



Microphysiological systems: analysis of the current status, challenges and commercial future

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Abstract: The field of microphysiological systems (or organs-on-a-chip) experienced, in the past decade, a surge in publications and efforts towards commercialization. Such systems hold the promise to advance drug discovery, diagnostics, and many other areas. In this review we summarize and analyze the current status of the field, describe the commercial advances and discuss standing challenges and the commercial outlook of the field.

Keywords: Organ-on-a-chip; commercialization; market; microphysiological system

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Introduction

Microphysiological systems (also termed organs-on-a-chip) hold the promise to improve and expedite the overall drug discovery pipeline. The rise of the field has been due to several factors including the continuous rising costs of developing new pharmaceuticals, the pressure to reduce animal experimentation, and the need for more predictive and high-throughput *in vitro* models. In the past decade, the advancement of microfluidics technologies has facilitated the development of microphysiological systems as simple, reproducible, and scalable platforms that recapitulate organ-level functions. The miniaturized biomimetic organ models, when interconnected together in a microfluidic circuit, can further recapitulate the physiology, compartmentalization, and interconnectivity of the human system. This then potentially enables the accurate prediction of human responses towards pharmaceutical compounds, and the development and testing of nanomedicines, chemicals, and

biological species (1-3).

Several initiatives and companies are operating to increase the adoption of these technologies more broadly by industry. In this review we summarize the key developments in the field of microphysiological systems, debate the challenges towards adoption by stakeholders, and analyze available data regarding the commercialization of such systems.

Methods

The companies included in this study are listed in *Table 1* and were obtained from web searches until June 20th 2018 including “organ-chip” keywords, as well as from other publications (4-6). The study is limited to the set of companies listed here, hence conclusions take into account only this information. In addition, funding or partnership information are sometimes unavailable to the public and it is one of the limitations of this review.

Table 1 Summary of companies working in the area of organs-on-a-chip

Company	Founding year	Location	Organ/model	Partnerships	Website
4Design Biosciences	2014	Corona del Mar, CA, USA	Cancer cell lines, cardiomyocytes, neural stem cells, hematopoietic stem cells, vasculature	–	www.4designbiosciences.com
AIM Biotech	2012	Singapore, Singapore	Stem cells, cancer, vasculature, neural cells	Distribution: Fisher Scientific Pte Ltd, Flexcell® International Corporation, Tebu-bio, Funakoshi Co., Ltd., Hangzhou Jiuyang Biotechnology Co., Ltd. (JoyingBio), Woongbee MeDiTech Inc.	www.aimbiotech.com
AlveoliX AG	2015	Bern, Switzerland	Lung-on-Chip	–	www.alveolix.com
Ascendance Biotechnology, Inc. (formerly known as Hepregen Corporation)	2007	Medford, MA, USA	Liver	–	www.ascendancebio.com
AxoSim	2014	New Orleans, LA, USA	Nerve-on-Chip	–	www.axosim.com
BI/OND Solutions B.V.	2017	Delft, The Netherlands	Cell lines, cardiomyocytes	–	www.gobiond.com
CN Bio Innovations	2009	Welwyn Garden City, UK	Single-Organ and Multi-Organ-Chip: 10-, 7-organ human body-on-a-chip model; a liver-on-a-chip model of cancer metastasis, a full viral lifecycle organ-chip model of hepatitis B and a liver-on-a-chip model of non-alcoholic fatty liver disease and steatohepatitis (NAFLD/NASH)	AstraZeneca, FDA's Centre for Drug Evaluation and Research, Alnylam Pharmaceuticals, Isis Pharmaceuticals, Benitec Biopharma	www.cn-bio.com
EmulateBio	2013	Boston, MA, USA	Lung, intestine, liver, kidney, bone marrow	Roche AG, Takeda Pharmaceutical Company Limited, Cedars-Sinai, FDA, Janssen Research & Development LLC., Covance, Seres Therapeutics, MSD	www.emulatebio.com
HemoShear Therapeutics	2008	Charlottesville, VA, USA	Models of nonalcoholic steatohepatitis (NAFLD/NASH), propionic acidemia and methylmalonic acidemia	Takeda Pharmaceutical Company Limited, UVA Health System, Pfizer Inc., Medivir AB	www.hemoshear.com
Hesperos Inc.	2015	Orlando, FL, USA	Multi-Organ-Chips (skin, endocrine, lung, intestine, lung, brain, heart, liver, bone marrow, kidney, pancreas), heart, muscle, liver, blood brain barrier	L'Oréal	www.hesperosinc.com

