ACS APPLIED BIO MATERIALS

www.acsabm.org Review

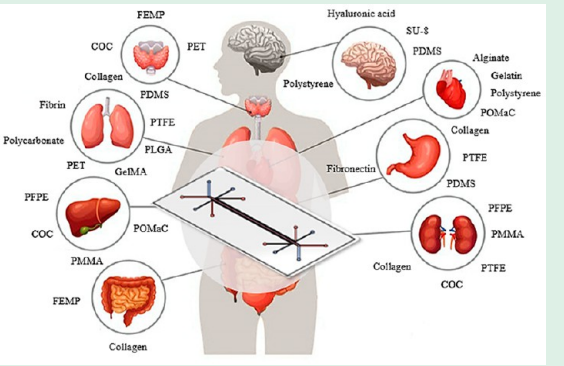
Advances in Organ-on-a-Chip Materials and Devices

Bishal Kumar Nahak,[∇] Anshuman Mishra,[∇] Subham Preetam, and Ashutosh Tiwari*

Cite This: *ACS Appl. Bio Mater.* 2022, 5, 3576−3607 Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: The organ-on-a-chip (OoC) paves a way for biomedical applications ranging from preclinical to clinical translational precision. The current trends in the in vitro modeling is to reduce the complexity of human organ anatomy to the fundamental cellular microanatomy as an alternative of recreating the entire cell milieu that allows systematic analysis of medicinal absorption of compounds, metabolism, and mechanistic investigation. The OoC devices accurately represent human physiology in vitro; however, it is vital to choose the correct chip materials. The potential chip materials include inorganic, elastomeric, thermoplastic, natural, and hybrid materials. Despite the fact that polydimethylsiloxane is the most commonly utilized polymer for OoC and microphysiological systems, substitute materials have been continuously developed for its advanced applications. The evaluation of human physiological status can help to demonstrate using noninvasive OoC materials in real-time procedures. Therefore, this Review examines the materials used for fabricating OoC devices, the application-oriented pros and cons, possessions for device fabrication and biocompatibility, as well as their potential for downstream biochemical surface alteration and commercialization. The convergence of emerging approaches, such as advanced materials, artificial intelligence, machine learning, three-dimensional (3D) bioprinting, and genomics, have the potential to perform OoC technology at next generation. Thus, OoC technologies provide easy and precise methodologies in cost-effective clinical monitoring and treatment using standardized protocols, at even personalized levels. Because of the inherent utilization of the integrated materials, employing the OoC with biomedical approaches will be a promising methodology in the healthcare industry.



KEYWORDS: *Advanced materials, Biomedical engineering, Biodevices, Organ-on-a-chip, Microfluidics*

1. INTRODUCTION

Organ-on-a-chip (OoC) materials represent an emerging research field that has recently attracted substantial attention, because of their conceivable role in the development of microfluidic systems for physiological monitoring, precise diagnosis, drug discovery, etc. The recent research demonstrates a portable fluorescence resonance energy transfer (FRET)-based Pb-biosensor for environmental applications and microfluidic technology-based optical and electrochemical sensors for disease detection.[1−3] The detection of pathogenic bacteria, with diversified biosensors (such as electrochemical, optical, microfluidic, etc.) and signal amplification technologies (such as enzyme catalysis, nucleic acid chain reaction, biotin−streptavidin, click chemistry, cascade reaction, nanomaterials, etc.) were important aspects that have been researched recently.[4] Most importantly, the design of aptamer sensors and mechanisms is based on three signal transduction modes, i.e., electrochemistry, colorimetry, and fluorescence, which are helpful in tumor theranostics and post-treatment monitoring.[5]

Furthermore, cellulose-based flexible bioelectronic devices and their application in biomedicals have been emerged as climate neutral approach.[6] The advancements of materials play a significant role in the diagnosis, treatment, and disease prevention.[51] The state-of-the-art multifunctional biomaterials, such as smart polymers, nanostructures, and interfaces, along with biodevices, incorporate therapeutic, molecular targeting, and diagnostic imaging capabilities.[51] The emerging biomedical research on biosensor and bioelectronics has conceived ooportunities for next-generation healthcare devices.[316,318,328] The main goal of OoC devices is to work as a holistic platform of partial human organs for physiological monitoring of consequences and, subsequently, drug interactions. It is a physiological organ mimetic materials system that operates between the tissue interfaces and biosensing-based microfluidic chips in the microenvironment of the human body. The OoC device is informative and is involved in diverse fields, such as medicine, biology, physics, chemistry, and engineering

Received: January 16, 2022
Accepted: June 21, 2022
Published: July 15, 2022

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

approaches, to deliver the fundamental and translational applications.

The recent development of advanced materials field can outperform physicochemical-based precise activity and is guided through techniques to impart huge efficiency and transforming the healthcare field. Intelligent materials reveal diverse functionalities and, thus, open the door for specific experiments, functional therapeutics, quality interface synthesis, bioengineering devices, and intelligence identification for translational healthcare research.[303] Prior to the clinical evaluation, considerable preclinical research and verification of prospective medicinal substances is highly essential. This procedure is time-consuming, very expensive, and has low efficacy. Some of the medicines have demonstrated preclinical efficacy; however, in the clinic, they have failed and sometimes caused fatalities. For instance, encainide and flecainide, even though Class One antiarrhythmic agents, looked very promising in preclinical studies in 1980 for suppressing abnormal cardiac pacing, and yet a later cardiac arrhythmia suppression trial revealed the possibility that the threat of catastrophic heart attack was coparively more than twice in people having encainide and flecainide.[1,7] Over the course of time, the amount of investments made for pharmaceutical research and development has surged to over 2.5 billion dollars.[8] However, over the last few decades, the number of medicines approved by the U.S. Food and Drug Administration (FDA) has decreased.[9] The lack of physiologically realistic preclinical models that anticipate human responses to novel drugs has been one of the key factors that lead to the high expensive and low efficacy of standard drug research. Unfortunately, the use of animal models has ethical issues, performance issues, and cost effectiveness problems.[10] Thus, better human tissue models for drug screening in preclinical studies are required in order to enhance the speed and success rate of clinical trials.

To address this issue, microfluidic-chip-based devices, or so-called organ-on-a-chip (OoC) platforms, can be employed. These devices imitate in vitro physiological functions at the organ level through a seamless integration of 3D biomimetic-tissue structures and dynamic microenvironment into chip-based devices. Some of these commonly used OoCs include lung-on-a-chip,[11,12] brain-on-a-chip,[13,14] heart-on-a-chip,[15,16] kidney-on-a-chip,[17,18] liver-on-a-chip,[19,20] and gut-on-a-chip.[21] Based on particular applications such as lab-on-a-chip, pathogen detection, electrophoresis, DNA analysis, etc. the structure of the microchannels in a system should be modified to suit the criteria in order to achieve the required result. An important element of these OoC devices is that the materials that comprise the device determine how well the functions can be implemented. A variety of advanced materials have been explored in microfluidics over the past two decades in order to advance its physiological characteristics.[22] The design of OoC-based microfluidic devices that has led to the incorporation of novel materials and new methodologies for integrating and arranging existing materials has produced an abundance of diverse OoC-based microfluidic systems. The most frequent substance for laboratory study was polydimethylsiloxane (PDMS). However, there are also many limitations to PDMS that encourage the move to alternate OoC materials. Some new materials, including hydrogel, paper, and hybrids, are being created to imitate drug interactions in vivo.

Moreover, although there is much good literature that is focused on specific organ development technology, there is not enough that can provide an overview or direction for developing OoC devices, although choosing the proper material is the first step of fabrication. The most recent advances in intelligent nanomaterials are helpful in the shaping and development of the bioelectronics field.[304,305,318,323−325] It is imperative to understanding sustainable chemical and technology reproductions for emerging healthier healthcare management.[326,327] The paper-, cellulose-, and graphene-based materials were involved in the RNA sensing, antigenic determination and immune response detection with sustainable application.

The initiation of evidence-based personalized practice in clinical research plays a key role in the healthcare industry. Clinical complications related to human adaptation, drug response, and emerging pathogens for the correct clinical decision, which is further dependent on a better understanding of the mechanism with standardized and precision-based clinical protocols. This is a literature review that includes important findings, conceptual analysis, and thematic overview. This Review provides a systematic examination of recent literature and describes a wide range of OoC materials and methods at various levels of completeness and comprehensiveness. This Review defines bioinspired OoC technology, materials utilization, device fabrication, preparation of interfaces, bioassays mechanism, data validation, and translational potential to understand the trending research and development. Most importantly, policy and adoption of OoC protocols for clinical research will reduce the burden of clinical trials by removing harmful complications and assisting to develop commercial clinical research products rapidly. In this Review, OoC materials and devices have been systematically illustrated to understand the developments of biomedical microfluidics. The first section discusses the evolution of different materials and design parameters for the fabrication of OoC devices. The second part addresses various materials ranging from elastomeric, thermoplastic, inorganic, and synthetic materials, with regard to their properties for organ remaking applications. The last part summarizes the commercialization of OoC devices and their future outlook for use as advance materials, such as bioinspired design, which have the potential to become a next generation of microfluidic devices.

2. ORGAN-ON-A-CHIP DEVICES

Microfluidic devices gained prominence in the late 1990s with the emergence of the polymer material poly(dimethylsiloxane) (PDMS), which is a soft, optically transparent elastomer that is mostly employed in small-scale bioapplications. Andre Kleber and colleagues used a spherical glass substrate to construct a ventricular myocardium in vitro via a patterned growth of cells.[23] This established the very first physiological model for explaining conduction blockage in the heart. In 1998, George and co-workers reported a method for drug screening and clinical diagnostics.[24] The system enables simultaneous execution of several trials, which minimizes variability and creates a physiologically more realistic tissue culture chamber.[25] Since then microfluidic systems have been designed to solve real-world problems mimicking the human organ level functioning such as the liver,[26] lungs,[27] intestine,[28] and kidney-on-a-chip. In 2010, Donald E. Ingber reported a microfluidic device to demonstrate organ level functioning of human lungs using a thin flexible PDMS membrane.[27] Later in the year, Wang reported on poly(ester amide), which is a

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

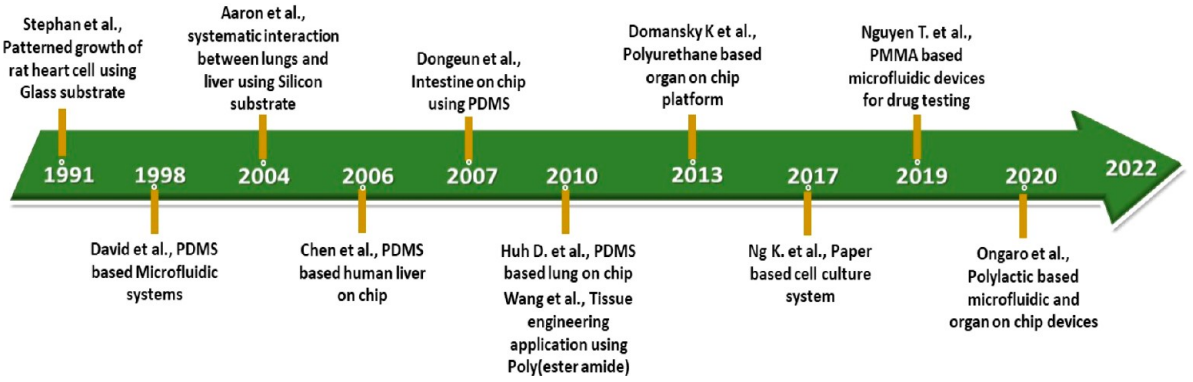


Figure 1. Key milestones of organ-on-a-chip (OoC) materials innovations during the period 1991−2021.

biodegradable elastomeric polymer used for microfluidic scaffolds formation.[29]

Polyurethanes are flexible, biocompatible, have the ability to be molded, and are resistant toward the absorption of small hydrophobic molecules; these features make it a more suitable and promising material that can replace traditional PDMS-based devices.[30] Other than polymer materials, paper has attracted consideration as a substrate for various biomedical claims. Because of its cost efficiency, eco-friendliness, biocompatibility, and large-scale fabrication, these can applied in studying various in vitro disease models, drug screening, and cell cryopreservation applications.[31,32] Nguyen et al. reported a simple and reliable process for developing lung adenocarcinoma cells cultured on PMMA-bonded PETE chips.[32] Recently, Ongaro et al. demonstrated polylactic-acid-based OoC devices that can overcome the shortcoming of PDMS.[33] Figure 1 shows the evolution of different microfluidic OoC devices using various chip materials from the last 30 years.

2.1. OoC Device Fabrication. The fabrication methods, techniques, and design are primarily utilized for the performance of OoC devices.[34,35,44] An ideal chip material must be biocompatible, since it comes direct contact with living cells; it also should not cause any inflammation or any allergic symptoms when comes in contact with tissue. Also, they must have good mechanical strength; such characteristics improve the production of tissue structures with high mechanical strength and robustness and maintain tissue matching mechanics.[35] These factors become more important when developing scaffolds, so that they will not collapse toward regular wear-tear applications. Moreover, the material should be easily sterilizable to prevent infection. For instance, for bone tissue-regeneration, there is seek for biomaterials that can provide vascularization in developed tissue. While choosing material to be considered for mechanical applications, it becomes essential to check some of these crucial parameters: Young's modulus, ductility, durability, elasticity, and fatigue. Importantly, existing knowledge for the best design, fabrication requirements, and challenges is imperative for understanding high-performance OoC devices.[43] With regard to designing microphysiological systems, the choice of materials is highly dependent on the targeted organ part. Since the cell structure and properties vary for different organs of human body, and in order to mimic them, a unique choice of biomaterial and design is required.

