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Opinion

Bridging the academia-to-industry gap: organ-on-a-chip platforms for safety and toxicology assessment

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Some organ-on-a-chip (OoC) systems for drug evaluation show better predictive capabilities than planar, static cell cultures and animal models. One of the ongoing initiatives led by OoC developers is to bridge the academia-to-industry gap in the hope of gaining wider adoption by end-users – academic biological researchers and industry. We discuss several recommendations that can help to drive the adoption of OoC systems by the market. We first review some key challenges faced by OoC developers before highlighting current advances in OoC platforms. We then offer recommendations for OoC developers to promote the uptake of OoC systems by the industry.

Highlights

Several organ-on-a-chip (OoC) systems have been shown to recapitulate human physiology and pathology, and have demonstrated similar or better predictive ability for drug evaluation than static cellular cultures and animal models.

Ongoing advances in the development of OoCs have emphasized the development of multi-organ platforms, termed 'human-body-on-a-chip', that establish physiologic flow between organs to produce organ–organ interactions and permit the analysis of interdependent pharmacokinetics, pharmacodynamics, and toxicokinetics/toxicodynamics relationships *in vitro*.

In the past decade advances in OoC technology have led to several OoC/multi-OoC startup companies.

Regulatory agencies have also launched initiatives to support the development of drug development tools including OoCs for regulatory use.

Potential of OoC systems in drug development

Taking a drug through from discovery to the market is a long and arduous journey (Figure 1) [1]. A drug goes through at least six stages before reaching the market: pre-discovery, drug discovery, preclinical studies, clinical trials, review, and approval, and are then continuously monitored to ensure safety. Since the thalidomide disaster in 1960 [2], regulatory agencies have emphasized the requirement for rigorous toxicity testing during drug development. Before a drug enters a clinical trial, it must be deemed safe or specific risk-assessed to balance benefits and harms [3]. To do so, the drug undergoes a series of stringent tests in 2D cellular assays and animal models such as non-human primates. Although these traditional methods successfully bring drugs to the market, >80% of drugs tested in humans fail to demonstrate safety and **efficacy** (see Glossary) in clinical trials [4–7]. Studies have consistently found that current preclinical tests are a poor indicator of human responses [8–10]. The limitations of current 2D cellular assays and animal models have prompted scientists to develop models with better predictive ability.

OoC systems are one such technology. An OoC is an *in vitro* high-content system aimed at recapitulating *in vivo* organ-level functions by mimicking a physiologically relevant microenvironment in a microfluidic (or equivalent) device. By using actual human cells in platforms analogous to their native microenvironments, scientists postulated that OoCs could become better predictors of human responses to adverse drug effects than conventional 2D or animal models. Over the past 15 years since their implementation, countless OoCs have to various degrees, recapitulated human physiology and pathology. They have demonstrated clinically relevant responses of drugs with a level of fidelity that is often as good as, and sometimes better than, animal models [7].

From an engineering perspective, OoCs are considered by the microfluidics community to be a 'killer application' [11,12]. By definition, a killer application refers to a technology or product that becomes indispensable because it is much superior to its predecessor. Developments

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in OoCs have indeed demonstrated that these platforms may become killer applications because they have superior predictive abilities than 2D cell cultures and often animal models [13,14].

The roles of OoCs are multifaceted. We not only expect OoCs to make strides in accelerating the development of new drugs and advancing personalized medicine but also anticipate their contribution to basic sciences (i.e., understanding the pathophysiology of rare diseases) [15,16]. Of the many initiatives in the field of the OoC, one ongoing effort is to bridge the academia-to-industry gap to gain wider adoption among the ultimate end-users of OoCs – academic researchers and industry [17]. Although not all OoC platforms are ready for academia-to-industry translation, this article focuses on recommendations for OoC developers when developing OoCs for translational purposes. We start by introducing the challenges faced in developing OoCs for drug development. We also discuss advances in the OoC field and highlight key hallmarks in the development of OoCs.

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Challenges and need for OoC development

Complexity of human physiology

To appreciate the magnitude of the challenge in predicting human responses to drug candidates, it is necessary to understand the complexity of human physiology and what happens to the drug after it is administered. Furthermore, OoC developers need to understand the requirements as mandated by regulatory agencies. For instance, evaluations of drug pharmacology, *in vivo* efficacy, and toxicology using standard 2D cellular assays, animal models, and *in silico* models are usually a requirement in the preclinical phase [18,19]. We frame these challenges and requirements into three perspectives: (i) the effects of the body on the drug, (ii) the effects of the drug on the body, and (iii) mechanisms leading to **drug-induced toxicity**.

The effects of the body on the drug

The study and characterization of how the body affects the fate of the drug are usually known in pharmacology as **pharmacokinetics (PK)**. The human body is a complex, highly