Table 1 (continued)

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Company	Founding year	Location	Organ/model	Partnerships	Website
Hurel Corp.	2006	North Brunswick, NJ, USA	Liver (hepatitis B disease model, hepatic co-cultures, hepatotoxicity screening, various primary hepatic co-cultures within one model, continuous monitoring)	Bristol-Myers Squibb, ACEA Bioscience, Astra Zeneca, Optivia Biotechnology, Quintiles, Sanofi US, UCB	www.hurelcorp.com
Kirkstall Ltd	2006	Rotherham, UK	Liver, kidney, intestine, blood-brain barrier, heart, lung	Distribution agreement with Lonza	www.kirkstall.com
Kiyatec	2005	Greenville, SC, USA	Breast cancer, glioblastoma, lung, ovarian, pancreatic cancer	Greenville Health System's Institute for Translational Oncology Research, Distribution: Sigma-Aldrich	www.kiyatec.com
Mimetas	2013	Leiden, The Netherlands	Breast cancer, neuronal networks, intestine, liver, blood brain barrier, kidney, vasculature, glioma, placenta models	Molecular Devices, Roche, Pfizer and GlaxoSmithKline, Galapagos, Biogen, Abbvie and Janssen	www.mimetas.com
Nortis Bio	2012	Seattle, WA, USA	Blood-brain barrier, vascular injury, kidney, liver, heart, intestine, cancer, and stem cell models	–	www.nortisbio.com
Quorum Technologies Inc.	1987	Puslinch, ON, USA	Vasculature	–	www.quorumtechnologies.com
SynVivo	2014	Huntsville, AL, USA	Cancer model, blood-brain barrier model, inflammation model, toxicology model	Distribution: Cosmo Bio Co. Ltd., Nakayama Co. Ltd., JSK Biomed, MolDiag Solutions, Lavi Med-Tech, Stratech Scientific Ltd., LuBioScience, PELOBiotech, Tebu-Bio	www.synvivobio.com
Tara Biosystems	2014	New York, NY, USA	Heart-on-Chip	-	www.tarabiosystems.com
TissUse	2010	Berlin, Germany	Adipose tissue, vasculature, bone marrow, liver, kidney, pancreas, intestine, brain, lung, heart, hair follicle, lymph node, skin	Roche, Astra Zeneca	www.tissuse.com

Company information such as founding year, location, and target organ models were obtained from their respective websites. Company size was determined by the number of full-time employees (FTEs) based on their LinkedIn company profile (ranges 1–10, 11–50, and 51–100). Funding and partnership information was obtained from press releases on company websites as well as Crunchbase and Pitchbook databases (www.crunchbase.

com, www.pitchbook.com). Companies active in the area of organoids, 3D bioprinting, or in the marketing of microfluidics systems that do not include cellular components, were not included in this analysis. The number of articles per year for different topics (“organ-on-a-chip”, “microfabrication”, “lab-on-a-chip”, and “CRISPR”) were obtained from Web of Science (www.isiwebofknowledge.com).

