Organ-on-a-Chip Technology: Progress, Challenges, and an Exciting Future

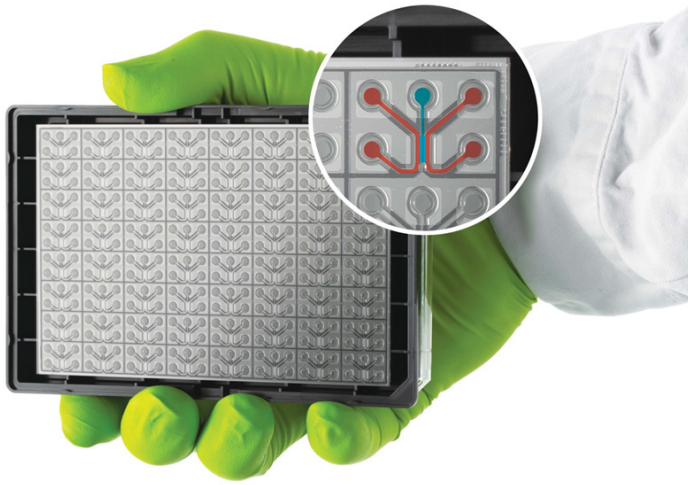

FIGURE 1. Schematic presentation of the MIMETAS OrganoPlate® 3-lane 64

Miniaturizing organs to the size of an AA battery may once have sounded like a prospect confined to the realms of science fiction. But, with organ-on-a-chip technologies seeing breakthrough after breakthrough, this concept has now become a reality – and without the use of a super shrink ray.

Organ-on-a-chip, an innovative technology developed over the past decade, can mimic the physiological environment and functionality of human organs on a tiny microfluidic device (Figure 1). They show great potential to revolutionize drug discovery and development, personalized medicine as well as drive forward the study of disease modelling.

While organ-on-a-chip technology has seen substantial advances and adoption within the pharmaceutical industry has even more exciting prospects on the horizon, a number of barriers need to be addressed to enable its wide-spread adoption in research. Speaking with experts in the field, we explore some of the impressive developments made in organ-on-a-chip research, and how biotechnology innovators and academic groups can collaborate to overcome these barriers and propel the field forward. By doing so, we can realize the full potential of organ-on-a-chip platforms and further increase confidence in this new technology.

From Organoids to Organ-on-a-Chip

An organ-on-a-chip can be defined as a bioengineered microdevice that can mimic the complexity of living human organs. Unlike organoids – that are grown in petri dishes - living human organ-specific cells line the tiny channels of microfluidic devices. While the two technologies share similar applications, an organ-on-a-chip offers several advantages over their organoid counterpart.

The complex 3D structure of organoids and their size and shape heterogeneity makes it particularly difficult to standardize experiments. With an organ-on-a-chip, on the other hand, you have high levels of control over cell numbers, cell type and placement and in turn, greater potential for reproducibility.

As well as being complex and heterogenous, organoids are also polarized. In other words, they have some level of shape and functional asymmetry and the wrong side of the epithelium is exposed to additives (e.g. compounds/microbial cells) in the media. Consequently, studying the interior of organoids is difficult and often requires specialist techniques.

For instance, microinjection – a particularly challenging technique - of microbial cells into organoids would be a pre-requisite to explore host-pathogen interactions in an organoid experiment. Moreover, the manual nature of the procedure complicates its scale-up to higher-throughput experimental setups.

However, chip technology simplifies the study of interactions. The ability to control the flow of chemicals, nutrients, and molecules or microbes of interest, facilitates straightforward co-culture experiments that enables insight into physiological and pathophysiological responses of tissues or organs.

Biotechnology enterprises such as MIMETAS develop groundbreaking organ-on-a-chip tissue models that will revolutionize the way we treat disease. As Arya Lekshmi Nair, an Early-Stage Researcher working at Mimetas as part of a Marie Curie fellowship, explains. “I’ve loved this technology ever since I first discovered it and I think it has many powerful applications; spanning drug discovery and

development, as well as disease-modelling. Since organ-on-a-chip technology has the potential to recapitulate complex tissue architecture and functionalities of the human body, it can be used to predict how we respond and react to drugs in a much more efficient way compared to other available models. This could potentially save a lot of time, money, resources, as well as offer better predictability."