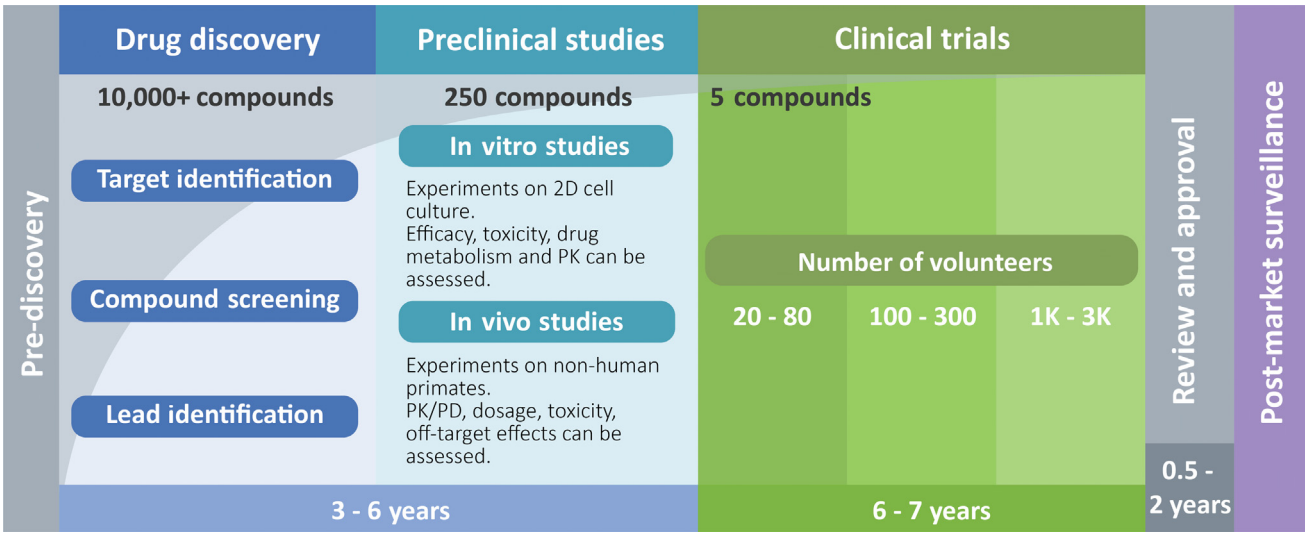

Figure 1. Diagram illustrating the typical drug development process. Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics.

interlinked system, and a drug administered to a human goes through at least four processes that include absorption, distribution, metabolism, and excretion (ADME) [20]. For example, when a drug is administered orally, the compound is first absorbed through the gut and enters the bloodstream, where it is distributed throughout the fluid and tissues in the body, then further metabolized (usually in the liver), and is finally excreted from the body (usually through the kidneys) (Figure 2A). One of the most common metrics measured in PK is the concentration of the drug circulating in the body over time. An equally important measurement is the bioavailability of a drug – the fraction of the administered drug that reaches the targeted site of action [21].

The effects of the drug on the body

The study and characterization of how the drug affects the body are known in pharmacology as **pharmacodynamics (PD)**. Importantly, after the drug enters the body, it becomes crucial to understand if the drug is efficacious and safe. For example, how might a drug circulate through an entire body to (i) specifically target a diseased organ (efficacy) and (ii) discriminate between its intended target and other parts of the host (safety)? Furthermore, in line with the famous dictum coined by Paracelsus (a Swiss physician in the 15th century) – 'the dose makes the poison' – the difference between efficacy and adverse toxic effects is a matter of dosage (i.e., therapeutic window). PK and PD are usually studied together, and they include important readouts that ultimately influence dosing, benefit, and adverse effects [22,23].

Mechanisms leading to drug-induced toxicity

Further adding to the challenges in developing OoCs, a drug can cause **adverse drug reactions (ADRs)** or drug-induced toxicity by more than one mechanism. These mechanisms can be interrelated, and the use of current single-tissue models to predict drug-induced toxicity may not accurately represent all these events. Briefly, mechanisms that can lead to drug-induced toxicity include (i) on-target adverse effects, (ii) off-target adverse effects, (iii) harmful **metabolites**, (iv) harmful immune responses, and (v) **idiosyncratic drug reactions** (Figure 2B) [24]. On-target adverse effects refer to drug binding to its intended receptor, but at an inappropriate dosage. Alternatively, the drug may bind to the intended receptor but in an incorrect tissue. These events may result in a biological response that produces toxic effects. Second, off-target effects refer to drug binding to an unintended target, regardless of the tissue, resulting in adverse effects. Third, almost all drug compounds are metabolized, usually in the liver, and may produce a harmful metabolite. Harmful immune responses are the fourth mechanism that can cause drug-induced toxicity. The two primary immune mechanisms that can elicit adverse effects are allergic responses and autoimmune reactions. Lastly, idiosyncratic drug reactions (IDRs) can occur in a small population of patients. Because IDRs are usually very rare, these events are difficult to predict using existing models.

Limitations of 2D cellular assays and animal models

The complexity of human biology and multiple modes of toxicity highlight the difficulty of predicting adverse drug effects in preclinical testing. Although the current tools – 2D cell cultures and animal models – have successfully brought numerous drugs to the market, it is undeniable that a more predictive tool is needed. For example, 2D cellular assays of a homogeneous population of cells cultured on a planar surface do not recapitulate human organs to allow accurate prediction. Human organs are assembled with various specialized cell types arranged in precise geometries with specific microenvironments. Furthermore, PK/PD or ADME studies cannot be meaningfully carried out because organ–organ interactions are not represented in 2D cellular assays.

Glossary

Adverse drug reaction (ADR): an appreciably harmful or unpleasant reaction resulting from the administration of a drug.
Angiogenic sprouting: the sprouting of new blood vessels from pre-existing vessels.
Biomimicry: the design and production of systems that are modeled on biological entities and processes.
Drug-induced toxicity: the degree to which a drug (or equivalent) can damage an organism.
Efficacy: the measure of the ability of the drug to treat the intended condition.
Extracellular matrix (ECM): a complex molecular network of noncellular components that provides physical support and biochemical/biophysical cues for tissue development and homeostasis.
Human-body-on-a-chip: an *in vitro* multi-organ system aimed at recapitulating *in vivo* organ–organ crosstalk.
Idiosyncratic drug reactions: unpredictable adverse effects that cannot be explained by the known mechanisms of action (i.e., pharmacology, safety, and toxicology).
Metabolite: the intermediate or final product of a metabolic reaction catalyzed by an enzyme that occurs naturally within cells.
Parenchymal tissue: the tissue that is responsible for the function of a particular organ.
Pharmacokinetics/pharmacodynamics (PK/PD): the pharmacologic disciplines that study the effects of the body on the drug (PK) and the effects of the drug on the body (PD).
Phenotype: the observable physical or biochemical characteristics of cells/tissue.
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): the strain of coronavirus that is responsible for the coronavirus disease 2019 (COVID-19) pandemic.
Spheroid: a 3D, usually spherical, cellular aggregate.