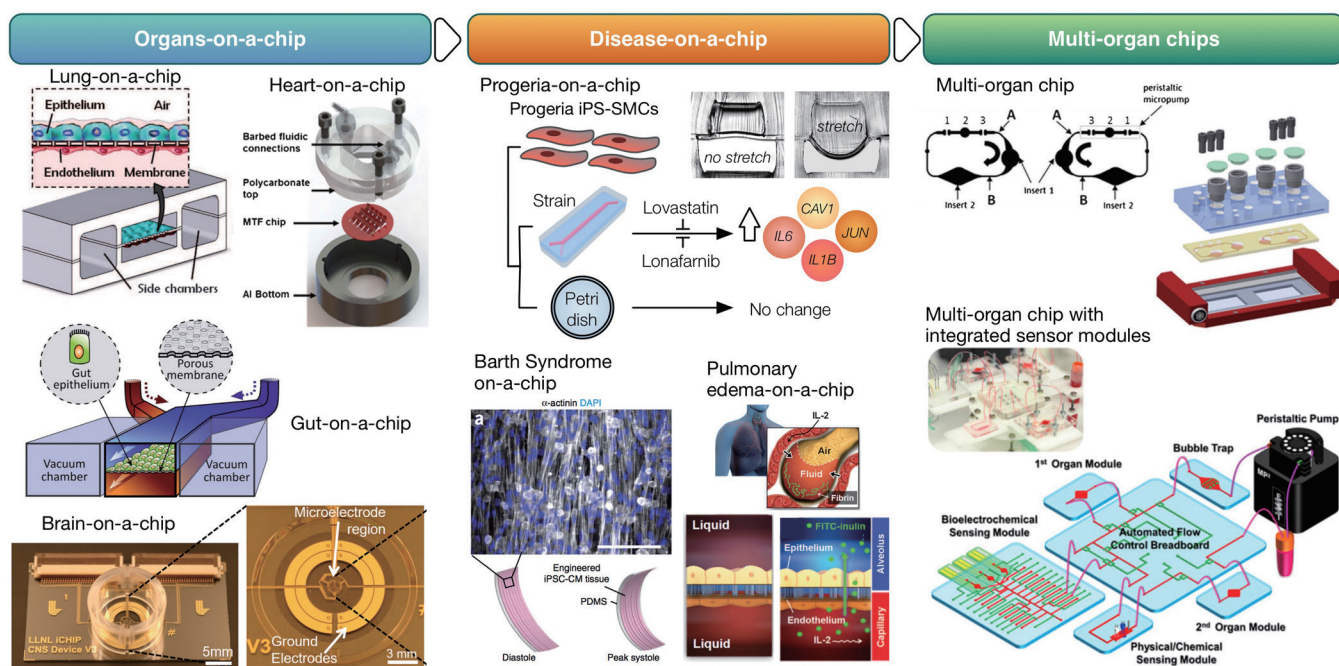


Figure 1 Overview of the progress of the organ-on-a-chip field, from healthy organ models, to disease ones, and ultimately the incorporation of multiple organs-on-a-chip. Left panel: organs-on-a-chip developed in the past years include the lung-on-a-chip [reproduced with permission from (10)], heart-on-a-chip [reproduced with permission from (13)], gut-on-a-chip [reproduced with permission from (11)] and brain-on-a-chip [reproduced with permission from (21)]. Middle panel: disease-on-a-chip approaches have emerged from normal organs-on-a-chip ones, including progeria-on-a-chip, Barth syndrome on-a-chip [reproduced with permission from (16)], and pulmonary edema on-a-chip [reproduced with permission from (9)]. Right panel: move towards multi-organ chips [reproduced with permission from (22)] and multi-organ systems with integrated sensors (23).

Current status of organs-on-a-chip

The scientific output of organs-on-a-chip drastically increased in the past years, with an initial focus on recapitulating normal organ functions. For instance, different microfabrication techniques have allowed the creation of dynamic mechanical microenvironments to apply shear stress, strain, and/or interfaces on different cell types (1,3,7,8). The creation of a lung-on-a-chip platform boosted the field by integrating mechanical strain and interfacing multiple cell types mimicking the respiration of the lung (9,10). The mechanical strain simulated the cyclic motions experienced by the lung alveoli and revealed unique responses under strain not observed in static conditions. Other approaches have been pursued to simulate dynamic mechanical environments of the gut (11,12), heart (13-16), and blood vessels (8,17-20), among others.