Nair is currently developing in vitro models for the blood-brain barrier and neurovascular unit to study neuro inflammation in the context of CNS disorders such as stroke, and multiple sclerosis.

The Butterfly Effect

Despite their overwhelming potential to transform the way we study organs and their interactions, there are some limitations to their current applicability in research.

The butterfly effect describes the compounding impact of small changes. Along the same vein, researchers have experienced how seemingly small, insignificant changes to protocols and reagents can result in massive inter-lab variability when working with organ-on-a-chip platforms. The slight differences in reagents, matrix gels, and passaging techniques, for example, can amount to massive variations between labs.

These variations can be further exacerbated by variation in the reagents. When working at the molecular level, even small variations can have a significant effect on the outcome of an experiment. Elaborating on reagent-related challenges in research, Nair explained: "We spend a lot of time developing protocols, identifying components that work the best and then sometimes, it can happen that they're not available anymore. And, consequently, you have to start optimizing everything all over again. This can take a lot of time, effort, and a lot of money. Utilizing a platform such as the OrganoPlate , which has an automated setup and multiple chips allowing for many co-cultures to be created in parallel, can help standardize a protocol and strengthen reproducibility."

MIMETAS rely on high quality reagents to develop these models. One of the fundamental reagents needed in organ-on-a-chip technology is consistent extracellular matrix (ECM). Nair revealed, "The ECM of choice at MIMETAS is Cultrex Basement Membrane Extract (BME) from Bio-Techne. It's routinely used for a lot of our organ models in-house. It works really well for us, it's convenient to use, and there's ease of handling. I've been using it for two years and it's been working well."

Radhika Menon, a MIMETAS Scientist overseeing the company's iPSC research, is currently testing Bio-Techne's newly launched ExCellerate iPSC Expansion Medium with her team. She is enthusiastic about their results so far; "Based on preliminary observations, the ExCellerate iPSC Medium works well in our hands. The tested iPSC lines show compact, homogenous morphology and are less prone to spontaneous differentiation. The fact that it is animal-component free and robust makes it a promising candidate for the translational research we do at MIMETAS."

Ready. Set. Go!

Researchers getting started with organ-on-a-chip research may face substantial upfront time and investment. For example, it is notoriously difficult to consistently generate iPSC derived organoids and the process can take months.

MIMETAS are answering the calls of scientists, by developing innovative, easy-to-use, cost-effective platforms. Last year, they launched the OrganoReady® line, removing many of the barriers to scientists wishing to embark on organ-on-a-chip experiments. "The OrganoReady product is basically ready-to-go 3D tissue models. It's an optimized 3D biological model in an assay-ready format, meaning customers can get started with their experiments right away. There are a number of formats available but we also collaborate with researchers to develop novel, custom models." Nair explained.

She continued "And for those scientists that want to develop their own model, we offer an OrganoStart Pro package that contains everything you need to get started with organ-on-a-chip, including e-learning and consultancy hours to ensure success. Additionally, users can depend on a variety of commercially available organ-on-a-chip platforms to meet their specific needs. For instance, the MIMETAS OrganoPlate features a standard microtiter plate format comprising 40 to 96 chips, which enables high-throughput capabilities and cost-efficiency.

Collaboration is Key

Collaborative efforts between multiple sectors will enable the continued expansion and adoption of organ-on-a-chip technology.

Nair explains "Collaborations are fundamental for organ-on-a-chip research to move forward. Because organ-on-a-chip technology is complex, you need expertise from a variety of fields. MIMETAS is a leader in developing organ and disease models and collaborating with pharma will drive forward the adoption of organ-on-a-chip technology in drug discovery and development." For instance, the company recently entered into a collaboration with Roche to characterize novel compounds in inflammatory bowel disease (IBD) and hepatitis B virus infections (HBV).

"This exciting collaboration enables our research and early development group to apply state-of-the-art organ-on-a-chip technology in the modeling of IBD and HBV. These models have the potential to improve our understanding of disease biology and transform our drug discovery process," said James Sabry, Global Head, Roche Pharma Partnering.