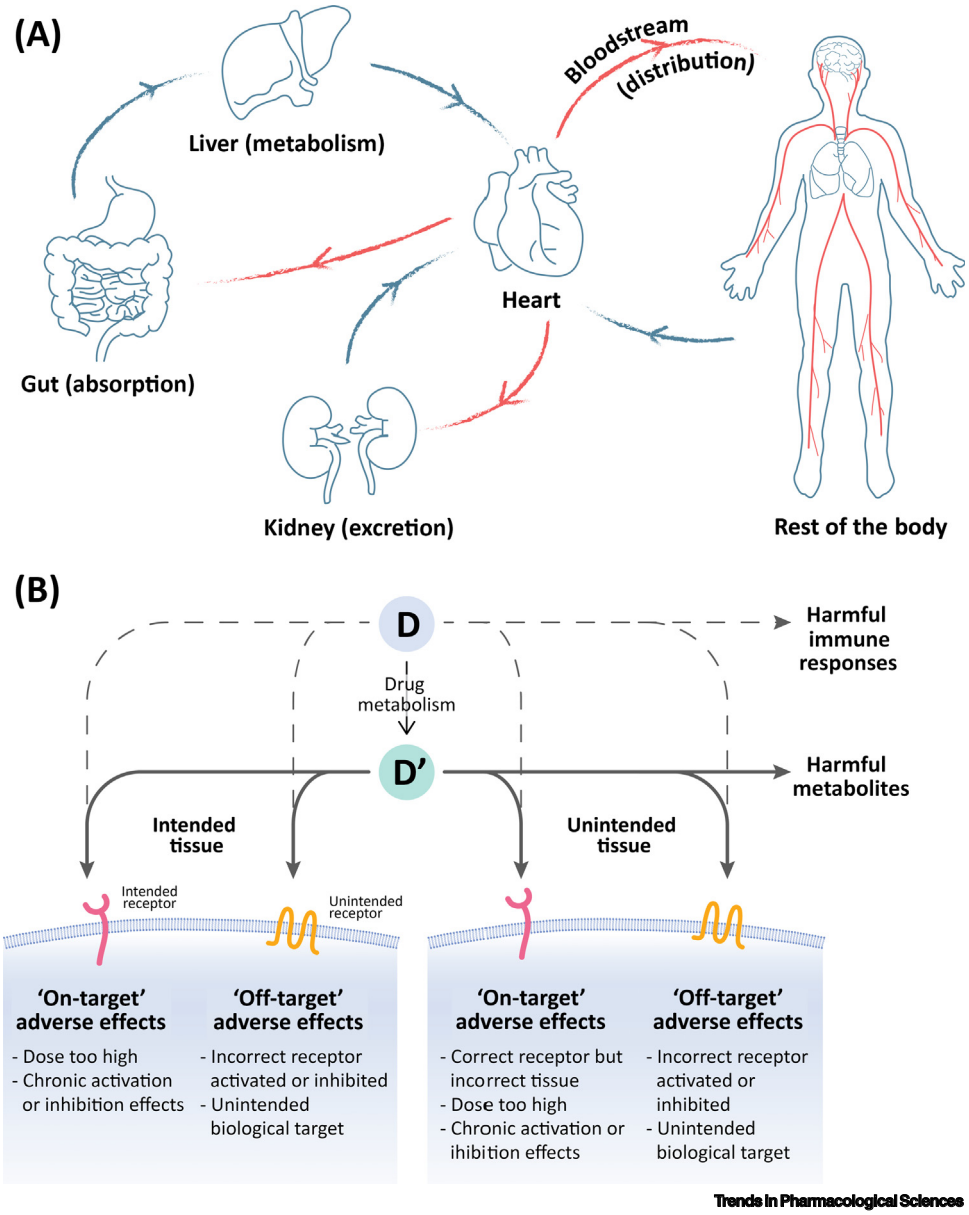

Figure 2. Systemic drug distribution/metabolism and on/off-target effects. (A) Schematic diagram illustrating drug absorption, distribution, metabolism, and excretion (ADME) within the human circulation system. (B) Schematic diagram illustrating the various mechanisms of drug-induced toxicity. Abbreviations: D, drug; D', drug metabolite.

To characterize the PK/PD or ADME of a drug candidate in the conventional sense, living animals must be used. Unfortunately, differences in the underlying molecular, cellular, and physiological mechanisms between animals and humans may result in inaccurate prediction of human drug responses. Furthermore, animal models require high financial investment and are usually not amenable to real-time monitoring of PK/PD profiles [25].

How Do OoCs Aim to Fill the Gap?

There is a urgent need to find a more predictive model than the current 2D cellular assays and animal models. As early as 1996 scientists began to propose and demonstrate the concept of

cell culture analogs (CCAs) or OoCs [26–31]. OoC is a technology that marries engineering disciplines such as microfluidics with advances in developmental biology and tissue engineering. Recapitulating key organ-level functions *in vitro* is by no means a simple endeavor given the complexity of human physiology. Therefore, researchers must meet several milestones. In the short term, the focus includes developing well-characterized and validated individual organ systems (i.e., liver, kidney, etc.) [32]. In the long term, the vision is to develop a **human-body-on-a-chip** system, where multiple organ models are fluidically linked to allow the study of interdependent PK, PK/PD, and ADME relationships that can benefit safety and toxicity assessments [33,34].

Existing OoC platforms

Biomimicry – key hallmarks of OoCs

Biomimicry

This involves the creation of an environment that resembles the native environment sufficiently precisely, in a compartmentalized and often non-planar manner, that human cells function like their native counterparts. **Biomimicry** is crucial for understanding highly complex human physiology. There are several key hallmarks that OoC developers aim to replicate, namely the mimicry of (i) fluid flow, (ii) mechanical stimuli, (iii) 3D spatial organization of cells, and (iv) crosstalk between cells/organs.