2.1.1. OoC Design Principles. Once all the ADME parameters are identified, it can be further implemented to the model proposed by the Michael Shuler group. Using the previously developed design criteria, the group devised a simple set of design requirements that could be utilized to construct an OoC platform. A holistic model describes absorption and metabolism to study the effect of chemicals as an ADME tool.[45] Relevant tissue study and drug discovery occurred based on ADME optimization.[46] Importantly, ADME parameters can be used to calculate parameters relevant to the OoC platform. These separate criteria governed the development of the equations. They concluded that steady-state nutrient concentrations in the OoC are similar to those in the human body. Also, the desired drug concentration is similar to that in the human body. The final part states that inside each organ, the unbound drug concentration released in the body in a time-dependent manner should be equivalent to that found in the organ. The basic parametric equation was further condensed into a set of five equations that deal with OoC development; three of them concern general OoC design, and two are used for targeted drugs. Table 1 presents the equations and parameter definitions in an abbreviated fashion.[38]

Table 1. Parametric Criteria for Organ-on-a-Chip Developments[a]

parametric criteria	parameters to be find	known parameters	description
$Ø^{chip} = Ø^{human}$	$Ø^{chip}$	$Ø^{human}$	cardiac output from targeted organ
	Q^{chip}	Q^{human}	blood-flow rate in targeted organ
$\frac{Q^{chip}}{R^{chip}{}_n{}^{chip}} = \frac{Q^{human}}{R^{human}{}_n{}^{human}}$	R^{chip} n^{chip}	R^{human} n^{human}	intrinsic-reaction rate in the tissue cells in targeted organ
$\tau^{chip}_{organ} = \tau^{human}_{organ}$	τ^{chip}_{organ}	τ^{human}_{organ}	residence time of each organ
$\tau^{chip}_{body} = \tau^{human}_{body}$	τ^{chip}_{body}	τ^{human}_{body}	residence time of the body
$\frac{K^{chip}}{B:P^{chip}} = \frac{K^{human}}{B:P^{human}}$	K^{chip} $B:P^{chip}$	K^{human} $B:P^{human}$	drug partitioning
$F^{chip} = f^{human}$	f^{chip}	f^{human}	unbound fraction of the drug

[a]Equations were taken from ref 38.

2.2. OoC Device Parameters. The OoC model is often employed as a human replica model for validating mathematical physiologically based pharmacokinetic (PBPK) models. Furthermore, pharmacodynamic (PD) models can be coupled with PBPK models to accurately expect drug usefulness, dosing, and toxicity. Certain parameters that are involved in drug characteristics can be easily evaluated from

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

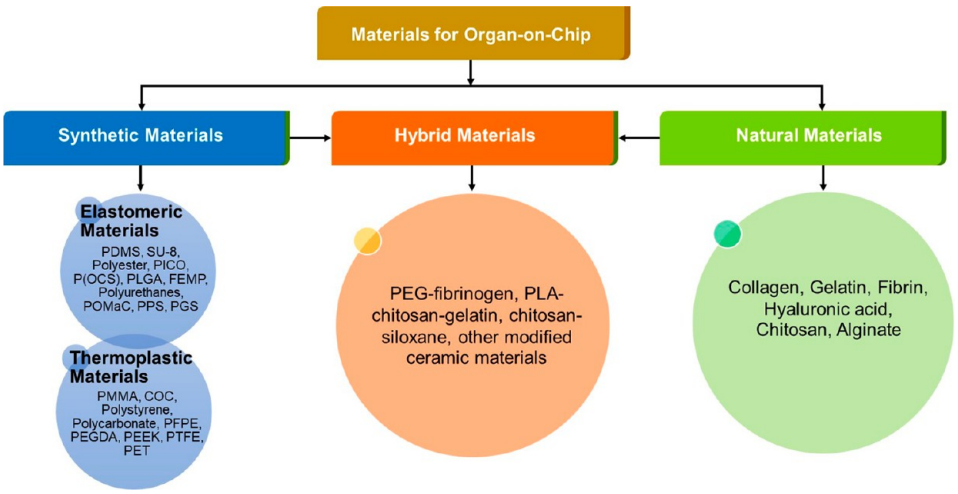


Figure 2. Classification of materials used for OoC developments.

drug studies that have been done previously, using a single-tissue construct. Once all the paramters are identified, they can be used in a PBPK model, which can be cross-verified with OoC devices containing various organs. Furthermore, PBPK models are additionally capable of examining spatial and temporal responses of an organ to a medication, and its interaction with other organs.

2.2.1. ADME Parameters. OoC models are generally used to determine the drug absorption, distribution, metabolism, and excretion (ADME) factors in human beings. To successfully complete OoC development, a variety of design parameters are significant. Features such as cardiac output (CO), blood flow rate (Q), number of cells (n), and the residence duration (τ) are among the metrics of widely accessible desired organ in the reported literature. In addition, there are certain other parameters that have a significant impact on designing a specific OoC-based platform. The parameters can be calculated from in vitro tests and consist of the distribution of a drug between various organs (K), the portion of a drug that is unused (f), the intrinsic reaction rate per cell and per drug concentration in tissue (R), the intrinsic clearance rate (C), and the blood-to-plasma distribution (B:P). Morover, techniques such as in-vitro-to-in-vivo extrapolation (IVIVE) can be utilized to validate the obtained experimental results with in vivo physiology.[36,37] Since these in vitro values represent the entire body, they can be used as a general approximation for in vivo measurements. This signifies that in vitro parameters can be used to represent the entire human physiology. The developing PBPK models become highly essential before designing an OoC device. The OoC model can be designed based on a single model molecule or with a mean of manifold ADME parameters.

(a) *Absorption*: It can occur through many physiological barriers, including the gastrointestinal tract, skin, and lungs. The solubility (S) and permeability (P) of a drug are assessed through individual OoC platforms, such as gut-on-a-chip, skin-on-a-chip, and lungs-on-a-chip, rather than using conventional cultures of human/animal cells or animal cadavers.[36−38]

(b) *Distribution*: After absorption, the drug is delivered to all of the body's various organs. Unused drug portions, the B:P ratio, and the drug distribution among the organs plays a vital role in this stage. Experimentally, the first two parameters can be measured using an OoC platform. Furthermore, the drug distribution coefficient is primarily dependent on the concentration of lipoproteins, especially that of lipoprotein complexes. Thus, it becomes easy to find these parameters once we have the proper molecular configuration of individual OoC.

(c) *Metabolism*: Here, the liver does play a primary role in metabolizing most of the drugs, although there may be some involvement of other organs in this process. In vitro, it is possible to calculate the intrinsic clearance rate of a drug for each hepatocyte or microsome. Using the IVIVE approach, these data can be extended to the liver-on-a-chip system.[39]

(d) *Excretion*: Renal or biliary excretion are the primary routes of excretion in the human body. Using the kidney-on-a-chip or renal proximal tubule-on-a-chip, we can calculate these values. The IVIVE method is used to extrapolate these in vivo total renal clearance values to the values seen in vivo.[40,47]

2.3. Common OoC Design. Understanding design from functionality, biomechatronic methodology as well as efficient guidelines can make new fabrication, theoretical, and experimental knowledge for device development.[41,42] It important to note that, similar to device rule, cell source, and culture media also play key roles in the development of new OoC devices. This also includes the combination of multiple OoC devices, or simply known as body-on-a-chip. A simple model by single section helps to investigate them implicitly. It is also results in a reduction in manufacturing costs and materials required. The final design parameters include controlling the flow rate and shear rates in the organ model. By adjusting the diameter of the tubes going to the tissue, the flow rate can be scaled and modified, and these values can be found the literature available. Once these comparisons have been completed, the OoC platform should be put through its paces and the outcomes compared to the PBPK platform. It is important to validate the OoC platform and continue to iterate the design to achieve a proper model.

3. OOC MATERIALS

The fundamental issue that remains as an obstacle to the development of OoC devices is the material utilized in chip production, as well as the weak enforcement of rules that regulate feasible commercial

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

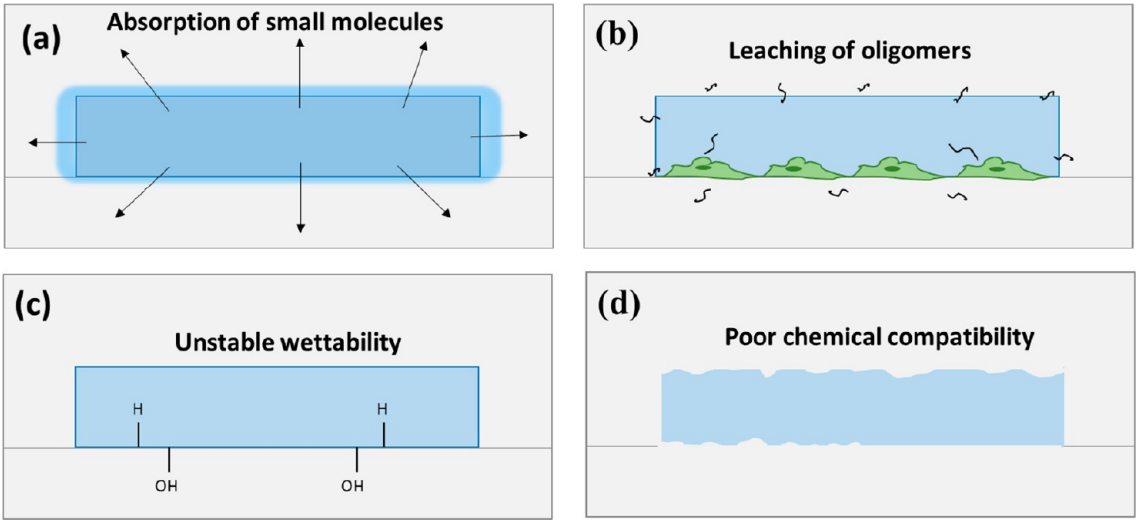


Figure 3. Disadvantages of PDMS-based microfluidic chips: (a) absorption of small hydrophobic molecules into bulk of PDMS, (b) leaching is caused by uncross-linked oligomers, (c) PDMS devices would be rendered hydrophilic by using oxygen plasma for further operation, and (d) the dissolution of PDMS in an organic solvent would cause swelling, which changes the cross-sectional area of the channel.

production of OoCs, similar to the well-established semiconductor sector.

3.1. Classification of OoC Materials. Polydimethylsiloxane (PDMS) is generally used to construct the majority of LOC and OoC devices utilizing soft lithography. Having advantageous properties such as simple fabrication, molding, elasticity, permeability, and biocompatibility activities, PDMS is an excellent rapid device with wide range of claims. Studies suggest that photo PDMS permits processing under normal ambient light and makes fabrication fast, simple, and cost-effective indisposable lab-on-a-chip applications. On the other hand, PDMS absorbs tiny molecules or other organic substances and medicines, limiting its applicability as an OoC material. Furthermore, despite its simplicity of PDMS manufacturing, it lacks industrial standards.[48,49] Several alternative natural and synthetic materials have recently been used in the creation of microfluidic/LOC/OoC devices to solve the shortcomings of PDMS. Furthermore, various hybrid materials have been introduced as a blend of synthetic and natural materials for the manufacture of microfluidic OoC devices with a wide range of properties; Figure 2 depicts a summary of these materials.[49]

Natural polymers do mainly exist in animals, plants, and microbial tissues in form of extracellular matrices (ECMs) or decellularized extracellular matrices (dECMs). These consist of protein materials such as collagen, elastin, keratin, and myosin; polysaccharides; glycoproteins; and proteoglycans.[49] These natural polymers are typically flexible and have good biocompatibility and gas permeability. Thus, they are highly suitable for drug delivery systems, tissue engineering, biosensor development, and organ-on-chip devices.[50,51] However, these natural polymers have few disadvantages. For example, these materials must be sterilized and purified before their use, which adds more complexity to the process. Also, the properties of these materials cannot be altered.

Synthetic biomaterials could solve some of limitations of naturally derived biomaterials. The physical and chemical properties of these materials seem to be more adjustable than natural materials, which is one of their key advantages. The strength and degradation rates of these materials can be modified based on particular applications. And these properties can be varied by changing the molecular weight, concentration, and cross-linking. Another favorable property of synthetic biomaterials is their reproducibility.[52,53] Furthermore, in case of natural materials, the batch-to-batch variability can be kept to a minimum by controlling the fabrication process.

3.1.1. Elastomeric Synthetic OoC Materials. Elastomeric polymer-based materials have had an essential role in the growth of organ-on-chip platforms and flexible microfluidic devices.[59−61] Compared to inorganic materials, elastomers have become a more renowned material in microchip development, because of the ease of fabrication and their low cost.[61] These are composed of cross-linked polymeric chains and are usually entangled; they can be easily stretched or compressed when an external force is applied, and gain its original shape when force released. Recently, the development of an elastomeric polymer-based microfluidic chip with excellent elasticity and stability was stated by ref 54. Of all the elastomeric materials available, PDMS has been widely used as chip material because it can be easily obtained from a commercial source, it is inexpensive, has optical transparency, high elasticity, and high gas permeability, and is biocompatible for longer periods in cell culture devices.[62,63] PDMS is a synthetic elastomeric polymer with Si−O bonds. It can be utilized for flexible membranes, has native tissue elasticity, and can induce cell orientation through topological cues.