More recently, there has been an increased emphasis on disease model generation and multi-organ systems (Figure 1). These approaches yielded new insights into

biological processes not achievable with other technologies or animal models. For instance, several organ-on-a-chip approaches focused on developing disease models or states, such as Hutchinson-Gilford Progeria syndrome and hypertension (8), Barth syndrome (16), pulmonary edema (9), and atherosclerosis (19). These systems use human cells and are becoming an invaluable tool for drug discovery and toxicity screening; they are expected to lead to the development of new therapeutic agents. For instance, a progeria-on-a-chip model (8) was able to recapitulate an inflammatory state observed in patients, which was then reversed by using therapeutic agents in promising clinical trials (24). Besides contributing to mechanical control, microfluidics technologies proved useful in modeling several human barriers. Platforms have been created to mimic the blood-brain barrier (25-27), placental barrier (28) and blood-lymphatic vessel barrier (29). The development of these models is instrumental in the studies of drug and toxin transport across barriers as they provide simple yet

robust systems to gain mechanistic insights into barrier disturbances. These are a few examples that illustrate the potential of using organ-chips during drug discovery.

Enabling technologies are playing an important role in furthering of the organs-on-a-chip field. Lee and Cho recently used 3D printing to create a single-step-fabrication procedure that generates microfluidic circuits embedded with relevant cell types. Using this approach, they could create a liver-on-a-chip system by sequentially printing different materials, from cell-laden hydrogels to polycaprolactone (PCL)-based microfluidic channels (30). Another approach used 3D printing to directly print polydimethylsiloxane (PDMS) structures (31). The capabilities of 3D printing can be applied to generate fluidic channels for organs-on-a-chip but are also valuable in generating complex micro multi-tissue structures that can mimic several more complex organ functions (32). We envision these novel fabrication techniques to expedite the scalability of organs-on-a-chip. Although most organs-on-a-chip devices use PDMS as the base material, approaches relying on hydrogel microfluidics have emerged in the past few years [reviewed by Verhulsel *et al.* (33)]. Compared to the inert elastomers and plastics, hydrogels with different compositions allow for precise control over the extracellular matrix (ECM) properties, such as cell binding, stiffness, porosity, and degradability that directly tailor the cell behaviors in 3D microenvironments. The utilization of microfluidics based on hydrogels alone or in combination with PDMS (14) will potentiate the creation of biologically relevant organs-on-a-chip by providing additional microenvironmental cues.

The technical advantages of microfluidics also make it an ideal technology for the design and creation of multi-organ human-body-on-a-chip platforms. Here, the complexity of the fluidic architecture can mimic the required compartmentalization, nutrient gradient, and micro-scale distribution of organoids in a manner similar to those *in vivo* (34-36). Challenges still remain, as do opportunities to determine the rational design of a body-on-a-chip by precisely understanding the scale of each organ module and thus engineering of the microfluidics connecting these organoids (37,38). Early efforts towards a body-on-a-chip included systems with three to four organs or cell types that explored multiple organ interactions and metabolism (39-41). With the development in the last few years of novel and robust single organs-on-a-chip, we envision their combination into larger-scale multi-organ-on-a-chip systems featuring proper microfluidics routing

and scaling (37,38). The different modules would have autocrine and paracrine communications, different organs would metabolize drugs or other agents to be tested, and multiple interactions could be identified (2). Since the replication at the level of a whole organism is challenging, these complex systems would allow studies of different diseases at a multi-organ level. Here, key organs known to be important players for a specific drug or compound would be represented, while using a simple and standardized setup. Complex microfluidic circuits would allow automation and integration of organ models with biosensors, which could evaluate organoid responses to various stimuli (23,38,42-44).

Challenges for adoption

Microfluidics research has come a long way in enabling the development of microphysiological systems. However, the progress and broad adoption of such systems still faces several challenges. Compatibility with existing equipment is crucial for academic and industrial research alike, where novel devices must operate with a minimum added equipment and work out-of-the-box with conventional microscopes, incubators, and other crucial equipment and techniques. Ease of handling is another factor influencing adoption, where end-users should be able to operate microphysiological systems without the need for extensive training or complex instructions. Here, design thinking approaches can be a tool to improve usability and downward end-user adoption. Several industries are moving towards automation, and microphysiological systems should be prepared to that future. This is especially crucial for high-throughput applications in pharmaceutical industry, where screenings for novel compounds are moving continuously towards automated systems. Some multi-organ systems have started to take automation in consideration by using computer-controlled arrays of microfluidic valves that manage fluid flow and sensor modules (23). Multiplexing is another challenge faced, but the inherent advantages of microfluidics make microphysiological systems a prime candidate for it. Organ- or multi-organ systems can be tested for multiple targets in real time, revealing dynamics and information not available up until now. With the rise of microphysiological systems we have seen a shift from normal organ modules to disease modules highlighting the importance of understanding biology and acquire the proper molecular and physiological readouts for applications in drug discovery. Most systems are still made out of PDMS, and there is a broader discussion in the field