Mimicking fluid flow

The first key hallmark of biomimicry in OoCs is fluidic flow, analogous to the vasculature whose main function is to transport nutrients and oxygen, and also remove waste products and CO_2. The bloodstream is the primary route where drug compounds are distributed across the whole body. Furthermore, fluid shear stress has been established to affect the **phenotype** and morphology of cells [35]. Therefore, to recapitulate key functions of organs, fluid control within OoCs is crucial. The challenge then lies in integrating cells in the presence of fluid flow. The traditional form of integration is to directly seed cells or organoids onto the surface of the microfluidic channels (Figure 3Ai,ii) [36]. The method of direct seeding depends mainly on the self-attachment abilities of adherent cells [37]. Another technique is the use of physical barriers to confine cells or **spheroids** in the 'cell compartment' while allowing the medium to flow in adjacent channels to permit nutrient exchange (Figure 3B) [38,39]. Alternatively, instead of relying on their self-attachment abilities, the cells can be encapsulated within a hydrogel-based **extracellular matrix (ECM)** with the help of microfluidic channels (Figure 3C,D) [40–43]. For example, we encapsulated tumor cells within a hydrogel matrix and incorporated bioprinted fluidic channels to mimic fluid flow analogous to both blood vascular perfusion and lymphatic drainage [44]. Because the hydrogels employed (e.g., collagen, Matrigel, gelatin, and fibrin) are usually highly porous, they are highly permeable to medium exchange and biomolecules. The methods mentioned earlier involve creating an artificial channel architecture that mimics the vasculature. However, by using OoCs (Figure 3D), researchers can use the inherent abilities of endothelial cells – **angiogenic sprouting** of the microvasculature network within the ECM – to mimic multiscale fluid distribution and fluid flow [45–47].

Mimicking mechanical stimuli

Another hallmark of biomimicry in OoC systems is the ability to incorporate mechanical stimulation. Several organs, including the lung, blood vessels, and intestinal tract, are not stationary *in vivo* but experience cyclic motions that are vital for their functions. In addition, mechanical forces affect cell behaviors, including growth, differentiation, programmed cell death, and migration [35,48]. One of the most representative platforms for on-chip mechanical stimulus was demonstrated by Ingber and colleagues, as shown by the lung-on-a-chip that incorporates

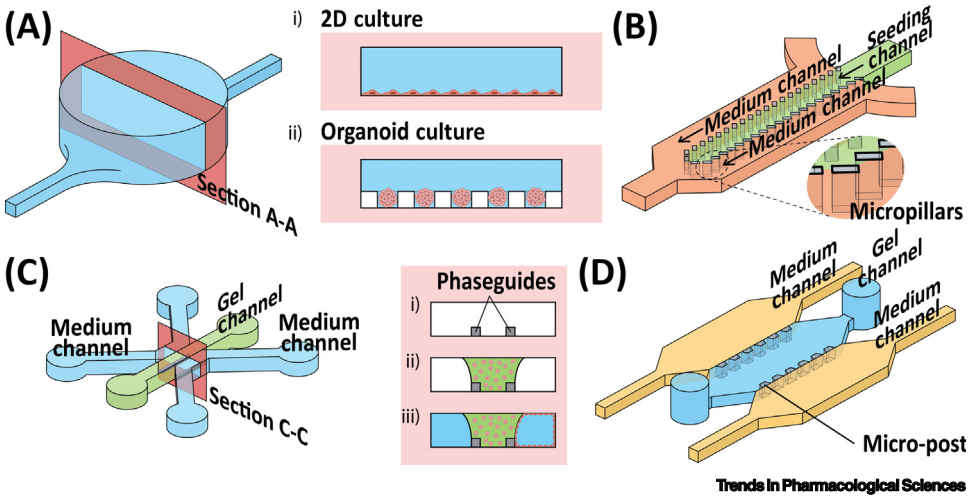

Figure 3. Microfluidic organ-on-a-chip (OoC) devices with biomimetic flows. (A) Schematic representation of a microfluidic culture chamber and cross-sectional illustration of (i) 2D planar cell culture and (ii) organoid culture. (B) Schematic representation of a microfluidic device with micropillars to constrain cells/organoids within the seeding channel. (C) Schematic representation of the three-lane OrganoPlate® (Mimetas) consisting of two medium channels (represented in blue) and a single gel channel (depicted in green). The cross-sectional view (section C–C) illustrates the multiple steps in (i,ii) seeding the extracellular matrix (ECM) gel, and (iii) subsequent seeding of a monolayer of barrier tissues in the medium channel. (D) Schematic representation of the 3D cell culture chip (AM Biotech) that consists of a micropost array to confine the gel within the gel channel (represented in blue).

cyclic stretching motions analogous to the breathing motions of human lungs [28]. The stretching motion was performed by incorporating vacuum channels on the sides of a porous membrane where relevant cells (epithelial and endothelial) are seeded (Figure 4A). Interestingly, the mimicry of cyclic mechanical strain was found to accentuate the toxic and inflammatory responses of the lung to silica nanoparticles. Other platforms mimicking the mechanical movement of the lung have been demonstrated [49]. Different cell types (Caco-2 intestinal epithelial cells, smooth muscle cells) have also been used in a similar chip architecture [16,50,51].

Mimicking 3D spatial organization

The next hallmark of biomimicry in OoC systems is the 3D spatial organization of cells. Various specialized cell types are arranged in precise geometries and interact with specific microenvironments. It has been established that cells cultured in 2D differ from cells cultured in 3D in terms of morphology and the expression levels of diverse proteins [52,53]. Researchers focus on two main types of tissue organization, namely **parenchymal tissues** and barrier tissues [25].