The transparent nature of it also helps in creating multilayer microfluidic devices. It is available as an uncross linked gel with a cross-linking solution. The mixture of these fluids triggers the material, to undergoes cross-linking and forms a solid chip device. After that, the poured solution is hardened at high temperatures and then peeled away from the mold.[64] Using plasma oxidation processes or pressure application, the resultant mold can be capped with a glass slide to form noncovalent bonding. In this phase, PDMS models can be used as on-chip devices or as a mold for a secondary material type, enabling further production.[65] The elasticity of PDMS may be adjusted, allowing the material qualities to be tailored to the specific tissue application within the device.[66]

Despite its many advantages, PDMS has severe drawbacks, particularly when it comes to the integration of biological components into the OoC systems shown in Figure 3. One of the most important issues facing PDMS structures is "the absorption of small molecules".[67] This becomes a more important problem to be addressed for applications having cell culture, because its presence can create an impact on the concentration of soluble factors in the media, which can lead to improper cell signaling and functioning.[68,69] The second most important issue is the "leaching of the un-cross-linked oligomers from PDMS". Cured PDMS have remained un-cross-linked polymer chains that get easily diffused into the bulk material. Furthermore, whenever they come into contact with a solution, these un-cross-linked oligomers can leach out into solution via the bulk. Such oligomers were discovered to be capable of penetrating into the membranes of grown cells.[69] The unstable surface property of PDMS facilitate better chip bonding between similar or dissimilar materials, where its polymer chains can cause hydrophobic recovery[70] and raises concerns related to practicality and accessibility.

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

Because of this uncertainty, it can bring dynamic change in cell-cultured devices, which limits its application. It is also slightly autofluorescent, which causes Raman scattering, and is incompatible with some organic solvents. This causes swelling in microchannels and lead to changes in the dimensions, integration, and surface properties of the channels.[71] This makes the development of OoC with substitute material for PDMS a crucial component. In this section, we describe alternative elastomeric materials, which includes SU-8, polyesters, polyurethane, tetrafluoroethylene propylene, poly(polyol sebacate), and poly(octamethylene maleate (anhydride) citrate), which can be potentially unitized for OoC device fabrications. A summary of the properties of these materials including its advantages, disadvantages and its bio specific applications is illustrated in Table 2.

3.1.1.1. SU-8 Polymers. SU-8 polymers include eight epoxy groups that form a strong crosslink when exposed to ultraviolet (UV) radiation. It is a thick, epoxy-photoplastic, high-aspect-ratio photoresist negative. Such a composition and technique results in the formation of chemically, mechanically, thermally stable materials. Because of its high internal stress, it has brittle qualities, which make it challenging to handle and transport. Nanometer- to millimeter-thick films can be deposited and patterned using these polymers by utilizing UV or electron beam lithography. SU-8's resins processing and other steps take a long time to complete. For instance, SU-8 adheres well to materials such as silicon and gold, but it has poor adherence to other materials such as glass nitrides or oxides; in addition, the resist delaminates quickly from the substrates during fabrication. While the SU-8 design modifies both mass and mechanical characteristics, such as the resonance frequency of the structure, the silicon will dictate the mechanical properties of the structure.[72] A unique SU-8 microfluidic system for the application of sensitive dielectrophoresis to budding yeast cells was reported in ref 73. This report revealed information about misalignment in the microchannel, in relation to electrode topologies on living cells. SU-8 has several other applications outside its use in microfluidic device production, because it has excellent mechanical strength and the ability to form complicated 3D networks and simple high-aspect-ratio structures makes it suitable for mold master making.[74] The SU-8 mold has seen significant application as a hot embossing technique for thermoplastic equipment, as well as being a first step in the injection molding process. In the case of SU-8 photoresist, adhesion selectivity, stress, and resist stripping are commonly found to be the most significant disadvantages.

3.1.1.2. Polyesters. The search alternative chip materials with easy fabrication processes have been extensively studied for many years. It was found that polyester-toner microfabrication can be a favorable process to create microfluidic chips with simple fabrication steps at affordable prices.[75] These elastomers feature low-absorption, soft-elastic, and biocompatible characteristics, which are appealing for developing organ-on-chip devices. The process employs a toner layer that is applied on a polyester film for designing the microfluidic channels, and this layer also serves as an adhesive to seal the device, as shown in Figure 4a. This makes polyesters a promising candidate for organ-on-chip applications. Urbaczek et al. demonstrated polyester-based microfluidic chips to mimic human blood vessels, and further studied its application in inflammatory response.[76] The developed microchip showed better cell growth and survival with less toxicity and good optical transparency. On the other hand, polyester materials offer desirable mechanical strength for soft applications; at the same time, they lack thermoplastic properties that require prolonged heating and reduced pressure to generate a branched elastomeric structure.

3.1.1.3. Polyurethane. Polyurethanes (PU) are a class of polymers that have been utilized successively in many biomedical applications. In microfluidics, they can be integrated with other materials, such as PDMS, for cell culture applications.[77,78] These polymers share some similar properties with PDMSs, including optical transparency, biocompatibility, and flexibility. However, they resist the absorption of small hydrophobic molecules, as well as degradation from water and UV light. Ingber demonstrated the excellent properties of PU made from GS polymer and procedures for creating strong bonds to itself. PDMS was found to have a greater transmittance than PU for

Table 2. An Overview of Elastomeric Materials with Their Properties, Limitations, and Organ-Specific Applications

sample	polymer name	properties	demerits	applications	refs
1	PDMS	flexible, transparent, low cost, high gas permeability, rapid prototyping, and biocompatible	absorption of small hydrophobic molecules, hydrophobicity, not compatible with organic solvents	lungs-on-a-chip, bone regeneration, drug analysis, heart-liver-on-a-chip, gut-on-a-chip, and tissue engineering	Shrestha et al.,[97] Carter et al.,[98] Li et al.,[99] Ferrari et al.,[100] Guo et al.,[101]
2	SU-8	mechanical strength, optical transparency, chemically stable, resistant toward other solvents	adhesion selectivity, stress and resist stripping	pancreas-liver-on-a-chip and blood-brain barrier modeling	Essaouiba et al.,[102] Zakharova et al.[103]
3	POMaC	biodegradable, nontoxic, inexpensive, controllable mechanical and degradation properties, and simple fabrication		soft tissue engineering, heart-on-a-chip, and liver-on-a-chip	Zhao et al.,[329] Lai et al.,[87] Polidoro et al.[104]
4	polystyrene	optically transparency, biocompatible, rigid, easy surface functionalization, and inexpensive	high cost equipments, poor resistance toward to other solvents	biosensors, blood-brain-barrier model, multilayer devices, and drug analysis	Bossink et al.,[105] Zakharova et al.,[103] Paoli et al.,[106] Onbas et al.[107]
5	P(OCS) and PICO	nontoxic, biocompatible, inexpensive, good machine strength, easy surface functionalization		tissue engineering	Huyer et al.,[95] Djordjevic et al.[94]
6	PPS	controllable mechanical and degradation rate, and biocompatible	rapid degradation rate, release acidic degradation that may cause unwanted inflammation in host tissue	tissue engineering	Chen et al.[84]
7	polyurethane	flexibility, good mechanical strength, resistance toward abrasion, and chemically inert	bad odor, release toxic fumes, causes skin problems, and breathlessness	tumor modeling and tissue engineering	Liu et al.,[108] Hammel et al.[109]
8	FEMP	handles high temperature and pressure, and excellent resistance toward inorganic and organic acids	less gas permeability, hydrophobicity than PDMS, require large vacuum compression molding machines and pression control molds for channel fabrication	intestine-gut-on-a-chip and drug analysis	Steinway et al.,[110] Sano et al.,[79]

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

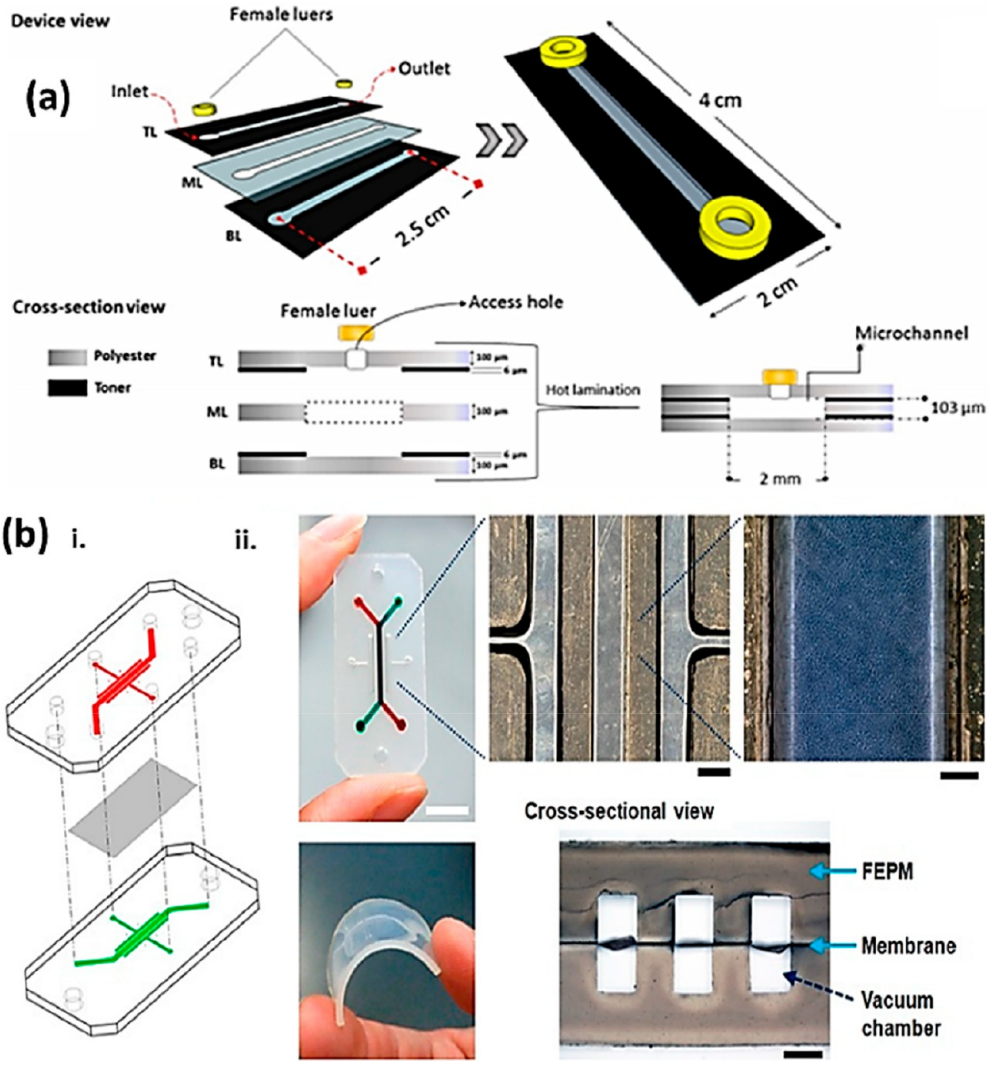


Figure 4. Development of SU-8 pillars on SOI cantilevers, polyester toner microfluidic device, optical transparency and mechanical strength of polyurethane, and compartmentalized microfluidic device fabricated from tetrafluoroethylene-propylene (FEPM) elastomer. (a) Design, dimensions, and microchip assembly structure. The inner side of the bottom layer (BL) was produced printing the polyester film with one layer of toner creating a channel of 2.0 cm long and 0.2 cm wide and two circles of 0.3 cm of diameter at each end. The top layer (TL) has the same layout printed in the inner layer, but with the circles punched, BL and TL were treated with oxygen plasma, and the three layers were laminated together. [Reproduced with permission from ref 76. Copyright 2017, Springer Nature.] (b) Schematic illustration. [Reproduced with permission from ref 79. Copyright 2019, MDPI Journals.] Panel (i) shows the microfluidic device and panel (ii) shows a demonstration of the device and channel layer. A cross-sectional view shows the dimensions of width and height (1 mm with a collagen membrane 10 μm thick). Cells are cultured in the central channel with mechanical strain to all the side vacuum chambers. Scale bars = 10, 1, and 0.2 mm for low-, medium-, and high-magnification views, respectively.

wavelengths of <300 nm, while the material transmittances remained equivalent at higher wavelengths (>350 nm).[30] This is essential as in fluorescence spectroscopy, where higher wavelengths are more sensitive for assays, which is crucial in the drug-development stage. Furthermore, it can be concluded that, while polyurethane elongation varies in certain ways from PDMS, there are no substantial differences. While polyurethane has many advantages over PDMS; there are also demerits. It is difficult to degas and mold, abd its components must be stored in sealed containers with dry gas.

3.1.1.4. Tetrafluoroethylene Propylene. Recently, the concern for high temperature and chemical resistance toward elastomer material has been growing and FEMP, having excellent chemical resistance toward inorganic and organic acids, has gained considerable attention. Torisawa reported a two-channel microfluidic-cell-culture device made using tetrafluoroethylene propylene (FEMP), as shown in Figure 4b. Furthermore, the drug absorption by the FEMP was compared to that of a standard polystyrene-based cell culture system.[79] However, the FEMP has some disadvantages, which limits its applicability. These include having extremely low gas permeability and hydrophobicity compared to PDMS, which causes generation of air bubbles inside the microchannels when solutions are introduced.[80] These air bubbles can be removed by incubating the devices within a culture medium in an incubator before seeding. Another major limitation for these elastomers is that they require huge vacuum-compression molding machines and pressure control molds for channel fabrication. This makes them less user-friendly and are only suitable for mass production.