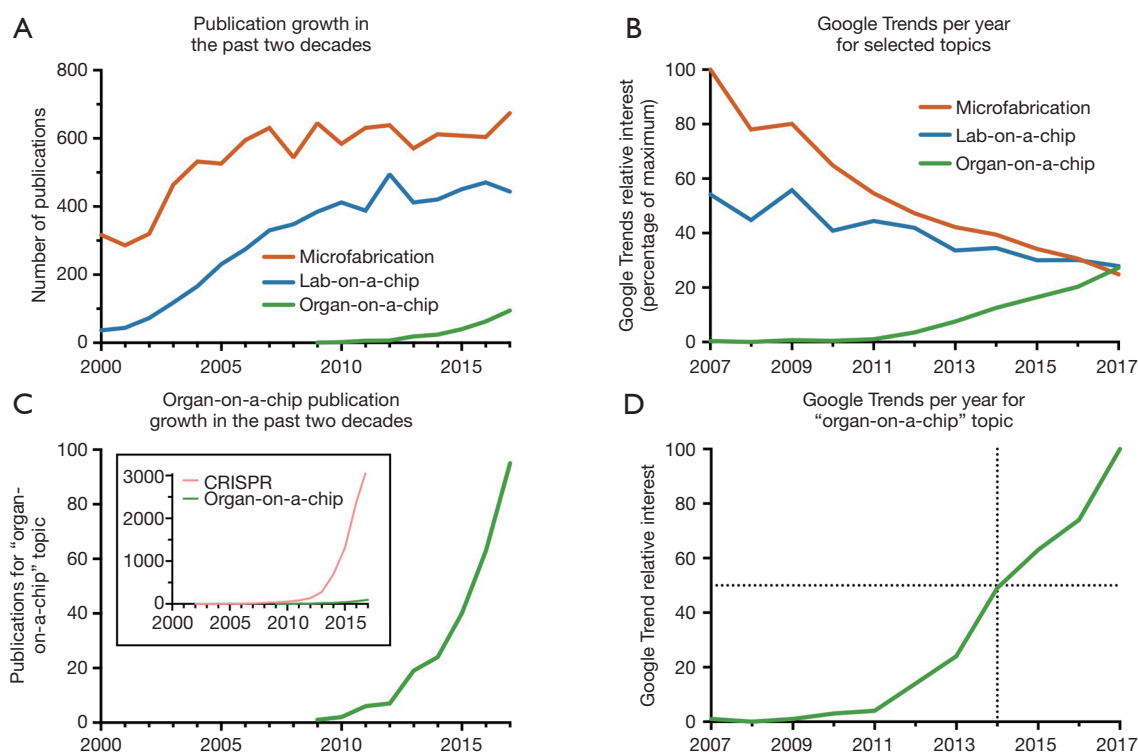


Figure 2 Evolution of the organ-on-a-chip field. (A) Increasing amount of scientific publications in the area of organ-on-a-chip, microfabrication, and lab-on-a-chip over the past two decades; (B) Google Trends interest history in the past decade normalized for the highest interest [100] comparing the topics “organ-on-a-chip”, “microfabrication”, and “lab-on-a-chip”; (C) detailed view of the publication growth of the topic “organ-on-a-chip” with an inset comparison against the topic “CRISPR”; (D) Google Trends interest history in the past decade normalized for the highest interest [100] for the topic “organ-on-a-chip”, with intersecting dotted lines indicating in which year the interested reached 50%.

of what are the best materials to use. Where PDMS has traditionally been the material of choice due to its favorable properties with regard to fabrication and permeability, other materials like hydrogels may be more suitable in supporting cell growth. And when selecting the optimal material, other factors such as optical properties to allow for imaging and drug adsorption and absorption should also be taken into account. All of these challenges affect most stakeholders involved with microphysiological systems, but one additional factor receives a growing importance—validation. Regulatory agencies are closely monitoring the progress of the field and broader discussions are in place to understand how novel microphysiological systems should be validated and what would be the impact of that.