In the context of ADME, mimicking parenchymal tissues is of great interest because they usually govern the function of a particular organ. For example, hepatocytes belong to the parenchymal tissue of the liver which plays a pivotal role in metabolism, detoxification, and protein synthesis. Organ-specific parenchymal tissues are typically densely packed and precisely organized to exhibit organ-specific functions. In OoC technology, parenchymal tissue types (i.e., cardiomyocytes, hepatocytes) are often incorporated on-chip with the help of 3D ECM [54,55]. These cells are mixed with uncured hydrogels and injected into the microfluidic channels before allowing them to cure. Crucially, flanking channels are usually necessary to facilitate the flow of the medium to maintain the cells within the hydrogel matrices. Surface tension can be employed to confine the cell-laden hydrogel within the predetermined channels. For example, the cell culture chips developed by Kamm and colleagues, now commercialized by AIM Biotech, use micropillars to confine the cell-laden hydrogels to their respective channels (Figure 3D) [41,47,56]. Mimetas, a platform that uses Phaseguide™

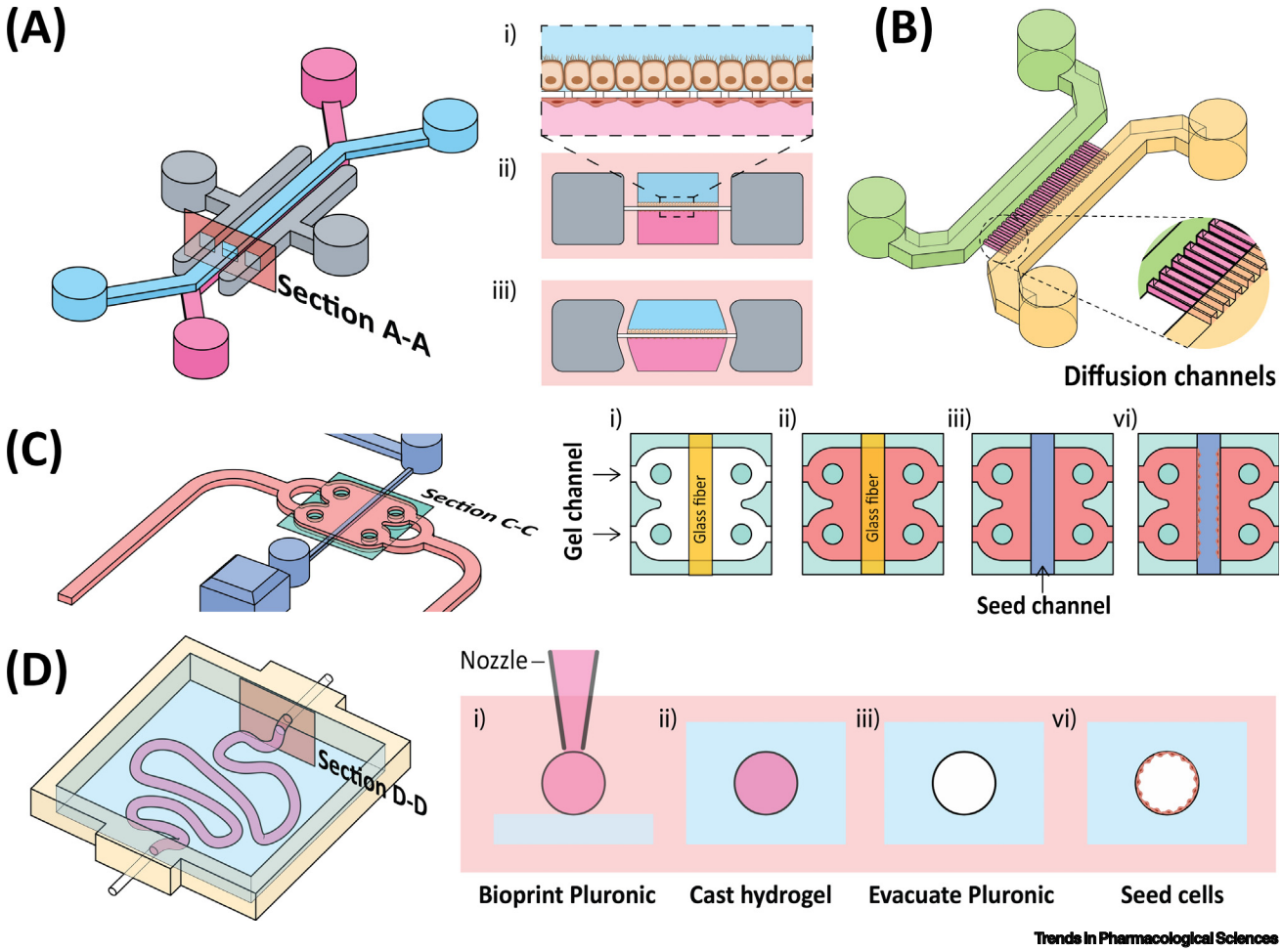

Figure 4. Microfluidic organ-on-a-chip (OoC) devices with mechanical stimuli and 3D cellular arrangements. (A) Schematic representation of the lung-chip (Emulate) and a cross-sectional view (section A–A) illustrating (i) porous membrane with epithelial cells on the top side and endothelial cells underneath, (ii,iii) mechanical stretching of the porous membrane when negative pressure is applied in the vacuum channel (depicted in grey). (B) Schematic representation of an OoC device incorporating diffusion channels. (C) Schematic representation of the ParVivo chip (Nortis) and a cross-sectional view (section C–C) illustrating (i,ii) casting the hydrogel (pink) via the gel channel with a glass fiber to form a lumen structure within the chip, and (iii,vi) seeding of barrier tissue within the lumen cavity. (D) Schematic representation of a bioprinted kidney proximal tubule and the cross-sectional view (section D–D) illustrating (i) 3D printing of sacrificial Pluronic filament, (ii) casting of surrounding hydrogel, (iii) evacuation of the Pluronic filament, and (vi) seeding of cells in the lumen cavity.

technology, can also be used to confine cell-laden hydrogels in channels (Figure 3C) [57]. Alternatively, ECM can be first coated on a porous membrane to allow the attachment and self-assembly of parenchymal tissues [58–60].