3.1.1.5. Poly(polyol sebacate). A new class of cross-linked elastomer, called poly(polyol sebacate) (PPS), was created in Langer's laboratory at MIT.[81,82] These are biocompatible, inexpensive, and have potential applications in nerves and vascular tissue engineering. Similarly, another elastomer—poly(glycerol sebacate) (PGS)—has been consistently reported, because of its nontoxicity and biocompatibility in vivo. It primarily gets degraded through surface erosion.[83] Both its mechanical strength and mass decreases linearly with the passage of polymer degradation time. This causes

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

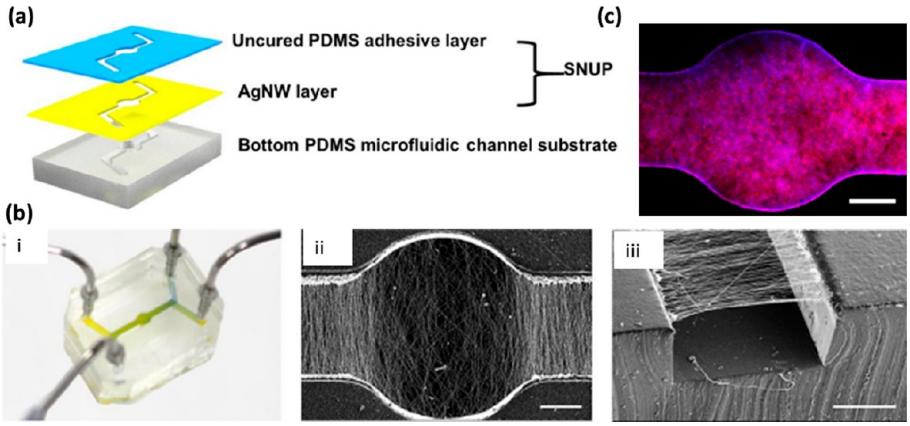


Figure 5. Schematic diagram of SNUP, NFM-PDMS chip fabrication, showing an SEM image and a representative stained cells image. (a) Schematic diagram of the composition of SNUP. (b) (i) NFM-PDMS chip fabricated with help of SNUP, which was filled with yellow- and blue-dyed solutions in the top and bottom microfluidic channels, respectively (schematic illustration indicates the composition of SNUP); (ii) SEM image of the elctrospun nanofiber membrane deposited on the microfluidic channel area of SNUP-PDMS substrate; and (iii) free standing configuration. All scale bars in panel (b) = 400 μm. (c) HaCaT cells stained with DAP1 (blue) and Phalloidin (red), covering the entire membrane. All scale bars in panel (c) = 500 μm. [Figure reproduced with permission from ref 355. Copyright 2021, American Chemical Society, Washington, DC.]

cytotoxicity, because of its excessive carboxylic groups, which lowers pH to below physiological levels (7.2−7.4).[84] Also, because of its rapid degradation, it limits its usage as a scaffold material in tissue engineering.

3.1.1.6. Other Polymers. Elastomeric polyesters based on citric acid have been studied as biological scaffolds.[86−88] Bacause of their optimal biocompatibility, scaffolds generated by these shows effective remaking of various types of tissues.[89−93] These polymers are providing the basic bioresponsive characteristics such as mechanical strength, hydration, and surface chemistry, which can be varied by reaction parameters during polyesterification. Also, polymers such as poly(octanediol-*co*-(citric acid)-*co*-sebacic acid) (P(OCS)) have huge applicability for tissue engineering applications.[94] Recently, poly-(lactic-*co*-glycolic acid) (PLGA)-based biomedical devices for drug delivery have received much attention. The main advantages of PLGA-based microfluidic devices are that it allows one to maintain continuous reactions and, therefore, it provides a way to overcome the problem of reduced reproducibility. Gao and colleagues devised a simple lung-on-a-chip with PLGA electrospinning nanofiber as the cell scaffold and utilized it to mimic the human alveolar microenvironment.[94−96] Davenport Huyer et al. studied the synthesis of polyester elastomer which includes citric acid, 1,8-octanediol, and ITA for the formation of poly(itaconate-*co*-citrate-*co*-octanediol) (PICO) with tunable soft elasticity. Furthermore, they demonstrated PICO-based scaffold cardiac tissue.[173] PICO could be easily shaped into controlled networks that contribute in the creation of cardiomyocyte tissue in therapeutic applications. On this chip, the 3D cell culture was evaluated and gefitinib, which is an EGFR-targeted antitumor drug, is present.[96] In contrast to existing lung-on-a-chip devices, the reported microchip provides a 3D cultured environment closer to the actual in vivo environment. In addition, the width of the PLGA membrane may be adjusted, making the membrane more ideal as a model for the alveolar respiratory membrane, which has a mean thickness of few micrometers. However, at higher elongations, these polymers either get fractured or undergo deformation, which restricts its usage in soft tissue engineering. Figure 5 demonstrates the functionality of SNUP, NFM-PDMS chip fabrication, where the SEM image shows the elctrospun nanofiber membrane deposited on the microfluidic channel area of the SNUP-PDMS substrate.

3.1.1.7. Poly(octamethylene Maleate (Anhydride) Citrate). In the fields of tissue engineering, scaffolds serve a crucial role in supporting and fostering the formation of functional tissues. Researchers have designed biomaterials to study scaffold designs and to develop improved medical devices. To meet the chosen biomedical application, certain scaffold design requirements must be optimized: mechanical characteristics, biocompatibility, geometries, surface energy, degradation, porosity and chemical composition. Tran and co-workers created an elastomer poly(octamethylene maleate (anhydride) citrate) (POMaC) to fulfill required functional qualities in order to satisfy all of the design considerations.[85] Zhao et al. denoted the Biowire II framework, which involves elastomeric wires made of POMaC polymer.[344] The elastic wire inside inert microwells of a microfabricated polystyrene surface enabled hydrogel encapsulated cardiomyocytes to directly attach to form atrial and ventricular tissues. Zhang and his colleagues exhibited vascular hepatic and cardiac tissues by manufacturing a POMaC Angio Chip device, which are marketed by the TARA Biosystems.[87]

3.1.2. Thermoplastic Synthetic OoC Materials. Thermoplastics are a class of materials that can be remolded after deformation. They have a property that allows them to maintain their shape, and they have potential applications in microfabrication and microelectromechanical systems (MEMS) applications. These materials are optically transparent, inexpensive, rigid, less prone to monomer leaching, biocompatible, and show resistance toward the absorption of small hydrophobic molecules. Furthermore, they can be surface-functionalized, depending on their applications, by means of dynamic coating and surface grafting techniques.[136,137] Table 3 discusses the properties and organ specific applications of thermoplastic materials in details. For instance, after oxygen plasma treatment, thermoplastic surface can maintain their hydrophobicity up to a few years. Some of the most common thermoplastic materials and their applications are shown in Figure 6.

3.1.2.1. Poly(methyl methacrylate). Poly(methyl methacrylate) (PMMA) offers thermal stability and insulation properties. It has strength, rigidity, and hardness, which makes it suitable for chip fabrication, replacing the traditional PDMS-based microfluidic chip.[134−137] Also, it possesses good resistance toward water and can be reused up to several rounds.[135] It is a biocompatible polymer, except when it is treated with ozone or plasma oxygen. For instance, study demonstrated a high-throughput three-layered PMMA open microfluidic device developed using computer numerical control micromilling and solvent-bonding method for mimicking the human respiratory microenvironment.[138] (See Figure 7.) PMMA microfluidic devices with low permeability to small molecules were also demonstrated by Nguyen.[32] The PMMA devices showed a significant and reliable cytoxicity to the drug vincristine.[32] Using a liver-on-chip model, Bhise et al. created a hepatocyte-spheroid-laden hydrogel that could be bioprinted directly inside the growth chamber of a bioreactor.[352] The developed bioreactor includes multiple layers of

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

Table 3. Properties and Organ-Specific Applications of Thermoplastic Materials

material	melting point	tensile strength (MPa)	solvent resistance	acid/base resistance	optical transparency	gas permeability	remarks	applications	refs
PMMA	250–260	70	good	good	excellent	good	inexpensive, low hydrophobicity, reusable, expensive equipment required to realize complex chips	tumor model, blood vessels, blood retinal barrier, metastasis-on-a-chip, liver-on-a-chip, and lung-on-a-chip	Palacio-Castañeda et al.,[216] Le et al.,[217] Shrestha et al.,[218] Arık et al.,[219] Wang et al.,[220] Bhise et al.,[342] Nguyen et al., 2019[32]
COC	190–320	60	excellent	poor	excellent	excellent	low autofluorescence, high heat resistance, and hydrophobic surface	multilayered microfluidic devices, drug analysis, and liver disease model	Paoli et al.,[221] Azizgolshani et al.,[222] Wen et al.[157]
polystyrene	240–260	50.9	poor	good	excellent	excellent	easily surface functionalized, rapid bonding, inexpensive, more channels collapsing when width-to-height aspect ratios are too high	heart-on-a-chip, mucus-on-a-chip, and cardiovascular model	Quirós-Solano et al.,[164] Jia et al.,[223] Inbody et al.[224]
polycarbonate	260–270	64	good	good	excellent	excellent	durable, low moisture absorption, poor resistance to certain organic solvents	lung-on-a-chip, drug analysis, and wound healing	Pauline et al.,[225] Magno et al.[176]
PFPE	NA	NA	excellent	NA	NA	excellent	low surface energy, nontoxic, bonding separate layer is difficult	liver- and kidney-on-a-chip	Essaouiba et al.[226]
PTFE	330 C	33.6	excellent	excellent	poor	poor	highly flexible, nontoxic, and nonuniform features below 200 μm	lung-on-a-chip, and tissue engineering	Nejatian,[227] Park et al.[213]
FEP	245–275	34.3	excellent	excellent	excellent	poor	nonsticky, antifouling properties and soft	tissue engineering	Fajstavrová et al.[228]
PET	248–260	90	excellent	excellent	poor	poor	NA	epidermis-on-a-chip, lung-on-a- chip, and liver-on-a- chip	Zhang et al.,[229] Artzy-Schnirman et al.,[230] Hegde et al.[214]
PEEK	340–350	110	excellent	poor	good	NA	biocompatible, swell when comes in contact with methyl chloride	bone regeneration, intestinal and epithelial cell culture	Loenen et al.,[231] Kulthong et al.[232]

PDMS and PMMA and has three chambers connected with microchannels shown in systems.[19,342]

The design of OoC model was selected in such a manner that introduced bubbles that would shift without being trapped in chambers. There are different types of bonding used for sealing PMMA−PMMA, such as chemical bonding, solvent bonding, adhesive bonding, and thermal bonding.[116,117] Although thermal bonding is the most-used method to obtain a uniform surface in PMMA-based devices, the dependency on heavy machineries and heaters can cause deformations in microchannels.[139,140] Although adhesive bonding uses low temperature and pressure, it involves the risk of clogging in microfluidic channels. Similarly, chemical bonding involves surface modifications, which are time-consuming, because of the involvement of a multiple number of steps.[141] To validate the bonding performance, several tests were performed and results showed that PMMA microchannels demonstrate viability and adhesion.[142]

3.1.2.2. Cyclic Olefin Polymers. Cyclic olefin polymers and copolymers (COCs/COPs) are amorphous thermoplastic copolymers and bear extremely low impurities and also other beneficiary properties, compared to other thermoplastics; it is a potential platform for LOC devices that are intended for biosensing applications.[143,144] It is found that research involving drugs and pharmaceuticals are not optimal with COC devices, because of their hydrophobic surface, which allows proteins to get and adsorb cells to adhere to when they come into contact with living tissue or fluid.[145] It is essential to treat the COC surface with different chemicals to minimize its the adsorption of proteins and also to decrease the overall adherence of cells.[146−148] The majority of the work on COC surface modifications has been done through the use of photografting techniques.[153,154] Most of the medical testing parameters have been measured in blood samples. Ahn et al. demonstrated COP-based lab-on-chip devices for point-of-care diagnosis of oxygen, glucose, and lactate in blood. COC-based microfluidic chips have shown toxicity, biotransformation, and codrug treatment of aflatoxin B1 and benzo[a]pyrene on an interconnected liver and kidney.[155]

Furthermore, COC-based devices are also used to study illicit drug analysis and DNA amplification by performing a chip multiple displacement amplification reaction.[156] Similarly, Wen et al. demonstrated the use of COP for modeling a nonalcoholic fatty liver disease microphysiological system.[157] The majority of microfluidic devices fabricated in laboratories required expensive equipment, which becomes difficult for all institutions to afford. COC-based microfluidic devices can be fabricated easily on a wide scale for commercial purposes. COCs can be used to build robust, cost-effective microfluidic devices using COC pallets. It includes two pieces of COCs and they were sealed by solvent treatment followed by heat and pressure to close the lid to the pieces containing microfluidic features.[158] A variety of drawbacks, such as fragility and low-heat diffusivity, limits the applicability of COC in several applications. Nonpolar organic substances, such as hexane and toluene, can easily degrade the material. Also, because of the material's hydrophobic interactions, COC devices require surface modifications to separate hydrophobic compounds.[159] This hydrophobicity of COPs can be problematic in some situations. To minimize adsorption of proteins and other compounds, the COC chip surface can be coated with a UV-initiated grafting of polyacrylamide, and then can be treated with oxygen plasma.[160] For example, when the inside of the microchannel walls are coated, electro-osmotic mobility is reduced and the walls become more hydrophilic.

