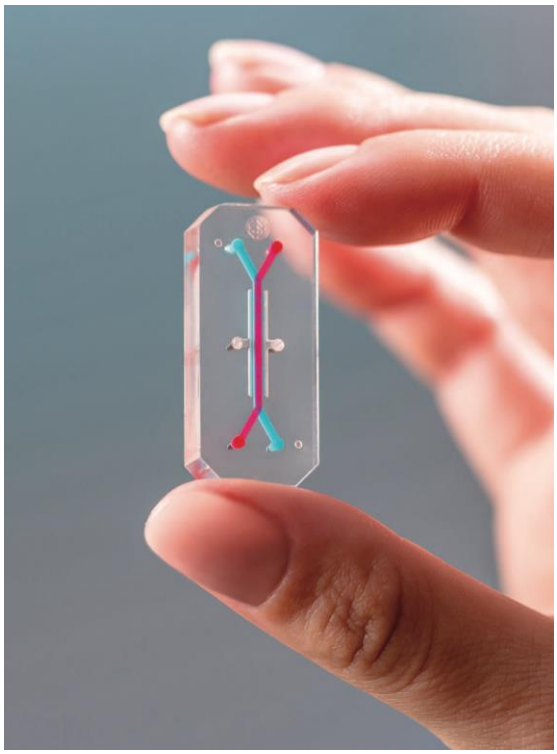
Why is there a need for better experimental models for medicines discovery and development?

If there was an engineering competition, mother nature would likely win. She is an extraordinary engineer and has created exquisite, yet complex structures that communicate with one another to deliver the functionality we know as life. But this complex biology makes it very difficult to study the potential impact of medicines (good or bad) on structure and function in experiments outside of the human body.

Scientists until recently have had two main choices to study potential effects of medicines, firstly using cells in dishes (cell culture) or secondly using animal models. However, cells in dishes are unable to experience the dynamic nature of the human body as they are bathed in the same fluid for 24 hours or more and are unable to communicate easily with other cells around them. They also lack essential cues that drive their function. In contrast, animal models do exhibit a dynamic nature and provide essential cues, but their physiology has frequently shown significant differences compared to humans. Together the lack of human-relevant biology in these two approaches contribute to the high attrition rates (>90%) experienced in the pharmaceutical industry. Improved model systems that can offer greater translational value to human health and disease are therefore needed. This is where microphysiological systems (MPS) – sometimes referred to as an organ-on-a chip (illustrated below) - have a unique opportunity to bridge the gap between the preclinical and clinical phases of medicines discovery and development.



Organ on a Chip - Emulate S1

What are microphysiological systems?

MPS include any advanced cellular model that combines engineering with cell biology to exhibit 3D architecture, multicellular interactions, tissue-tissue interfaces or organ-level mechanical cues and in some but not all, dynamic fluid flow.

Each of these components have been shown to help recreate the unique microenvironment cells are exposed to within the human body and the premise is such that these cells once outside the human body will behave as though they are still within it. Consequently, it is hoped that the translation of data from MPS to the clinical setting will improve, the lengthy process of medicines discovery and development will be reduced, and the probability of success increased.

Notable examples of MPS include:

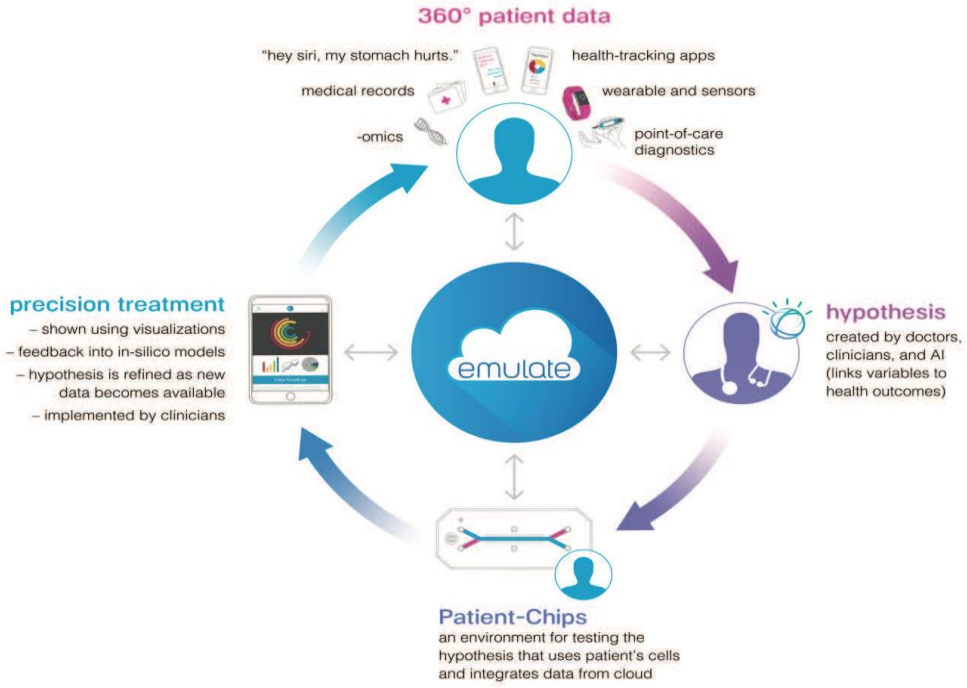
- A human Lung-Chip that applies a mechanical strain to the cells to recreate breathing mechanics (Huh et al., 2010)
- Interconnection of organs to model aspects of organ-to-organ communication such as the glucose-insulin axis (Bauer et al., 2017)
- A Liver-Chip that can recreate species-specific toxicities (Jang et al., 2019).