Barrier tissues are also of great importance because they are essential in understanding the absorption, first-pass metabolism, excretion, and toxicity of drugs across tissue–blood or tissue–tissue boundaries. A review by Sakolish *et al.* highlights the progress and challenges in modeling tissue barriers in OoC systems [61]. Briefly, mimicking barrier tissues (e.g., endothelial cells, epithelial cells) is usually achieved by using porous membranes. The most common porous membrane configuration employs Transwell® inserts that are optimized for use in conjunction with multiple-well plates [62]. Companies including CN Bio [63,64] and TissUse [65] utilize Transwell® inserts as part of their OoC platforms. Alternatively, the OoCs developed by Ingber and coworkers incorporate a porous polydimethylsiloxane (PDMS) membrane between two separate microfluidic channels (Figure 4A).

The advantage of this chip architecture is that a second cell type can be incorporated on the underside of the membrane. For example, this chip architecture allows the inclusion of an endothelial barrier on one side of the porous membrane, and a secondary cell type (e.g., liver, kidney, bone marrow, gut) on the other side. In addition to using a porous membrane, barrier tissues can also be seeded onto a prefabricated lumen structure, akin to the structure *in vivo* (e.g., vasculature, proximal kidney tubule). Several strategies involve seeding barrier tissues onto prefabricated lumen structures made out of hydrogel ECMs. The fabrication of the lumen structures may involve (i) casting the hydrogel by using glass fiber as a template (Figure 4C) [66], (ii) 3D bioprinting of a sacrificial filament that can be evacuated after casting the surrounding hydrogel (Figure 4D) [67–69], or (iii) confining hydrogels in respective chambers using Phaseguide™ technology (Figure 3C) [70,71]. In these setups, parenchymal cells can be encapsulated within the surrounding hydrogels (gel channels; Figure 4C,D), representing parenchymal tissues, while barrier cells can be seeded within the lumens to represent the barrier tissues.

Mimicking cell–cell/organ–organ interactions

Finally, predicting PK/PD profiles, ADME properties, and drug-induced toxicity requires consideration of cell–cell/organ–organ interactions. A simple way to mimic cell–cell interactions is the inclusion of diffusion channels (Figure 4B). These diffusion channels are smaller than the cells, thus restricting the cells to their respective culture chambers, but are sufficiently large to allow diffusion of smaller molecules, allowing crosstalk between chambers [72,73]. The greatest advantage of OoCs, however, is the ability to fluidically link multiple OoCs to mimic multi-organ physiology. Currently, multiple methods have been used to link multiple organs fluidically and reproduce organ–organ interactions. For example, the groups of Shuler and Hickman integrated multiple-organ chambers on a single platform where the medium is recirculated using a rocker (Figure 5A) [74,75]. Ingber and coworkers used automated liquid transfer to pipette medium from one chip to another (Figure 5B) [76], whereas we used fluidic tubing coupled to a pump linking multiple OoCs together (Figure 5C) [77,78]. Lastly, the group of Griffith in collaboration with Draper Laboratory designed an open-microfluidic platform with on-board pneumatic pumps to control medium circulation across multiple Transwell® inserts (Figure 5D) [62]. Qualitative and quantitative prediction of PK parameters, ADME profiles, and drug toxicity responses have been realized using these fluidically coupled OoC devices [10,79,80].

Current status of OoCs

Over the past 15 years, countless OoC platforms and organotypic models have been demonstrated to be better predictors of safety and toxicity than traditional methods [25,81]. We highly recommend reviews that discuss in greater detail the progress and validation of the many existing OoCs in the context of safety and toxicity assessment [10,32,34,82].

Advances in this field have also led to the emergence of several companies, and many are already in partnership with large pharmaceutical companies [17]. Furthermore, regulatory agencies and research agencies such as the US National Institutes of Health (NIH), FDA, and Department of Defense (DoD) are proactively providing momentum in this field. Pharmaceutical industries have also established partnerships with government agencies, academic innovators, and startup companies to support the development of OoCs and facilitate a path for successful adoption [22,83].

Recommendations for future steps

Despite the emergence of several OoC companies, OoCs are still in their infancy. However, if the imperative, as Caicedo and Brady have pointed out, is not simply to develop academic proof-of-concept but to ensure widespread adoption by industry, more deliberations should be undertaken by the researchers in the field of OoCs [84]. To achieve this, we suggest several elements for researchers to consider.