3.1.2.3. Polystyrene. Polystyrene (PS) is a transparent, nontoxic, stable, rigid polymer with a readily functionalized surface. Various physicochemical methods, such as gas-plasma, and irradiation are generally used to make its hydrophobic surface become hydrophilic.[161] Moreover, the high cost of equipment that is needed to make intricate chip designs for such polymers could be a deterrent to widespread implementation. Some PS microfluidic chips take advantage of the thermoplastic sheets.[162,163] PS is, by far, the most widely used substance in culturing, because of its widespread commercial availability and low cost. A heart-on-chip system involves

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

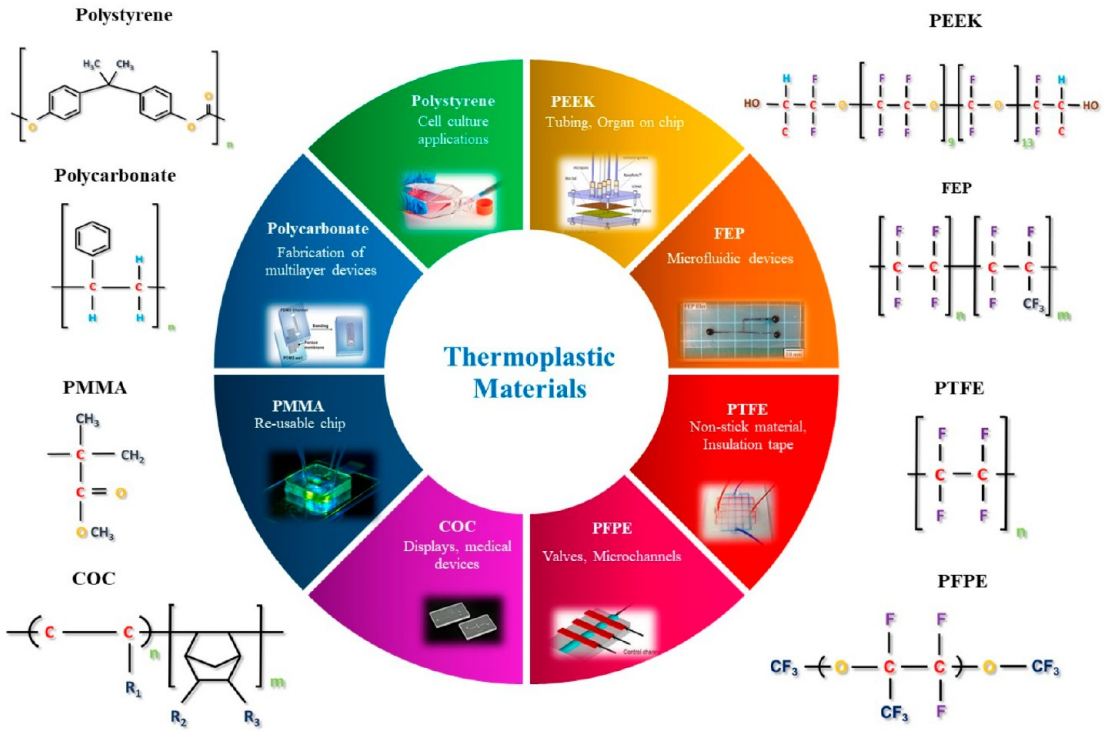


Figure 6. Different thermoplastic materials that can be used for OoC development.

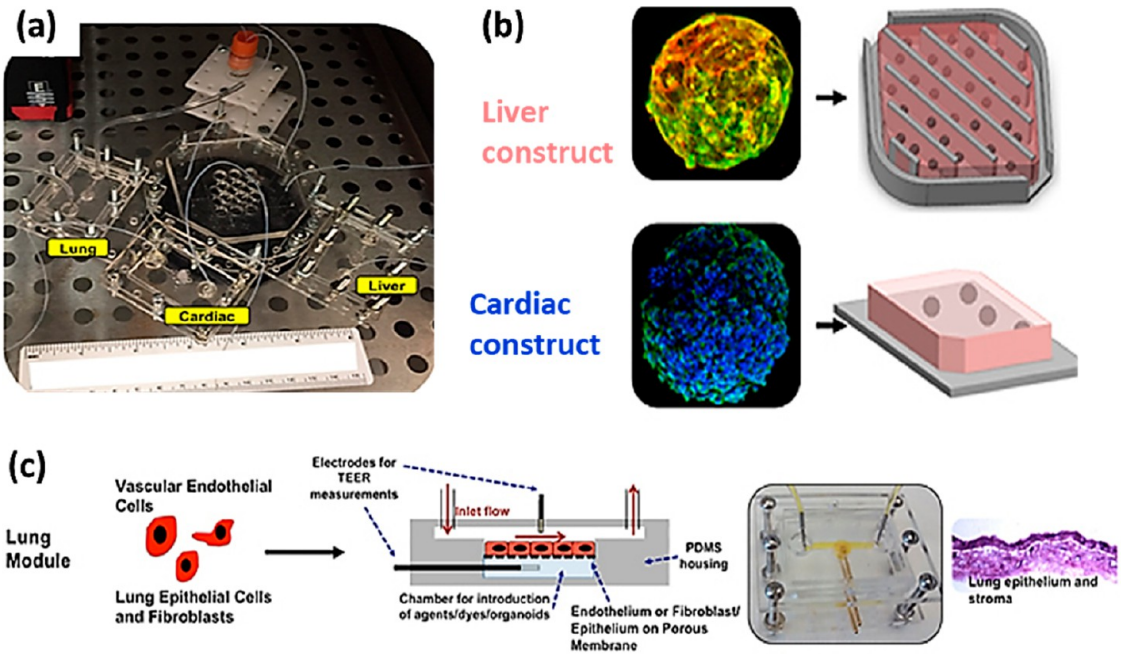


Figure 7. Design and implementation strategy for the three-tissue representative OoC system, using a variety of biofabrication approaches. [Reproduced with permission from ref 356. Copyright 2017, Nature.] (a) Demonstration of the modular multitissue organ-on-a-chip hardware system setup for maintenance of the three-tissue model. Individual microfluidic microreactor units house each organoid or tissue model, and are connected via a central fluid routing breadboard, allowing for straightforward "plug-and-play" system preparation initialization. (b) Liver and cardiac modules are created by bioprinting spherical organoids within customized bioinks, resulting in 3D hydrogel constructs that are placed into the microreactor devices. (c) Lung modules are formed by creating layers of cells over porous membranes within microfluidic devices. Introduction of trans-endothelial [or epithelial] electrical resistance (TEER) sensors allows monitoring of the tissue barrier function integrity over time.

pluripotent cells, for functional and structural purposes. In order to understand the biological process involved, one must develop an electrical sensing system without affecting the mechanical functionality of its membrane. This requires a material with low stiffness and good electrical conductivity. The main steps of the patterning process of the PEDOT:PSS microstructure in OoC have been defined in study.[164] Quiros et al. demonstrated the integration of a PEDOT:PSS-based microstructure into a thick PDMS membrane representing the flexible substrate in a heart-on-chip system.[165] Figure 8 defines the design and microfabrication of the molecular devices extensively.[356]

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

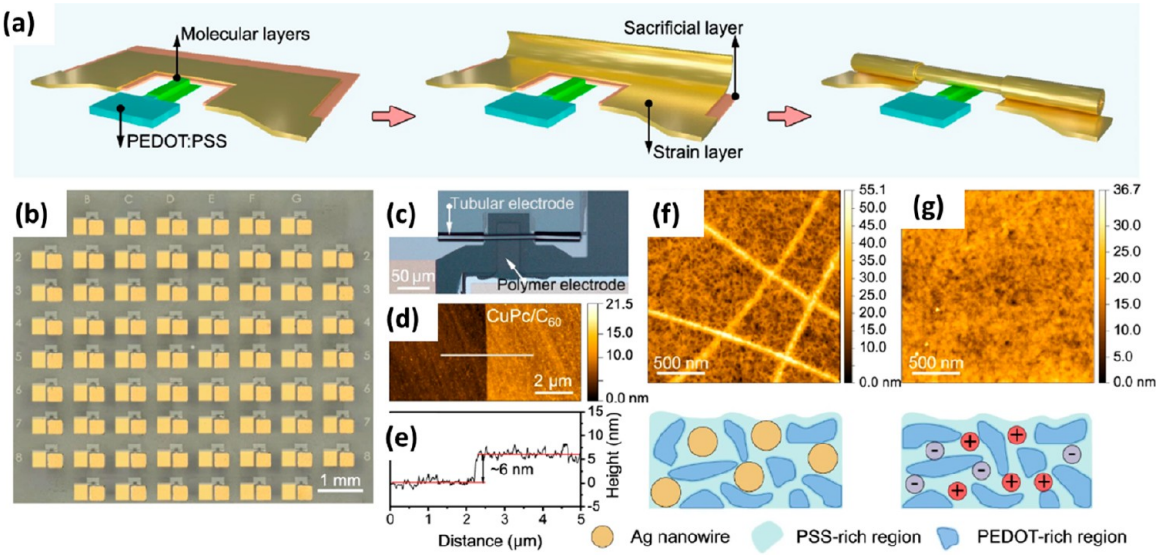


Figure 8. Design and microfabrication of the molecular devices. [Reproduced with permission from ref 357. Copyright 2022, Nature Publications.) (a) Formation of rolled-up soft contacts. The finger-shaped mesa structure provides a platform for the bottom electrode, onto which molecular layers are grown. Here, Au/Ti/Cr nanomembranes rolled-up and bonds to top electrode, forming a sandwich structure. (b) Micrograph of the molecular device array. (c) Typical single device based on a rolled-up soft contact. Panel (d) shows that the width of the bottom electrode and the diameter of the rolled-up metallic tube are ~40 μm and ~10 μm, respectively, and panel (e) shows the corresponding height profile AFM images of the spin-coated PEDOT:PSS:AgNWs film before wet etching (panel (f)) and after 30 s of wet etching (panel (g)).

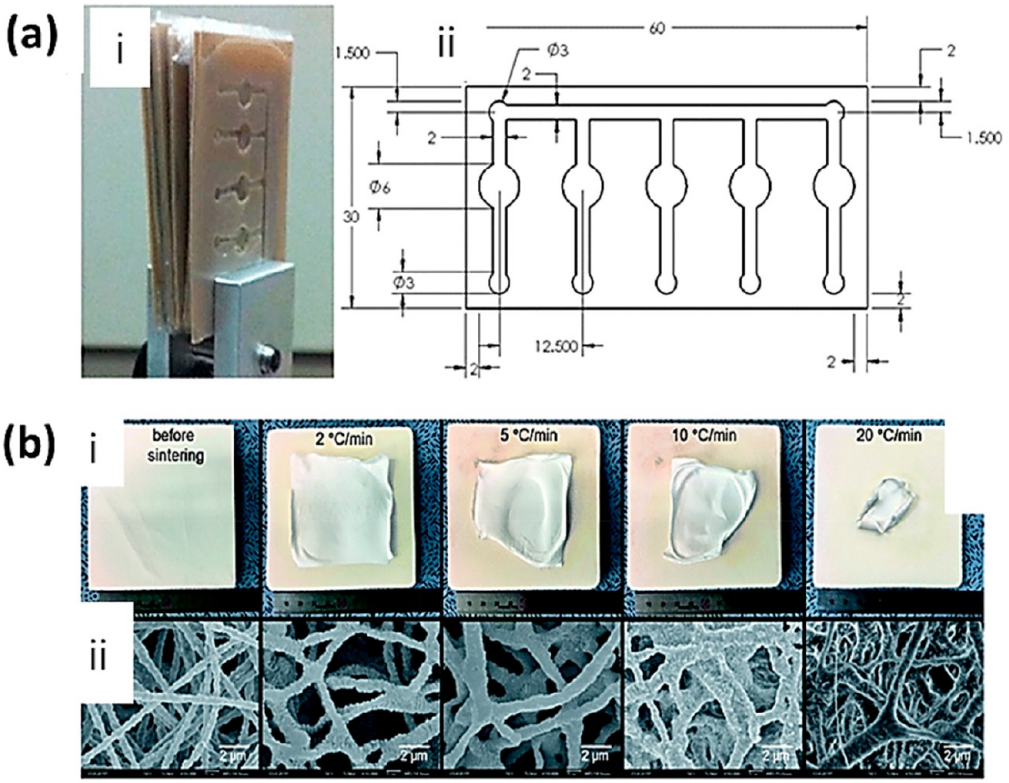


Figure 9. PEEK-based lab-on-chip, bone-on-a-chip, and principles and design of integrated dynamic cell cultures in microsystems, and multilayer microfluidic PEGDA hydrogel. Panel (a) shows (i) the PEEK–PS lab-on-a-chip devices and (ii) the technical design drawing of the chip including the microchannels and the reservoirs. [Reproduced with permission from ref 189. Copyright 2018, Springer Nature.] Panel (b) shows (i) digital and (ii) SEM images of the PTFE nanofibrous membranes before and after sintering at 350 °C for 30 min with different heating rates. [Reproduced with permission from ref 345. Copyright 2018, Royal School of Chemistry, London.]

All these organs on chip-based technologies require an external pump that is connected to the device through tubing to enable the perfusion of cell culture medium and buffer within the microfluidic channels. Ultimately, these external supplies increase the cost to establish the organ-on-chip device. To address this issue, Delon et al. reported a simple robust approach to build a pumpless organ on chip devices.[165] It is based on gravity-induced bidirectional flow and application of a hydrostatic pressure and resistance circuit. The surface of the PS can

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576–3607

be functionalized by oxygen plasma to promote better cell adhesion and development while inhibiting bubble formation. To avoid this, a masking layer might be used to protect the top surface. Another option could be to wrap microchannels with extracellular matrix components such as proteins prior to cell seeding to improve cell adhesion.[166] Other drawbacks of using PS microfluidic chips include difficulty with thermal bonding. In addition, channels collapse due to high width-to-height aspect ratios.