Commercial perspective and drivers (Figures 2,3)

Since the field of organs-on-a-chip is relatively recent, most

publications focus on new technologies and applications, with only a few dedicated to market adoption and commercialization efforts (4-6,45). Over the past decade we observed an increase in the number of publications containing the keywords “organ-on-a-chip” (Figure 2A). Although initially a very technology-oriented field, aiming to develop prototypes and concepts, the organ-on-a-chip sector is currently transitioning into a more commercial focus. Indeed, since 2012 the number of organ-on-a-chip companies on Table 1 more than doubled (Figure 3A). We hypothesize that since 2012, the field has grown and matured to a point of justifying venture investment for potential applications in drug discovery. At the same time, the global interest in the field increased. An analysis of the Google Trends topic “organs-on-a-chip” (Figure 2B,C,D) in web searches identified continuous growth, with a peak interest as of 2017 and mid-point in 2014 (Figure 2D). The Google Trend analysis also revealed that topics in a similar

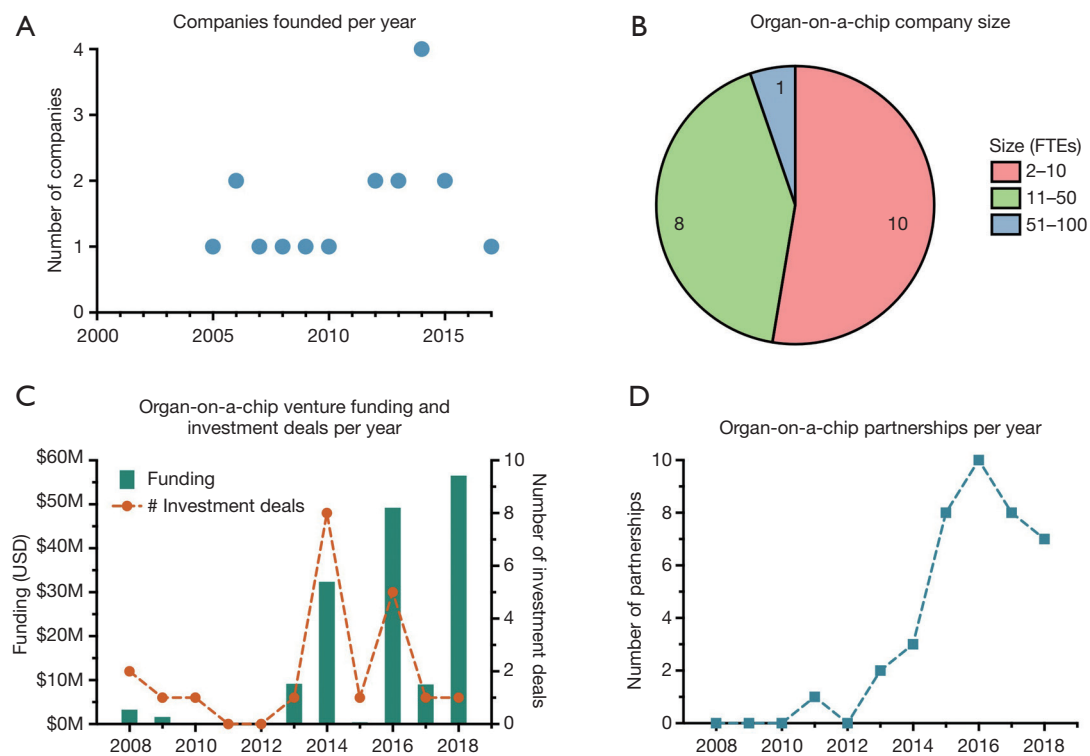


Figure 3 Progression of organ-on-a-chip startup companies. (A) Number of organ-on-a-chip companies founded per year; (B) size of company based on the amount of full-time employees (FTEs); (C) venture funding of startup companies and number of investment deals made over the past decade; (D) number of partnerships with pharmaceutical companies, distributors, and other companies over the past decade.

area (“microfabrication” and “lab-on-a-chip”) have seen a steady decline reaching a similar level to “organs-on-a-chip”. Furthermore, the publications trend as seen for organs-on-a-chip differs from other developing technology fields like lab-on-a-chip, microfabrication or CRISPR. Analyses for these keywords show a more stable profile over the last decade for lab-on-a-chip and microfabrication (*Figure 2A*), indicating that the developments seen for organs-on-a-chip cannot be explained by a general rise of interest in new technologies. However, the total amount of publications and growth is significantly smaller compared to CRISPR (*Figure 2C*), which has attracted more research and overall funding.