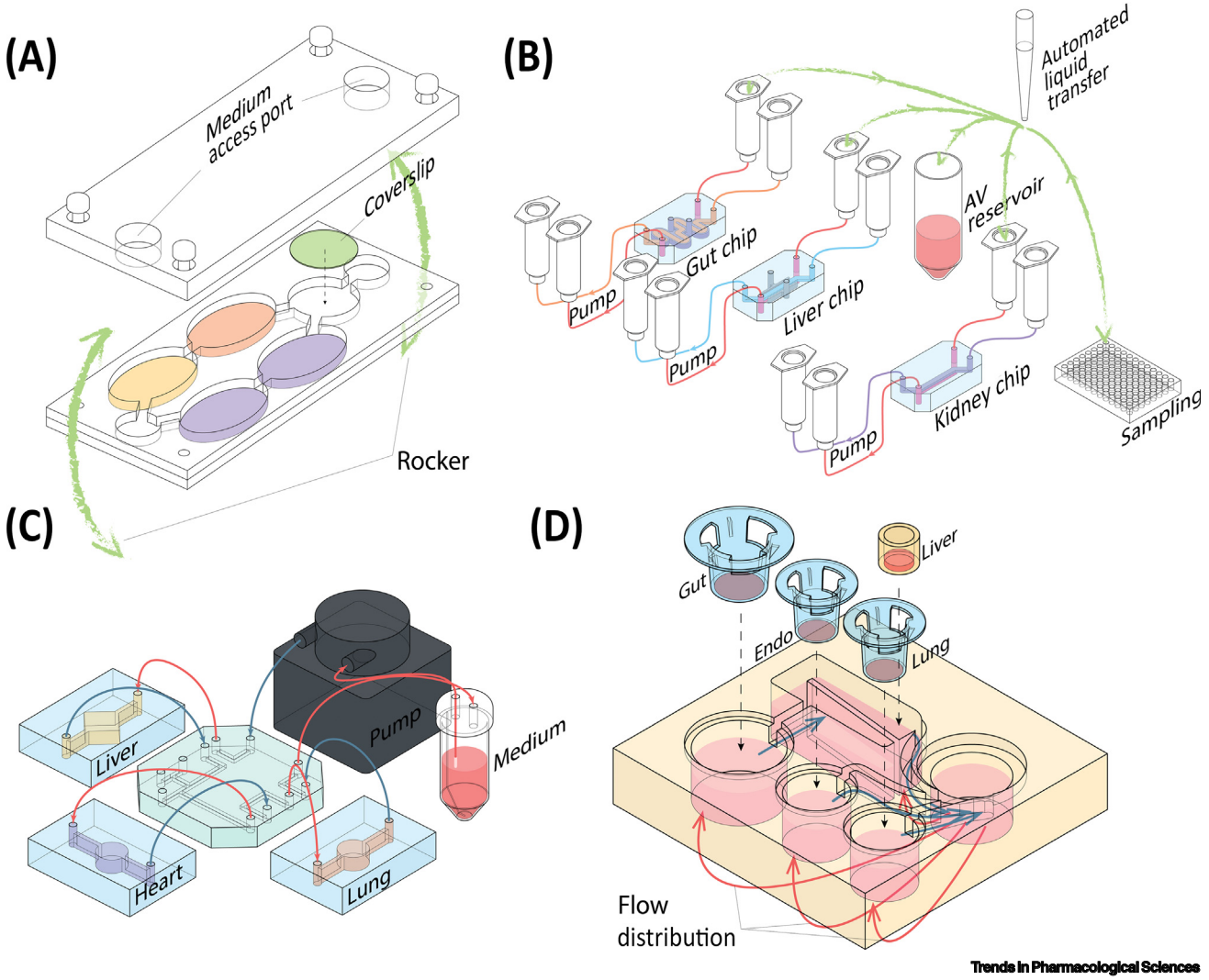

Figure 5. Multiorgan-on-a-chip systems. (A) Schematic representation of a pumpless, multi-organ system consisting of five culture chambers. Fluid circulation is driven by gravity, using a rocker. (B) Schematic representation of the fluidic linkage between organ chips (gut, liver, and kidney) and an arteriovenous (AV) reservoir using an automated liquid transfer robot. (C) Schematic representation of a microengineered heart–lung–liver model that is fluidically linked using tubing coupled to a peristaltic pump. (D) Schematic representation of the PhysioMimix™ organ-on-a-chip (OoC) platform (CN Bio). Cells are cultured on Transwell® inserts that are loaded into the platform integrated with pneumatic pumps for recirculating flow distribution.

Integration with existing pipelines

How easily can the OoC be integrated into the existing biotechnology infrastructure? For OoC platforms targeted for higher-throughput assessments, integration with the existing infrastructure may be important. The existing biotechnology infrastructure in the pharmaceutical industry represents many years of refinement and substantial financial investment. There will need to be significant operational and financial advantages to convince the pharmaceutical industry to opt for new technologies (i.e., OoCs) when that becomes a necessity [85]. Bridging the academic-to-industry gap may be facilitated by designing OoC platforms that permit easy adaptation to the existing biotechnological infrastructure. To that end, some OoC platforms adopt workflows that are familiar to existing pipelines, such the familiar multiple-well plate configuration (e.g., Mimetas, Alveolix, CN Bio, and Draper), a format that is recognizable to biologists and technicians in industrial

laboratories. For instance, the Mimetas platform (Figure 3C) is not only designed with the well-plate configuration but is also designed to be operated with pipetting, a familiar workflow in biology and related disciplines. Another method of integration may involve the use of automated liquid-handling robots that are already widely adopted by the pharmaceutical industry. Large pharmaceutical companies are already using automated liquid-handling robots to rapidly screen thousands of drug compounds in 2D cellular assays. For example, the approach by Ingber and colleagues (Figure 5B), where robotic liquid-handling robots are used to fluidically link multiple OoCs, can take advantage of the existing liquid-handling infrastructure in the pharmaceutical industry. It should be noted that, although complete integration of OoCs with the existing infrastructure would be ideal, it may not be the most practical or economical approach. To that end, intermediary organizations such as contract research organizations (CROs) and tissue-chip testing centers (TCTCs)[i] may be a practicable approach in the broad context of integrating OoC devices into the drug development pipeline.

User experience

How will the end-user rate OoC usability? Unlike the developers of the devices in academic laboratories, biologists and technicians in industry may not be interested in handling the cumbersome tubing and pumps found in many OoC setups. A platform that is cumbersome to operate may impact on the level of adoption by the end-users and may become a barrier in translating these OoCs to the industry. Therefore, the development of OoCs should emphasize the design of workflows that enhance usability. One good example is the company Emulate (a company based on the platform developed by Ingber and colleagues) (Figure 4A), where much emphasis has been placed on the development of supporting devices and workflows to improve usability. This is accomplished by designing modular pods to house individual chips to improve portability, as well as by including an integrated culture module to automate the maintenance of multiple pods concurrently. Another example is CN Bio (a company based on the platform developed by Griffith and colleagues) which also developed a docking station that takes care of all the plumbing functions such that end-users do not need to handle the cumbersome tubing and pumps. Alternatively, platforms can eliminate the use of cumbersome tubing by opting for a pumpless configuration based on gravity-driven fluid control. Hesperos (a company based on the platform developed by the groups of Shuler and Hickman) (Figure 5A) and Mimetas are examples of platforms that have adopted this strategy.