3.1.2.4. Polycarbonate. Polycarbonate (PC) is a robust polymer synthesized by polymerizing Bisphenol A and phosgene to form repeated carbonate groups. Its transparency in the visible range and extremely high glass-transition temperature (145 °C) makes PC suitable for DNA thermal cycling applications.[167] In addition, it is inexpensive, has excellent resistance, and exhibits low moisture absorption.[168] However, PC has a low resistance to some organic solvents and UV absorption. PC is considered to be the best option for a variety of microfluidic applications in biomedical research and bioanalyses, including polymerase chain reaction applications. In addition, this polymer offers a practical substitute to well-established techniques for multilayer device fabrication based on lithography and molding in PDMS. A microfluidic electrochemical biosensor chip has been constructed for the amperometric measurement of glucose by microflow injection.[169−171] The photodirected electroless deposition process is then used to create a micro gold film electrode base on a PC cover sheet. Finally, a micro flow-injection biosensor system with PC was developed and utilized in determining glucose concentration in with pharmaceutical injections. PC is a hard material that many devices use as a tissue-bearing porous membrane component and inexpensive alternative to all other materials that are used for organ-on-chip device fabrication.[172−174] An PC-based human-microbial crosstalk (HuMiX) model was reported made by sandwiching two micromilled PC microfluidic channels enclosed between silicon rubber gaskets.[175] In many cases it was seen that aliphatic polymers shows a demerit of creating an acidic environment which limits its application in biological sector. To overcome this, a tyrosine-derived polycarbonate tetrapolymer is introduced as a new class of biodegradable potential alternative.[176] Furthermore, a detailed study was done to demonstrate the fabrication of tissue scaffolds and in vitro cytoxicity and biocompatibility on a rabbit model. The results showed that the tyrosine-derived polycarbonate tetrapolymer exhibits minimal cytotoxicity and wound healing response with minimal tissue inflammation.

3.1.2.5. Polyether Ether Ketone (PEEK). Inorganic materials such as glass and silicon, which possess a brittle nature and a complicated sealing process, make the fabrication process expensive and inconvenient, to which polyether ether ketone (PEEK) can act as a substitute, because of its inexpensive, high-quality fabrication technology. Using these techniques, microchannels with dimensions of ∼15−30 μm could be created. Because of all of the advantages of PEEK, it has replaced PDMS as the preferred material. This makes it suitable for OoC device applications, which will provide outstanding chemical and hydrolysis resistance, as well as mechanical and thermal stability, compared to others.[184,185] A PEEK device cannot be manufactured using traditional polymer manufacturing techniques, because of the high melting point, while conventional sealing approaches in miniature devices avoids adhesives and temperature supply to maintain the normal fluid flow.[186−188] In order to accomplish autohesion, which is a potential thermoplastic sealing technology, adequate activation processes involving pressure and mild temperature are required. In Figure 9a, Awaja et al. have shown that the autohesion of PEEK and PS at a temperature near the glass-transition temperature can be used to produce LOC devices at a cost-effective rate.[189] Because of the advantage of toxic-free adhesive technology, it has several potential applications where microfluidic channels must be clean, as well as enclosed entirely and firmly.

The breakdown rate of PEEK is exceptionally low, making it difficult for the extracellular matrix to proliferate after implantation.[190,191] In order to overcome this amalgamation of biomaterials with diverse degradation rates, an operative path is followed to overcome the restriction of a solitary material.[191−193] Biomaterials such as polyglycolic acid (PGA) have attracted much interest, because of its easy ability for degradation and biocompatibility. To overcome the low degradation rate and enhance the strength of PEEK, it can be blended with PGA.[194−196] Later, a simulated body fluid immersion test was used to evaluate their deterioration behavior. And it was found that the amount of PGA in scaffolds could be changed to alter their degradation rates. In addition, the scaffolds could aid in cell adhesion and proliferation; overall, PEEK/PGA blend scaffolds have showed promise for tissue engineering.

3.1.2.6. Poly(tetrafluoroethylene). Poly(tetrafluoroethylene) (PTFE) is another polymeric material with reasonably high oxygen permeability (DuPont Co.). Because of its chemical and physical inertness, it is highly used in microfluidic applications.[197,198] Fluorinated polymers have refractive indices ranging from 1.32 to 1.38 and can be adjusted, which makes it quite exclusive, comparaed to other polymers that have refractive indexes on the order of 1.4−1.6.[199,200] To overcome some of the problems associated with PDMS chips, including nonspecific protein adsorption, PTFE was offered as an alternate material. According to the cellular interactions in the kidney and liver, PTFE and PDMS microchips showed similar results. Particularly in its hydrophilic form, PTFE is a common material for porous membranes. It is mostly used as a thin porous membrane that is optically transparent (does not scatter light due to porosity) when it is wet, because PTFE and water have similar refractive indices (pure water has a refractive index of 1.33). For microfluidic systems developed for microscopic imaging, membranes with this feature can be very beneficial. PTFE and related fluorocarbons have a low surface energy, making them appropriate for antifouling and antistick coatings.[201] PTFE can also be utilized in microdevices as a gas-permeable liquid barrier. PEEK has a poor affinity toward absorption of small molecules and has relatively low oxygen permeability, compared to PDMS and PTFE, but it does have high resistance toward different solvents and is mechanically strong.[202−204] However, the high cost, poor bonding, and lack of transparency make it impossible to use this polymer in the building of microdevices, because of its low transparency.[205,206] Therefore, the production of microdevices is more typically performed using various thermoplastic polymers, such as polystyrene, COCs and COPs, PMMA, and polycarbonate. Materials with somewhat higher oxygen permeability than PEEK, easier processability, and visible light transparency have emerged as promising alternatives. In addition, optical transparency of COCs extends into the UV range. It is possible to produce microdevices on a large scale by using thermoplastic polymers and fabrication techniques such as injection molding.[207]

The slight superficial energy, the solid carbon−carbon and carbon−fluorine interactions, and the high degree of crystallinity make PTFE a good choice for medical claims such as a vascular graft and a bone regeneration membrane, among others.[208−210] Generally, PTFE membranes are produced by thermomechanical stretching.[211] Because of PTFE mixing with a lubricant, billet production, and extrusion phases in this approach that result in significant lubricant contamination of the environment, this method is not recommended.[212] By sintering the electrospun PTFE/poly(ethylene oxide) (PEO) nanofibrous membranes, PTFE nanofibrous membranes were created.[213] A porous morphology was created in the membranes by interlacing nanofibers. Because of the differences in chemical and mechanical possessions of the PTFE nanofiber membranes due to the sintering temperature, these membranes were shown to be much less hazardous. Last but not least, the nanofiber membrane created was used for tissue engineering and bone regeneration, as shown in Figure 9b.

3.1.2.7. Perfluoropolyethers. In contrast to PDMS, various other materials have been explored, and of those, the predominant usage of fluorinated polymers has been widely reported. Because of the inertness of these perfluorinated compounds, the materials are promising for various applications. Desimone and his colleagues have created a photocurable perfluoropolyether (PFPE) that can be used in medical applications.[177] It is nontoxic, has low-surface energy, and shows resistance to many solvents. For a multiphasic microfluidic environment, the primary reasons for its selection are both its

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

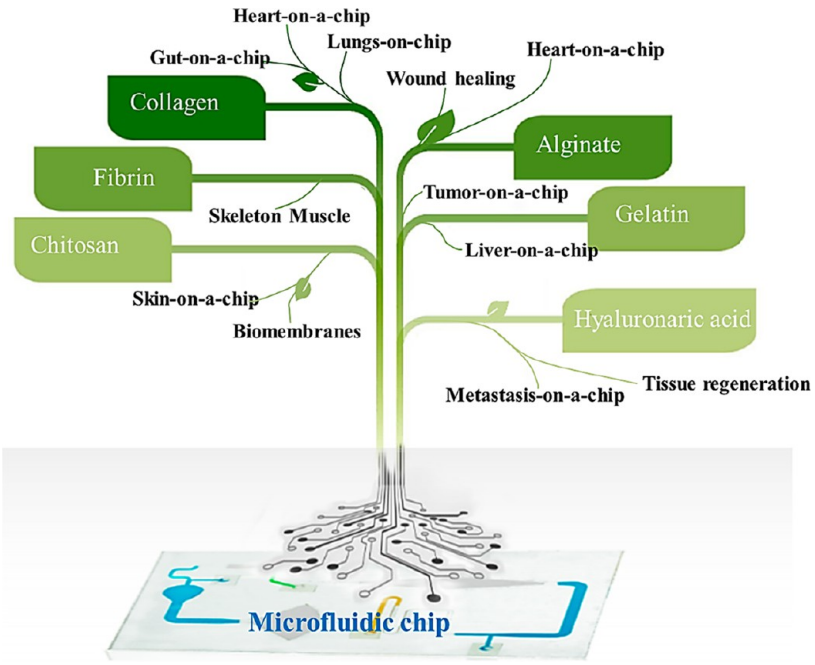


Figure 10. Different natural materials used for OoC development.

oleophobic and hydrophobic capabilities. Lately, through photolithographic processing, high-aspect-ratio (up to 6.5) PFPE microfluidic devices have been developed. By means of mask-assisted photopolymerization, it was possible to construct a process that could be completed within <5 min, while also demonstrating significant sealing capabilities.[178] Finally, the devices have been tested with several model reactions involving organic solvents in order to determine how well they perform. Furthermore, a microfluidic device based on PFPE for the analysis and growth of liver and kidney cells has been developed.[346] It was constructed by photocuring polyfluoropolyethers (PFPEs) to create two patterned layers with regular and precise microchannels. Jellali et al. have reported on a culture of liver HepG2/C3A and kidney MDCK cells and here, PFPE and PDMS biochips connected under the IDCCM bottom layer.[346] As a result of this, both PFPE and PDMS-based devices were determined to have identical biological performance.[179]

3.1.2.8. Poly(ethylene glycol) Diacrylate. Poly(ethylene glycol) diacrylate (PEGDA) is a polymer with similar possessions to PDMS, in terms of permanency, transparency, and little fluorescence. However, on the other hand, it has less nonspecific adsorption and is more resistant to the penetration of tiny hydrophobic compounds than PDMS.[180] This polymer could be considered a practical material, because it polymerizes quickly at room temperature and requires minimal energy. This biologically inert polymer possess excellent and variable mechanical characteristics, which may explain its widespread application as scaffolds in tissue engineering. PEGDA microfluidic devices devices are typically manufactured in the same way as PDMS devices.[181] Mass transfer and cellular migratory characteristics have been improved using a variety of scaffold building techniques. Multilayer microfluidic devices integrating PDMS and hydrogel microarchitectures have recently been designed to explore cell migration and spatially manipulate microenvironment features within perfused channels.[181,182] One study has referred to a simple, reliable multilayer replica molding approach in which PDMS and PEGDA are serially replica molded to form microfluidic PEGDA hydrogel networks contained within separately produced PDMS housing.[183] Another study shows the isometric view of PDMS/PEGDA microchannel device perfused with Toluidine Blue, where the diffusion of Toluidine Blue into a PEGDA diffusion chamber has been demonstrated.[347] When compared to static controls, cellular viability was observed to be improved within the perfused microfluidic hydrogel. Furthermore, since PEGDA is a biocompatible polymer, it can be used in small volume analysis and biomedical research, because of its resistance to nonspecific adsorption. This substance is also nonimmunogenic and resistant to protein adsorption, but it does not allow cell attachment.

3.1.2.9. Poly(ethylene terephthalate) (PET). Another common polymer used in commercial membranes and microfluidic devices is poly(ethylene terephthalate) (PET). PET membranes have been used in many OoCs and microfluidic cell-culture platforms; they are frequently extracted straight from porous filter membranes. It is a nonbiodegradable and transparent material, also to increase its cell adherence, it must be treated with plasma. With a melting temperature of 70 °C and a Young's modulus within 2−3 GPa, similar to PC, PET is also not suitable for OoC applications. However, it has been used for OoCs that demonstrate the gut-on-chip and liver-on-chip models and studies on endothelial cells.

For drug toxicity screening platforms, bioartificial liver support systems, and models for studying liver physiology and disease, steady flow cultures of hepatocytes are greatly desired. Hegde et al. described an easy process for culturing hepatocytes in a microfluidic device using a sandwich configuration.[214] The fabricated device consists of a two-layer PDMS chip with a porous PET membrane that separates the channels, with collagen and fibronectin-sanded rat primary hepatocytes continuously perfused into the lower channel through the top chamber. Over a two-week period, hepatocytes in flow cultures performed better than those in static cultures. Shim and his fellow researchers reproduced the gut's three-dimensional villi structure and fluidic shear using a microfluidic device.[215] The device consists of a PET membrane, PDMS, and slide glass, which was manually removed from the transcellular inserts; these make up the three layers of the chip. They also examined the effects of 3D culture and perfusion culture on cell physiological activities, such as differentiation, drug absorption, and metabolism, alone and in combination.

