytes (derived from induced pluripotent stem cells)⁵ to study pharmacokinetic/pharmacodynamic (PK/PD) relationships for terfenadine and the proprietary compound AZ12818677, which also enabled assessment of the cardiotoxicity of liver metabolites. In a second example, scientists from TissUse and Bayer developed a chip-based human lung tumour–skin co-culture assay, which was used to simultaneously evaluate the anticancer effects and skin toxicity of epidermal growth factor receptor inhibition by the antibody cetuximab⁶.

OoC models have also been applied by industry researchers in disease modelling, compound screening and target identification. For example, scientists from Roche reported a human retinal microvascular tubule-on-a-chip designed to mimic the blood–retina barrier⁷, which can be disrupted in diabetic retinopathy and age-related macular degeneration.

The model was based on the OrganoPlate platform marketed by MIMETAS, which features a standard microtiter plate format comprising 40 to 96 chips, making it compatible with high-throughput screening. It was used to screen a small library of small molecules and biologics that are known modulators of VEGFA signalling, and several compounds that inhibited VEGFA-induced permeability were identified. Another team from Roche used the OrganoPlate platform to develop an immunocompetent intestinal model designed to mimic impairment of the epithelial barrier due to inflammation caused by neutrophil infiltration following activation of resident macrophages⁸. PhaseGuide technology enables layering of extracellular matrix gel and tissues without using artificial membranes, allowing free migration of immune cells through the extracellular matrix gel. The model captured elements of the inflammatory cascade, including migration of neutrophils, matrix interactions, cytokine production and their impact on the target tissue, and was used to study the role of bioactive products in extracellular matrix degradation during inflammation and evaluate them as potential drug targets.

The highlighted publications describe the application of OoC technology by industry researchers in various phases of drug discovery. However, the contribution of OoCs to advancing candidate drugs remains elusive. On this topic, a survey conducted among the authors of a multi-stakeholder report from the pharmaceutical industry and the OoC community provides valuable information⁹. The survey results, summarized in TABLE 1, provide examples of commercially available OoC platforms impacting pipeline decision-making (reproduced with adjustments⁹). These testimonies of pipeline impact cover multiple phases of preclinical drug development, including target evaluation, efficacy evaluation, mechanistic understanding, safety and PK/PD.

Outlook for industry adoption of OoCs

Although the application of OoCs in industry may often not be shared publicly in a timely way when the studies are part of ongoing drug development programmes⁹, published literature provides evidence that OoC technology is being evaluated by the pharmaceutical industry and can influence pipeline decision-making. These reports by early adopters provide valuable insights into how the technology is being deployed and may guide other pharmaceutical companies that are yet to get started or are in an evaluation phase.

Companies that have commercialized the platforms referred to in this commentary and

Table 1 | Impact of commercial organ-on-chip platforms on decision-making in industry

Pharmaceutical company	Target organ	Organ-on-chip developer
Target identification and validation		
Novo Nordisk	Blood vessel, vasculature	MIMETAS
AstraZeneca	Liver, pancreas	TissUse
Discovery		
Galapagos	Blood vessel, vasculature	MIMETAS
Galapagos	Gut	MIMETAS
Roche	Gut	MIMETAS
Pharmacokinetics and pharmacodynamics		
Astellas	Renal proximal tubule, blood vessel	MIMETAS
AstraZeneca	Liver	Emulate
Preclinical safety		
Roche	Liver	Emulate
Roche	Gut	Emulate
Janssen, AstraZeneca	Liver	Emulate
AstraZeneca	Bone marrow	Emulate
AstraZeneca, Roche, Bayer	Bone marrow	TissUse
Bayer	Liver–thyroid	TissUse
Bayer	Skin–tumour	TissUse
Clinical development		
Roche	Gut	MIMETAS

TABLE 1 is adapted from REF.⁹, CC BY 4.0, including commercial organ-on-a-chip developers only.

the Supplementary information have been in business for more than half a decade. These companies have extensively invested in their platform's manufacturability, quality control standards, usability aspects, compatibility with standard equipment, and the availability of robust protocols and logistics for assays and biological materials. All these are prerequisites for routine adoption by end-users^{9,10}. Pharmaceutical companies have also made investments in adopting the technology, as transitioning established routines to a novel platform requires time and money. Moreover, scientists need to build trust and experience

with these platforms. Building a data legacy and cross-industry adoption are further aspects that increase confidence in this new technology^{9,10}.

Given these investment needs, it is to be expected that only a limited number of OoC platforms will become standard. The companies described here are well-positioned to set these standards; however, we also believe there is space for newcomers. We expect the broader OoC community's focus to shift from platform development towards developing new culture protocols, disease modelling, assays and validation.

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P.V. and J.J. wrote and edited the manuscript and created the tables.

Competing interests

P.V. and J.J. hold equity in MIMETAS B.V. and serve as CEOs and executive board members of the company.

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