Scalability

How scalable is the OoC platform? To translate a specific OoC platform, it must be viable for scalability. In practice, pharmaceutical companies need to screen hundreds to thousands of drug candidates (Figure 1). Platforms that are fine for small-scale research in academic laboratories may not be easily scaled up for the requirements of pharmaceutical applications in industry. OoC developers should consider factors such as manufacturability. Not all platform designs are amenable for cost-effective, high(er)-throughput manufacturing. In general, the additional complexity of channel architecture will affect manufacturability. Furthermore, manufacturability may be hindered by the choice of materials. For example, it may be preferable to avoid using PDMS owing to its inherent ability to absorb small molecules [86], and this can be circumvented by choosing thermoplastics [87,88]. Unfortunately, unlike PDMS, not all chip designs can be effectively manufactured using thermoplastics in academic research laboratories [89]. In addition, OoC developers should consider scalability from the viewpoint of the workflow. Ultimately, the platform is handled by a large number of biologists or technicians in industrial laboratories. Do the preparation, maintenance, and sampling of the OoCs involve complex procedures that are prone to experimental error? Importantly, the key to scalability is the ability to ensure reproducibility and robustness, even when operated by different users who may have limited experience with

these devices. To ensure good scalability, the entire workflow should be viable for automation with minimal human intervention. To that end, platforms such as OrganoPlate® by Mimetas and PREDICT96 from Draper Laboratory aim to provide higher-throughput systems that are suitable for automation. Lastly, scalability also refers to the scaling of organ volumes and perfusion rates to maintain physiological relevance [82]. The ability to conveniently scale organ volumes and perfusion rates can be helpful to end-users.

Versatility

Can the same chip design/workflow be repurposed for different organ models? Ideally, the same chip design should be able to mimic various types of organs. Although careful consideration of maintaining biological relevance is necessary, a versatile chip design/workflow ensures that the skills and techniques gained from the mastery of a particular OoC can be transferable to the creation of other OoCs. Designs similar to those of commercially available platforms such as Emulate, Nortis, and Mimetas can be adapted to accommodate diverse cell types and configurations to mimic different organ functions. Another feature potentially useful to end-users is the ability to interconnect OoC devices from different manufacturers. OoC developers could consider platforms with standardized designs that are compatible with existing platforms or those produced by other developers.

Partnership with industry and regulatory agencies

Importantly, translation to the industry will require understanding the end-users and careful definition of their needs (i.e., physiology, endpoints, key readouts). Caicedo and Brady concluded in their letter [84] that academic researchers should engage in thoughtful and meaningful partnerships with biologists and industry scientist. In another opinion article published in this journal, Levin and Behar-Cohen [90] also suggest that the most advantageous way to deal with the complex nature of academia–industry collaboration is to establish early partnerships between the two. To this end, it is encouraging to see initiatives such as the NIH Tissue Chip Consortium[ii] that is aimed at bringing together academic institutions and pharmaceutical industry partners to determine the marketability and adoption of OoCs into the research community (see Outstanding questions).

Concluding remarks

The 2020 **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)** pandemic is another stark reminder that we need better predictors of drug safety and efficacy to accelerate the development of drugs from the first phase to market approval. Several OoC platforms, including those from our group [91] and that of Ingber and colleagues [92], have demonstrated potential in assessing antiviral therapeutics against SARS-CoV-2. Emulate[iii], Mimetas[iv], and CN Bio[v] are companies that have already formed partnerships with the industry to employ their platforms to test potential therapeutics for SARS-CoV-2. In addition, cross-border partnerships between multiple agencies have also been formed to promote the adoption of OoC for SARS-CoV-2 research[vi]. Novel viral disease outbreaks may occur again in the future [93], and we hope that these initiatives will pave the way to accelerating drug development that might potentially prevent a future pandemic of similar proportions.

More recently, the FDA instigated the Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot program to support the development of Drug Developmental Tools (DDTs), including OoCs, that may be acceptable for regulatory use[vii]. The ISTAND initiative is exciting for the OoC research community because it has the potential to accelerate the industrial translation of OoCs for drug development and approval (see Outstanding questions).

Outstanding questions

How can we consistently validate and characterize each OoC platform for its ability to recapitulate physiological relevance?

How can we ensure the repeatability and reproducibility of OoC devices between batches, particularly because most rely on primary human cells that are susceptible to batch-to-batch variation?

How can OoC platforms fit into the existing pharmaceutical/biotechnology infrastructure?

Do existing OoC platforms have the ability to scale up to a level where pharmaceutical companies can meaningfully and practicably employ them?

How can we achieve wider adoption of OoC systems by academic researchers and industry?

It is undeniable that OoCs have the potential to provide better predictive models that will benefit the drug development process. To further develop OoCs as the standard to accelerate drug development, the next step is to gain industry acceptance and adoption (see Outstanding questions). Academic researchers will continue to innovate and develop better predictive OoC models. At the same time, academic researchers are also in a unique position to make specific design considerations that can help to drive industry adoption of OoCs. Long-lasting partnerships between academic researchers and industrial partners can widen OoC adoption and ultimately accelerate drug development by providing a more accurate predictor for safety and toxicity assessment.

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Declaration of interests

The authors declare no conflicts of interest.

Resources

[i] https://ncats.nih.gov/tissuechip/projects/centers

[ii] https://ncats.nih.gov/tissuechip

[iii] www.emulatebio.com/press/fda-organ-chip-crada-2020

[iv] https://mimetas.com/mimetas-news/predicting-and-preventing-covid-19-1-million-corona-research

[v] https://cn-bio.com/cn-bio-and-the-university-of-melbourne-collaborate/

[vi] https://ntp.niehs.nih.gov/whatwestudy/niceatm/test-method-evaluations/mps/index.html

[vii] www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program

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