3.1.3. Hybrid OoC Materials. A distinct advantage of hybrid biomaterials provides the best of both natural and synthetic biomaterials. The development of hybrid biomaterials offers substantial value for the novel products and provides the desired properties. The degradation rate of materials produces natural components and supports better cell affinity. The promising interest in developing degradable and controlled hybrid polymer biomaterials mimics the extracellular protein structure for biomedical applications.[278] Functionalization for improved cellular interaction, signaling,

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

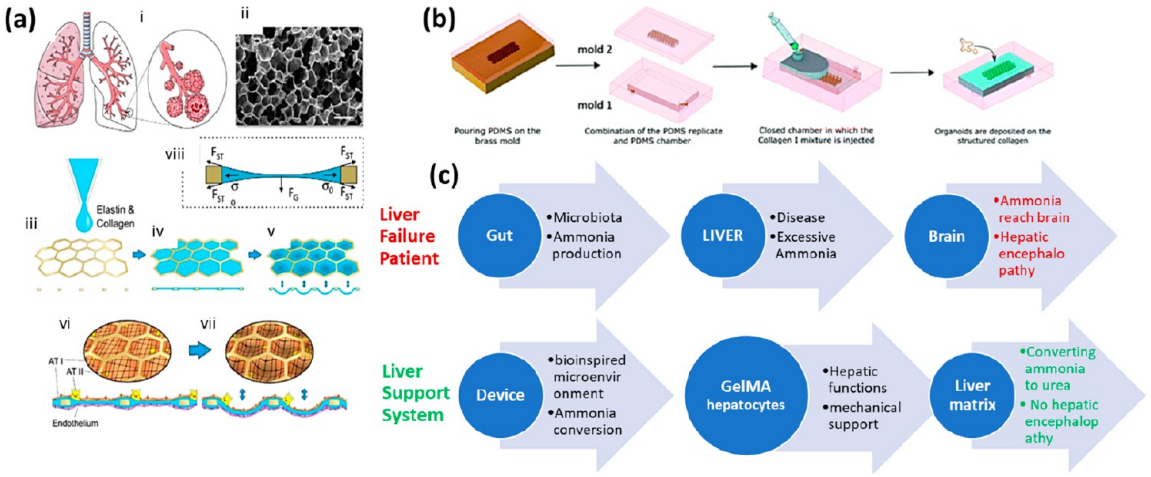


Figure 11. Lung-on-a-chip, gut-on-a-chip, and BLSS integrated with a DLM/GelMA-based bioengineered liver. Panel (a) has the following components: (i) a schematic of the respiratory treelike structure, ending with alveolar sacs; (ii) an SEM image of a slice of human lung parenchyma with tiny lung alveoli and their ultrathin air−blood barrier; (iii, iv) a schematic of the production of the CE membrane used in the second-generation lung-on-a-chip (here, a thin gold mesh with an array of hexagonal pores ∼260 μm in size is used as a scaffold, upon which a drop of collagen−elastin solution is pipetted); (v−vii) the collagen−elastin gel forms a suspended thin membrane that can be stretched at the alveolar level by applying a negative pressure on the basolateral side of the membrane (components (vi) and (vii) show Type I (ATI) and type II (ATII) primary human lung alveolar epithelial cells that are co-cultured with lung endothelial cells on the thin collagen−elastin membrane); and (viii) a schematic of the force balance during the drying of the membrane. (Legend: F_{ST}, surface tension force; F_G, gravity; and σ_o, residual stress.) [Reproduced with permission from ref 239. Copyright 2021, Springer−Nature.] Panel (b) shows scaffold microfabrication: PDMS (mold 2) replica of the micromilled brass mold is microfabricated. This PDMS replica is then noncovalently sealed with a second PDMS mold (mold 1) that consists of an open chamber (previously treated with APTES and glutaraldehyde). [Reproduced with permission from ref 348. Copyright 2021, Royal Society of Chemistry, London.] Panel (c) shows a graphical representation of a liver support system that defines the biotransform ammonia processes under various conditions and generates the risk of hepaticencephalopathy.

and regulate cellular behavior is directed toward the direction of future research. PEG−fibrinogen is used in tissue engineering as hybrid biomaterials,[55] including PLA−chitosan−gelatin and chitosan−siloxane.[56−58]

3.1.4. Natural OoC Materials. Manufacturing demands for bioartificial organs for replacement and drug testing analysis are continuously growing. With regard to organ regeneration, natural polymers are better suited to provide a stable environment for stem cells to develop, migrate, and proliferate, as opposed to silicon and glass and other synthetic polymeric materials. Many organic compounds are found in Nature; similarly, polymers that occur in Nature may be extracted via the physical or chemical processes mentioned in Figure 10. Some polymers, such as chitosan, gelatin, fibrin, hyaluronic acid, and collagen, can be easily degraded in water and other cell culture solutions, such as phosphate buffer saline. The polysaccharides and proteins could be potential candidates for diversified applications in OoC technology.[311−319] The natural biomaterials are crucial to consider with certain properties to be followed. In order to rebuild tissue properly, the degradation period of the natural material should sync with the regeneration process. Second, the material must be highly gas-permeable and easy to process. Furthermore, the material properties must mimic the daily functionality of human activities.

3.1.4.1. Collagen. Collagen is the most ubiquitous protein in the human body, and because of this, it provides physical support to tissues by inhabiting the intercellular space, as well as participating in cell behavior and tissue function.[233] It has emerged as a possible viable option for several pharmaceutical applications, because of its enzymatic degradation, mechanical strength, and physicochemical features, as well as its nontoxicity.[234−236] Chemical cross-linking, such as glutaraldehyde, has been utilized to improvise its mechanical characteristics and stability.[236] One of the beneficial functions of collagen are its cell-adhesive domains which makes it more suitable for OoC platforms and other adhesion sites for cells.

Ank reported a microfluidic device made of collagen-I hydrogel as a membrane and a method for injection molding the resulting material. This combined approach was used to encapsulate the created membrane within an organ-on-chip platform and then study the cell adhesion, structure, and gas permeability. Proteases can also be used as membranes in order to modify their thickness and permeability.[237] The Biowire-II platform allows for the formation of cylindrical cardiac microtissues and has open access liquid dispersal. Furthermore, investigations were performed for cell seeding density, nonmyocyte populations, hydrogel scaffolds, and electrical stimulation protocols.[238] Zamprogno demonstrated a lung-on-chip model that was comprised of biodegradable collagen and an elastin membrane that replicates an array of alveoli in vivo, as illustrated in Figure 11a.[239] This membrane has several distinct advantages: it is biodegradable, it can be easily fabricated, it does not absorb Rhodamine B, and its thickness can be easily changed using its composition. There are many simulations using microchip models of the gastrointestinal tract. However, they do not have a completely accurate representation of the multicomponent nature of the intestinal wall. Figure 11b shows a unique gut-on-chip model in which epithelial and stromal cells can be co-cultured. The device is built on a 3D Type 1 collagen scaffold that has topography and a small stomach. The scaffold was stabilized by threose-based post-polymerization treatment to maintain its cytocompatibility while keeping the scaffold structure.[240] A microfabricated bioreactor has been designed to replicate the form and function of natural cardiac bundles in vitro, utilizing cardiac biowires. The ECM was based on Type I collagen, which is one of the primary components of native myocardium. Perfusion within a cardiac bundle model better replicates myocardial mass transport features and was utilized to test the medication effects on cardiomyocytes.[241]

The antigenic sites in central helix and the nature of the terminal area limits the applicability of collagen-based natural materials.[242,243] On the other hand, animal-derived collagen has drawbacks, such as varying physical and chemical properties and allogeneic or xenogeneic sources, which increases the risk of infectious disease transmission.

3.1.4.2. Gelatin. Gelatin is naturally occurring polymer obtained through controlled alkaline, acid, or enzymatic hydrolysis of collagen. Because of its biological source, it is highly biocompatible and biodegradable, and given its widespread availability, it is a comparatively inexpensive polymer.[244] Gelatin has been utilized as a

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

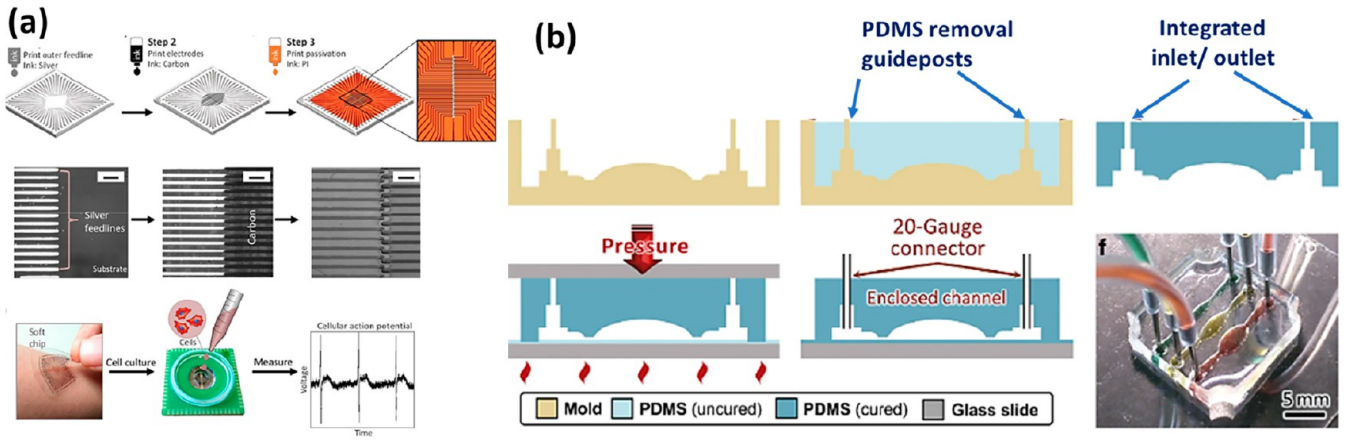


Figure 12. The myotube/fibrin gel sheet combined with the PEDOT microelectrode array chip, microfluidic biopolymer membranes, and fabrication of sacrificial template and casting of patterned vascular networks. Panel (a) has three sketches. The upper sketch shows the device principle and printing procedure demonstrated from step 1; the outer feedlines are printed with a silver nanoparticle ink on a 12 mm × 12 mm substrate. In step 2, the inner feedlines and microelectrode arrays (MEAs) are printed with carbon nanoparticle ink. In step 3, a 9 mm × 9 mm passivation layer is printed with polyimide ink (PI). The middle sketch shows microscopic images of the successive printing process of a carbon MEA on PDMS, subsequently depositing silver ink, carbon ink, and PI ink. Scale bars = 200 μm. The lower sketch depicts the principle of recording action potentials from electrogenic cells using the printed soft MEA. [Reproduced with permission from ref 358. Copyright 2018, Nature Publications.] Panel (b) depicts single-sided fabrication and bonding process flow. In the upper scheme, a 3D-printed mold is printed from a CAD file, including integrated inlet/outlet ports and guideposts to assist with the removal of PDMS. Here, the mold is filled with *l*PDMS, degassed, baked, and cured PDMS is demolded. In lower scheme, cured PDMS is bonded to glass using the PDMS−glass *l*PDMS spin-bonding technique to compensate for surface roughness. The final conceptual image is shown with the enclosed channel and 20-gauge connector pins attached. The last image is a glass-bonded device with colored fluid. [Reproduced with permission from ref 359. Copyright 2016, Nature Publications.]

matrix for implants and also as a stabilizer in vaccines against measles, mumps, and rubella in the pharmaceutical industry.[245] In addition, gelatin is water-permeable and has ability to dissolve in it, making it a versatile drug delivery vehicle.[246] The mechanical and physical properties, swelling actions, heat resistance, and a variety of other physiochemical properties of gelatin are highly variable, depending on the collagen source, method of extraction, and degree of cross-linking, which makes it an incredibly versatile polymer.[247]

Moreover, gelatin's capacity to form a thermally reversible gel makes it an excellent choice for drug-delivery systems. Gevaert et al. explored the impact of galactosylated gelatin on HepG2 cells that had been encapsulated. The study indicates that additional alterations to methacrylamide-modified gelatin are feasible without damaging the viability of the encapsulated cells.[248] The development of an anisotropic cardiac tissue on micromolded gelatin hydrogel cantilevers was done for use as muscular thin films (MTFs) for assessing contractile tissue stresses. It facilitated the long-term growth of synthetic rat and human cardiac tissues, it is likely that they more closely resemble the heart's chemical and mechanical milieu.[249]

The inability to re-create the structure and function of vascular networks and blood vessels is a significant unresolved obstacle in tissue engineering. Yang and colleagues described the development of a multicellular vascular channel utilizing the 3D printed designs implanted in a gelatin methacrylate (GelMA) hydrogel structure. This technique resulted in the formation of a two-cellular channel, with murine 10T1/2 cells contained within the GelMA matrix and human endothelial cells lining the lumen surface.[250] GelMA hydrogels can also be used as raw material in the development of artificial organs.[251] The discipline has made a significant contribution in liver-on-chip materials, which may be used to replicate the native liver milieu and assist in drug screening, clinical diagnostics, and tissue regeneration in vitro. Wu et al. recently introduced a liver support system in which GelMA and hepatocytes were integrated into a decellularized liver matrix.[252] In patients with liver failure, hepatocytes cannot biotransform ammonia from the intestine, and excessive ammonia passes through the blood−brain barrier and enters the brain, which can cause hepatic encephalopathy.[252] The device provides a bioinspired microenvironment for hepatic functions, as well as mechanical support. GelMA's biomechanical support promotes cell engraftment, which is critical for converting ammonia to urea and preventing hepatic encephalopathy. In addition, certain OoC models can be used to examine the development of tumor diseases.[252] Lu et al. established artificial tumor-on-chip devices using a microfluidics-based 3D dynamic culture system to simulate the tumor microenvironment (TME). The raw biomaterials used were GelMA decellularized liver matrix (DLM). It was discovered that when cells are exposed to flow environments, their viability is preserved and their hepatocyte activities are boosted. These findings demonstrate the potential of this TME biomimetic tumor-on-a-chip for pathological and pharmacological research.[253]

Gelatin's key benefits include its biodegradability, accessibility, and low cost. In addition, there are concerns about the spread of disease vectors, such as prions.[254] Recombinant gelatins can be used to address some of the difficulties associated with products derived from animal tissue. However, the use of gelatin in medical applications is often hindered, because of its weak mechanical characteristics. Because of the enormous number of functional side groups found in gelatin, these mechanical qualities can be improved through physical as well as chemical cross-linking; however, the compounds employed to stabilize cross-linked gelatin have frequently been rather hazardous to the human body.[255]