In addition, the fluidic conditions enable MPS to emulate clinical pharmacokinetic profiles, with the prospect of a greater understanding of the relationship between pharmacodynamics and pharmacokinetics (McAleer et al., 2019; Chou et al., 2020).

How are microphysiological systems being used in the pharmaceutical industry?

Despite being at an early stage in its genesis, MPS has gained significant attention within the pharmaceutical industry as a potential tool to address some key challenges it faces such as understanding the lack of efficacy that frequently occurs in Phase II clinical trials, or the unacceptable side effects found preclinically or in clinical trials. Through a greater understanding of mechanism of action, it is widely anticipated that MPS will make a positive impact on the industry by reducing failures and thereby reducing cost. There is also considerable collaboration amongst academics, small biotech companies, pharmaceutical companies and regulatory authorities to refine the developing MPS to meet the need and quality standards within a pharmaceutical setting, helping scientists realise the true value of this technology (Marx et al., 2016).

Preclinical toxicology applications have to date seen the most interest. One example is the human blood vessel-chip which, when used, was able to recreate the thrombotic toxicities of a therapeutic monoclonal antibody that led to its failure within human clinical trials (Barrile et al., 2018). Personalised treatments that address inter-individual differences in biology and response to a medicine are often seen as the holy grail within the pharmaceutical industry and real advances have been made towards this with the use of rectal organoids to develop therapeutics for cystic fibrosis (Berkers et al., 2019). As the pharmaceutical industry focuses increasingly on human-specific targets and makes use of engineered molecules that do not cross-react with animals, it is envisaged human MPS technologies will play a key role in the future of preclinical safety and efficacy testing – as shown below.



What are the challenges in the use of microphysiological systems?

There are still challenges to be overcome with this technology. Many of these systems are developed using the silicone polymer polydimethylsiloxane (PDMS). This polymer is preferred because it is gas permeable and also transparent which enables imaging, but absorption or adsorption of chemicals or pharmaceuticals can occur making it difficult to accurately quantify overall cell exposure. In addition, because this is still a developing field, there are multiple fluidic platforms and approaches. This results in a lack of standardisation and can make inter-laboratory comparisons tricky. Finally, broader acceptance and adoption of the technology will be driven by regulatory acceptance, and there remains extensive debate regarding the criteria that need to be satisfied to achieve this and importantly who will pay for this work to be done.

Can microphysiological systems be used in other industries such as cosmetics, agriculture, chemicals and food?

It is not only the pharmaceutical industry that could benefit from MPS. Indeed, many other industries are engaged in active dialogue regarding the use of non-animal approaches (https://www.thebts.org/wp-content/uploads/2020/05/InVitro-Approaches-for-Toxicity-Testing-v1-May-2020.pdf), especially in the realms of toxicity assessment, chemical safety, and medical countermeasures development. The contribution of MPS here relates to greater understanding of mechanisms of action and describing and quantifying key events that lead to toxicity. For these industries, models of key organs such as the skin, intestine, liver and kidney are thought to be of particular importance as well as models of the brain, lung and placenta which can help to inform better risk assessment, including any potential risks to unborn children. The exploration of such systems in these industries continues, but often is hampered by the ability to apply and measure the tiny amounts of chemicals that are of interest. Furthermore, data demonstrating long-term viability of the models, both at a functional and genomic level, are required to use these models to assess chronic systemic toxicity.

Summary

Although still a young, developing field, MPS will increasingly contribute to the pharmaceutical and other industries in the coming years. The potential of this technology to recreate the unique cellular microenvironments experienced by cells, offers the promise that it will be better able to translate data generated in a preclinical laboratory to the effects seen in subsequent clinical trials. Further development of these models is undoubtedly required, but emerging literature suggests that they can live up to their promise.

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