Suzan Commandeur, Biomaterials Manager at MIMETAS, adds "In addition to pharma and academia, we have many collaborations with suppliers of vital equipment and biomaterials. Our active collaboration with Bio-Techne helps us in selecting relevant extracellular matrices and reagents, and ensures reliable and continued access to such materials, which is critical to supplying our customers with consistent products and services."

Looking to the Future

As a rapidly developing technology, with a seemingly limitless range of application, it's no wonder organ-on-a-chip technology is drumming up so much excitement. Year on year, we see an increasing number of organs going on chips and in turn, greater opportunity to study even more diseases.

Emulating human biology is the ultimate goal of organ-on-a-chip technology. By interconnecting different organ models to resemble the human body, researchers are developing a human-on-a-chip. Nair explained "It would provide much greater insights into pharmacokinetics and pharmacodynamics of drugs to understand how the human body [not just an organ] responds to drugs. For instance, you could look at how a drug is absorbed by the gut, then metabolized by the liver, and then how different molecules are excreted by the kidneys. In addition, you may want to see how drug molecules are transformed by different organs and then investigate if they have toxic effects on other organs, such as the heart or brain. You could have a whole human platform on a tiny microfluidic chip."

She elaborated "Organ-on-a-chip technology has great potential in the market, particularly in drug discovery and development. 3D tissue culture such as organ-on-a-chip is one of the most promising ways to model and understand disease and it could be a crucial aspect for personalizing medicine. Since we're all individuals with unique biology, our bodies can react or respond differently to drugs. By using organ-on-a-chip technology, we can accurately recreate a tumor microenvironment, for example, and speed up drug testing so medical experts can then tailor-make therapies for patients based on their individual needs and specificity. For instance, we can take stem cells from patients, reprogram these cells to cells of interest, and culture them in a high-throughput platform like the OrganoPlate to create a functional organ model and use it for developing personalized drugs for patients based on their individual needs."

Commandeur adds "Organ-on-a-chip models are fully geared towards human biology, mostly using patient cells and tissues as starting materials, resulting in highly relevant human organ models that reflect human tissues and human diseases. This technology, therefore, offers a meaningful alternative to animal testing in pre-clinical drug development, which has interesting ethical and economic advantages."

Meeting Demands

As organ-on-a-chip research becomes more accessible to labs worldwide, the demand for consistent, reliable reagents will only increase. Yas Heidari, Product Manager of Protein & Cell Biology for Bio-Techne Europe shares how Bio-Techne are addressing the needs of organ-on-a-chip research scientists. "At Bio-Techne we try to work with organ-on-a-chip scientists to eliminate variation in their systems and strive to develop the most consistent reagents on the market in order to help advance these novel technologies."

She elaborated, "We hear from researchers that standardization and use of high-grade matrix, cytokines, media and related reagents are key, and we strive to develop and manufacture to the highest possible specification each time."

Touching upon the future of organ-on-a-chip, Heidari explains "We see organ-on-a-chip as an exciting, evolving technology - especially for studying interactions within multiple systems or cells such as the immune system - and one that will surely develop with greater clinical applications in the future for the benefit of patients. It's an area that we're committed to supporting and we hope to be a key player in helping to drive forward its progress and development."

Related Content

Organoid and 3D culture resource page – Explore in-house validated recipes, blogs, webinars, protocols, videos and more! As well as a very handy organoid recipe selector.

Evolution of model systems for toxicology, drug screening, and disease modelling – Discover more about the history, current state and future use of 2D and 3D model systems for toxicology, drug screening, and disease modelling in our exclusive eBook.

Cultrex™ Ultimatrix scientific poster – Find out how Cultrex UltiMatrix BME can accelerate your 3D and 2D model development.

Step-by-Step video for working with Cultrex Basement Membrane Extract (BME) – Get to grips with the best practices and protocols.

Mimetas' OrganoReady® – Ready-to-use 3D tissue models for drug exposure, transport, and permeability studies.

Mimetas' OrganoStart Pro package – Getting started with organ-on-a-chip models and assessing barrier integrity of 3D tissue models.

Adoption of organ-on-a-chip platforms by the pharmaceutical industry – Nature Reviews 2021

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