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Editorial

Beyond PDMS and Membranes: New Materials for Organ-on-a-Chip Devices

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The field of organ-on-a-chip engineering is focused on dynamically controlling the microphysiological environments that the cells are surrounded by in order to produce functional human or animal tissue counterparts that enable measurements of key physiological functions of native organs. This approach relies on engineered, microfabricated devices to drive the establishment of 3D tissues starting from either cell lines, primary cells, or human stem cells that often additionally feature integrated sensors to measure critical physiological properties (e.g., contractility).[1] Vasculature is often incorporated into these devices as well as the ability to mechanically and electrically stimulate embedded tissues.[2]

The recent decade has witnessed an explosive growth to this field, with examples of essentially all human organs reproduced on-a-chip including: heart,[3] tumor,[4] eyes,[5] lymph nodes,[6] etc. Concurrently, there was rapid growth in the number and size of the companies commercializing organ-on-a-chip devices (∼30 companies in 7 years), fueled by their promise to transform drug discovery.[7] There are, however, still no approved drugs on the market as a result of organ-on-a-chip efforts as the field is only ∼10 years old, and it takes ∼15 years for an approval of a single drug.[8] The initial efforts largely focused on organs affected by drug toxicity such as the heart,[3] liver[9,10] and kidney,[11] with cardio and nephrotoxicity still remaining the leading causes for withdrawal of already approved drugs.[12] Recent efforts focus, for instance, on the development of lymphoid tissues and the integration of immune cells because of their promise to offer venues to study immune therapies for lethal diseases such as cancer.[13]

The one-size-fits all paradigm, where a drug is tested in a large number of patients regardless of their genetic background, is thought to be an important contributor to a lengthy drug approval process and limited efficacy post approval.[8] Initially, the rapid expansion of the field was driven by the promise of organ-on-a-chip devices to act as alternatives to animal testing in evaluation of drug safety. In recent years, however, the development of specific models of both monogenic and polygenic human diseases that can be used to discover new druggable targets became increasingly a focus. Although the first organs-on-a-chip almost exclusively relied on the use of human cell lines, profound and rapid advances in induced pluripotent stem cell (iPSC) differentiation have enabled the derivation of essentially unlimited amounts of patient-specific cells, laying the foundation for personalized organ-on-a-chip models.[14] Organ-on-a-chip engineering allowed for development of human models of diseases as diverse as cardiac fibrosis,[15] SARS-CoV-2 infection,[16] and rheumatoid arthritis.[17]

Importantly, organ-on-a-chip engineering shares many similarities with the field of organoids in terms of the ultimate utility and the promise of the technology; however, it offers additional advantages in terms of improved environmental control, reproducibility, and the ability to incorporate sensors, thus motivating the integration of the two technologies as described in recent studies.[5a,18]

Polydimethylsiloxane (PDMS) was the material of choice in majority of the pioneering work and still remains one of the most widely used materials for device fabrication. This comes from the fact that PDMS has several key properties that are highly advantageous for soft lithography and cell culture, including relatively low cost, optical transparency, high elasticity, excellent oxygen permeability, and long-term biocompatibility. It is relatively straightforward to fabricate flexible membranes, microfluidic channels and topographically patterned surfaces using PDMS to easily control cell responses in organ-on-a-chip devices. However, PDMS also features several drawbacks that are fueling the demand for new alternative materials, including absorption of small hydrophobic molecules from culture media components and tested drugs.[19] This leads to the danger of misinterpretation of drug toxicity and efficacy and of nondetection of secreted factors.

In addition, it is difficult to make PDMS-based devices at industrially relevant scale since the molding technique used in PDMS device fabrication has limited scalability. Similarly, scalable approaches to incorporate in-line sensors to automate physiological readouts in organ-on-a-chip devices are required. Current organ-on-a-chip devices can be thought of as artisanal devices, where each one is made by hand by a skilled researcher, at a production throughput of several devices per day. This approach cannot meet the demand of the growing industry. It is required to automate the production and sensing, enabling the manufacture of thousands of devices per day, while improving consistency and increasing the number of tissues grown per device. For this goal to be realized, it is necessary to employ more scalable technologies such as 3D

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printing and injection molding strategies. Additionally, the utilization of alternative materials such as thermoplastics must be implemented and fabrication processes adopted.[20,21] Recent work also describes the use of polymeric materials as embedded sensors in organ-on-a-chip devices. For example, through the wire deflection in the Biowire II heart-on-a-chip platform[3] and cantilever deflection in the InVADE platform,[2] it is possible to characterize the contraction force of heart tissue and facilitate noninvasive temporal assessment of drug effects. Interestingly, the same polymer serves as an anchor point for the tissue growth and a noninvasive force sensor. The Young's modulus of the polymer can be adjusted to match that of the native tissue by tuning synthesis conditions.[22]

In this special issue, we bring you a number of papers that discuss the use of new materials for the fabrication of organ-on-a-chip devices and development of new systems with integrated and improved analytical capabilities.

We open the issue with a review paper by Kang et al. on the use of alginate as an alternative material to PDMS for fabrication of microsystems.[23] Campbell et al. then provide a review of other alternative materials such as thermoplastics, ceramics, and resin.[24] Fuchs et al. highlight the challenges related to incorporating new inline sensors into organ-on-a-chip devices for automated readout of cell responses and metabolism.[25] We close the review section of the special issue with a manuscript by Hayward et al. describing the use of organ-on-a-chip systems to model pathological tissue morphogenesis in fibrosis and cancer.[26]

In the research papers section, Hosic et al. report a new approach to rapidly prototype organs-on-chips via laser cutting and assembly with double-sided adhesives, a technique that could be implemented by many laboratories using relatively inexpensive equipment.[27] Lin et al. describe a scalable system for vascularization of liver spheroids in a 384-well platform.[28] To replace PDMS in devices that mimic barrier function, Arik et al. describe a viable new approach to construct membranes from collagen type I.[29] Furthermore, Zamprogno et al. elaborate on the development of collagen/elastin membranes and assessment of their mechanical properties.[30] Importantly, electrospun membranes based on poly-L-lactide can also be used in lieu of PDMS and incorporated into low absorption thermoplastic devices as described by Chuchuy et al.[31] The use of a free-standing extracellular matrix is described to engineer a lymphatic vessel model situated in a plastic well-plate like platform.[32] Finally, new multimaterial processing approaches with 3D printing are described by Kundu et al. to develop 3D microelectrode arrays for interfacing with a peripheral nerve-on-a-chip.[33]

Importantly, if PDMS cannot be avoided, its surface properties can be improved by covalent immobilization of various molecules. Guo et al. describe iPSC-derived micro heart muscles cultivated on surface modified PDMS of various stiffness to investigate the effects of mechanical loading on cardiac physiology.[34] Lastly, in an effort to facilitate data collection and analysis from the sensors, Vunjak-Novakovic et al. provide a study focused on machine learning techniques to classify healthy and diseased cardiomyocytes by contractility profile.[35]

We hope that this special issue will provide you with an exciting overview of activities currently underway in the field of organ-on-a-chip engineering and that you will enjoy reading the contributions.

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Notes

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