A recent survey analyzed the opinions of stakeholders such as pharmaceutical companies and universities (4) regarding the use of organs-on-a-chip in drug discovery and development. Respondents to the survey predicted improvement possibilities in basic research, including target validation, while also considering pre-clinical development. Opinions diverged regarding clinical trials, with respondents from pharmaceutical companies mostly disagreeing on the

replacement or reduction of human trials whereas university respondents were more divided (4). This study highlighted the relevance of understanding stakeholder opinions and needs early-on, to maximize the adoption and successful implementation of organ-on-a-chip technologies. Another important aspect relevant to the discussion is the business model behind such companies. Burgwal and co-workers analyzed different business models applicable to organs-on-a-chip companies and surveyed potential end-users (life science companies, pharmaceutical companies, contract research organizations (CROs), and universities/research institutes) (5). For most potential users, the preferred model included the product and a free basic startup service. An exception to this were pharmaceutical companies who weighed more relevance to models using CRO. Such information indicates that pharmaceutical companies might not be as willing to invest in new technologies for drug discovery, and instead prefer outsourcing it to CROs. Big pharmaceutical companies have been outsourcing innovation and research services to other companies, hence

it is not surprising to observe the preference for CROs where they can rely on external expertise to obtain fast and trustworthy results. Despite differences in preferred business models, the majority of end-users agree on the relevance and future value of organ-on-a-chip technologies (5). However, the willingness to invest in new hardware is still limited, which can slow down adoption. In addition, most companies are operating with a hybrid business model that combines product and service offerings. Since the adoption is in early stages, end-users often require more specific solutions that need to be especially developed or tailored, which deviates organ-on-a-chip companies from a more scalable razor-blade model (5).

On *Table 1* we list companies working more exclusively on organs-on-a-chip (not including 3D bioprinting or organoid companies). These companies are working on a variety of organ models and have already entered partnerships with bigger companies including well-known pharmaceutical companies. Most of the organ-on-a-chip companies are still young and relatively small in number of FTEs (*Figure 3B*). Venture funding and number of deals peaked in 2016 and 2018 (*Figure 3C*), and the results of such investments may still require more time to see fruition. We observed also an increase of funding per investment deal which indicates the maturation of the investments from seed stages to later stages (series A, B, and other types). Another indicator of the growth of the field are the increasing number of partnerships over the past decade (*Figure 3D*), where more and more pharmaceutical companies engage in partnership agreements geared towards drug discovery. It should be noted that information on partnership agreements and funding rounds is not always publicly available and therefore the data in *Figure 3D* and *Table 1* cannot be seen as a complete overview of the adoption of organs-on-a-chip by the pharmaceutical industry. However, it is likely that an increase in the number of publicly communicated partnerships corresponds with an increase in the number of total partnerships. Overall, there has been a positive increase in venture funding and partnerships, highlighting a continuous investment in the area and commercial potential. At the same time several governmental grant schemes have been created to specifically support the field, such as the Tissue Chip Discovery Program from the National Institutes of Health.

Conclusions and future outlook

The organs-on-a-chip field has seen an increase in scientific

output (publications) but also in the number of startup companies created and total funds raised. Early assessment of potential end-users and stakeholders point towards the importance of the technology in drug discovery and development, with a special emphasis on discovery and pre-clinical stages. The next 5–10 years will be crucial for the technology to overcome challenges with standardization and regulatory endorsement. Judging by the number of partnerships between established corporations and organ-on-a-chip companies we believe the field will help mitigate current business needs in the drug discovery arena and consequently achieve commercial success.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/mps.2018.10.01>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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