3.1.4.3. Fibrin. Fibrin is highly biocompatible and biodegradable, with a high degree of elasticity and viscosity.[256,257] Because of its injectability and biodegradability, it has been utilized to assist in the regeneration of variety of tissues, including adipose tissue, bone, cardiac, cartilage, muscle, neural, ophthalmic, respiratory, skin, tendons, and ligaments.[258−261] Numerous studies have demonstrated that using fibrin in the treatment of chronic periodontitis has resulted in increased healing of intrabody abnormalities.[262,263] Because of its versatility, this material has been utilized to construct scaffold-like cells, delivery matrices, and several tissues.[264,265] In OoCs, fibrin is often used as a artificial ECM component. Huh et al. introduced a lung-on-a-chip model using fibrinogen and prothrombin to explore fibrin clot formation in fluidic channels. Nagamine and colleagues demonstrated the skeletal muscle cell-based bioassay device on a microelectrode array chip for maximum durability, and to enhance muscle tissue for an extended period of time, the electrodes were coated with PEDOT.[266] Studies have shown that myotube/fibrin gel

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

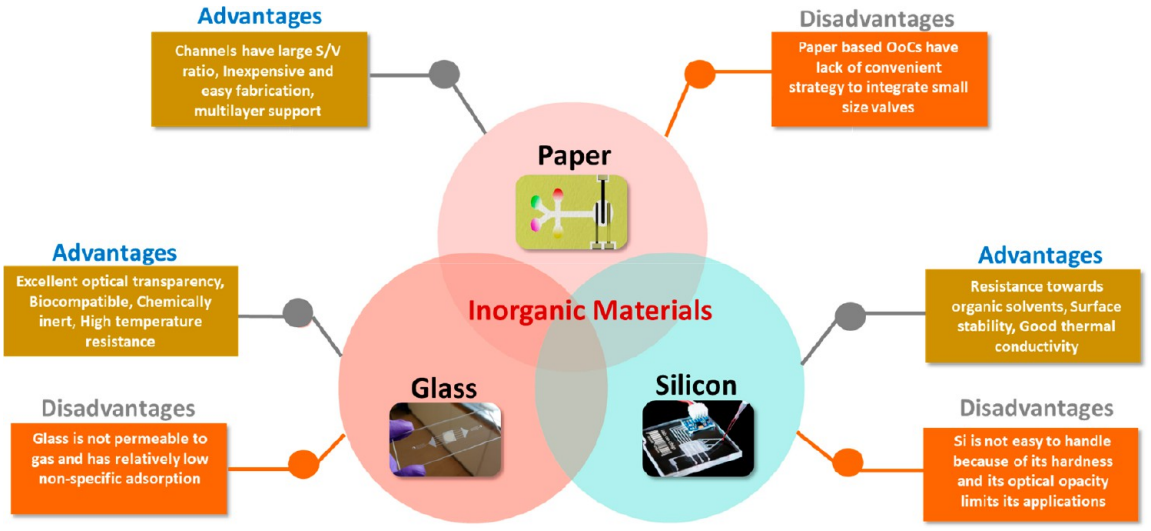


Figure 13. Advantages and disadvantages of silicon-, glass-, paper-based microfluidic devices.

sheet combined with the PEDOT microelectrode array chip, cell transfer from a glass substrate to a fibrin gel, and further attachment of the myotube/fibrin gel onto the microelectrode arrays.[266] This technology may be utilized to focus on a specific tissue construct, such as a neuromuscular junction.

Fibrin scaffold systems are effective for cell adhesion, proliferation, differentiation, and growth factor release.[262] Fibrin-based scaffolds have certain limitations; for example, they are highly fragile and decay rapidly. However, the mechanical strength and degradation rates of these materials have been improved by using stronger natural and synthetic polymers, various cross-linking processes, and micro/nanospheres.[267] The myotube/fibrin, PEDOT microelectrode array chip, microfluidic biopolymer membranes, fabrication, vascular networks, and 3D-printed mold are demonstrated in Figure 12.[358,359]

3.1.4.4. Hyaluronic Acid. As an essential part of tissue regeneration, as well as for 3D cell culture and 3D tissue engineering, hyaluronic acid (HA) has gained prominence in recent years.[268−270] The significant involvement of HA in wound healing makes it suitable for wound dressing purposes.[271,272] HA plays a crucial role in tissue repair by promoting epithelial and mesenchymal cell migration and differentiation.[273] The use of HA in OoC models is quite limited, although the use of HA in the form of thiolated gelatin, together with thiolated gelatin and PEG diacrylate, can be found in an OoC metastasis-on-a-chip platform that employs the gelatin as the hydrogel for tissue constructs.[274] There have been many research endeavors focusing on HA-based materials in biomedical engineering for applications such as tissue regeneration scaffolds. Because of the viscous nature of HA, scaffold preparation via this methodology becomes difficult. In order to overcome this problem, poly(ethylene glycol) (PEG) and polylactic acid (PLA) are cross-linked with HA to boost the gel forming abilities and mechanical strength, while offering a tunable degradation rate to the polymer.[275] However, various cross-linking modalities are not well-represented in the literature, and it is unclear how the different scaffold properties vary based on the chosen cross-linking technique. Based on the findings of Spearman, it is possible to apply two distinct methacrylation procedures (MAHA and GMHA) for the methacrylation of HA; these properties can also be varied by adjusting the degree of methacrylation.[275] It is possible for metastatic breast cancer cells (BCCs) to remain dormant in the location of the metastasis for many years following the treatment of the initial tumor. The urgent need to find a solution to this problem led Narkhede to develop an in vitro HA hydrogel platform that could accurately simulate brain metastatic cancer dormancy by providing in vitro physical cues in addition to providing a biological construct that exists in the range of normal brain and brain metastatic malignancy stiffness.[276,277]

3.1.4.5. Chitin and Chitosan. Chitosan is an another naturally existing polysaccharide that is typically applied in tissue engineering. The substance is derived from chitin, the second most abundant natural polymer found in crustacean and insect exoskeletons, as well as fungal cell walls.[278,279] Chitin/chitosan-based biomaterials have a wide range of uses, including synthetic biology, wound healing, and drug delivery. In addition, it has been claimed to have excellent biodegradability and biocompatibility, as well as anti-neoplastic, anti-ulcer, and hypocholesterolemic properties.[280−282] Its physical and chemical characteristics enable them to be molded into porous structures, contributing to the formation of polyelectrolyte complexes including anionic GAGs and cationic chitin or chitosan. This enables the chitin/chitosan complexes to make a significant contribution in tissue engineering by modulating the action of different growth factors and cytokines.[283] Rosella investigated the characteristics of collagen, chitosan, and collagen-chitosan hybrid biomembranes under a variety of hydrodynamic circumstances.[284]

Another work described the fabrication of a porous structure: a biodegradable chitosan sponge that was coupled with lithium chloride. The sponge had been prepared to aid in the healing process. The repaired skin exhibited normal thickness of the epidermis and hair follicle development.

In addition, mRNA expression analysis demonstrated that sponge-treated tissues maintained high levels of β-catenin, which is a critical factor in wound repair and dermis development.[283,284] The healing potential of a chitosan hydrogel synthesized with oxygenated fluorinated methacrylamide was investigated. Histological examination of diabetic rat skin treated with hydrogel revealed increased collagen fiber content, better re-epithelialization, and neovascularization.[285] Chitosan materials also possess few demerits. It is not soluble in organic solvents, which causes difficulty in the delivery of hydrophobic drugs. Moreover, the various processes that have been adapted for the solubilization of chitosan come with certain drawbacks and limitations.[286,287]

3.1.4.6. Alginate. Alginate is a commonly used natural material, primarily in tissue regeneration engineering, because of its non-toxicity, gentle, physical, and chemical cross-linking properties, and nonthrombogenic nature.[288] Furthermore, alginate can be integrated with other natural materials to create, enhance, and improvise existing properties.[289] Alginate is one of the most abundant natural materials on the planet, making it a very inexpensive and viable biomaterial to use.[290] Introducing cell-interactive qualities to alginate is becoming important in the future for the effective development of replacement tissues and organs.[291] Alginate-based gels must be more active in wound healing applications, containing one or more bioactive agents to assist wound healing, as opposed to the rather passive function that they now serve in therapeutic trials.[291]

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

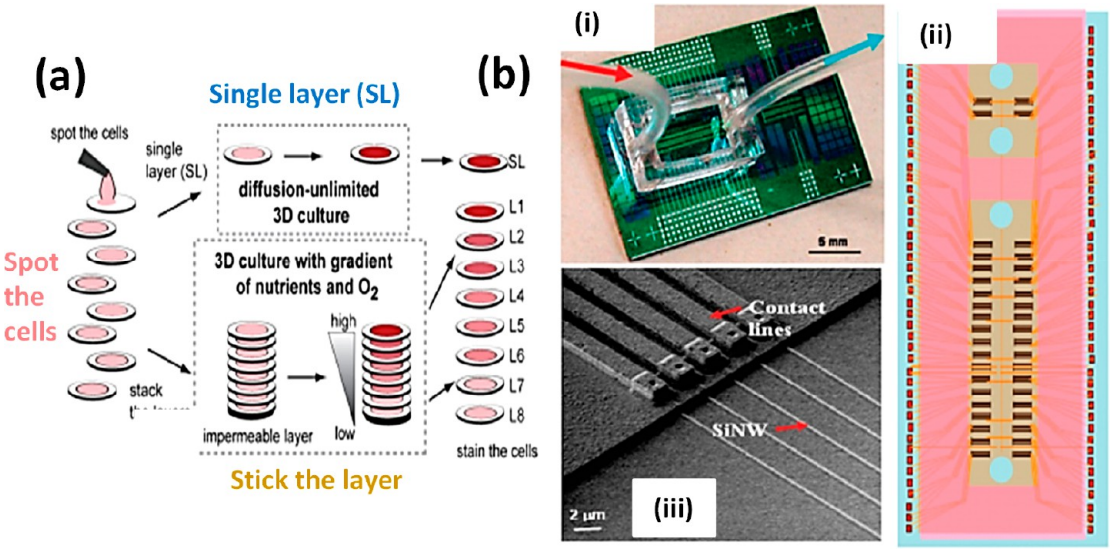


Figure 14. Paper and glass-based microfluidics for OoC. In panel (a), paper-based microfluidics have been investigated using a stacking method. [Reproduced with permission from ref 350. Copyright 2009, National Academy of Sciences, USA.] Panel (b) shows (i) an image of SiNW device array chip, integrated with microfluidic system for fluid exchange, used in the experiments (fluids are deposited into the acrylic well through the inflow tube on the left (red arrow) and removed from the outflow tube on the right (blue arrow)), (ii) a schematic showing the layout of the SiNW device array on the chip (a total of 36 clusters of 5 nanowires each are available for use, potentially allowing for simultaneous, multiplexed detection of assorted proteins), and (iii) an SEM image of a cluster of nanowires. Each nanowire is individually addressable by oxide passivated metal contact lines running out to the external edge of the chip. [Reproduced from ref 118. Copyright 2009, American Chemical Society, Washington, DC.]

The development of advanced in vitro models of the human heart occurs through cardiac spheroids (CSs). CSs were obtained using human cardiac myocytes, fibroblasts, and endothelial-cells and then bioprinted on a multielectrode plate for drug screening.[292] Alginate microgels based on microchips have revealed good prospects for encapsulating cells in a high throughput and controllable manner. However, cell development and bioactivities are significantly reduced as a result of severe gelation circumstances, which remain a significant barrier to cell encapsulation. An effective and biocompatible approach to develop microchip alginate microgels for single-cell encapsulation involves the use of chip-induced gelation. Two calcium complexes—calcium ethylenediaminetetraacetic acid (Ca-EDTA) and calcium nitrilotriacetic acid (Ca-NTA)—were compared and studied for tissue engineering and cell therapy applications as cross-linkers for inducing the gelation of alginate.[293] Alginate has also been used in other OoC platforms; for example, 3D alginate hydrogels used to encapsulate cells are employed to fabricate various patterns that use an electrodeposition method that uses visible light and has various other applications, including a sacrificial material for quickly fabricating patterned vascular networks.[294] Studies have demonstrated a multilayered microfluidic system comprised of a structure-patterned PDMS layer (sodium alginate layer) and another PDMS layer ($CaCl_2$ layer) sandwiching a porous polycarbonate membrane and other characteristic features, such as encapsulation, for diverse functionality.[349]

3.1.5. Inorganic OoC Materials. Initially, inorganic substrates were favored for microfluidic systems, because of their greater surface stability, variable heat conductivity, and solvent compatibility. Even before the notion of microfluidics was defined, microchannels in the glass capillaries were used in gas chromatography. Early, microfluidic devices were developed using silica or glass. At the time, silicon increasingly became the predominant chip material; even so, silicon is optically opaque, creating a difficulty for applications that involve optical measurements. In contrast, glass exhibits exceptional optical clarity, a well-defined surface chemistry, and greater resilience to high pressure, making it ideal for use in microfluidics. The primary issue is in fabricating high-aspect-ratio anisotropic structures from amorphous glass. Interestingly, little literature has demonstrated liquid glass in the form of a photocurable amorphous silica nanocomposite. A summary of silicon-, glass-, and paper-based microfluidic devices is illustrated in Figure 13.

3.1.5.1. Paper. Prior to the discovery of paper-based microfluidics, most of the devices were developed in closed channels. However, these microfluidic devices do not always need to be sealed, for which paper-based devices are a good example.[295] These papers are cellulose-based materials that have recently emerged as a viable microfluidic substrate for OoC and other biomedical usage, because of a variety of factors, including its high flexibility, low cost, biocompatibility, and ease of commercial availability.[126] Furthermore, it can be easily modified via a variety of chemical processes, such as changing the composition. It can be degraded easily through natural processes and does not release any harmful byproducts. Its white background provides contrast for colormetric-based detection approaches.[127,128] By using capillary action, aqueous solution applied to the paper will be carefully guided via a hydrophilic zone while some portions of a paper are transformed hydrophobically. It is possible to find a variety of methods for patterning paper microfluidic channels. Meanwhile, each of them possesses their own sets of pros and cons. Example, inkjet and solid wax printing make design and development easy to functionalize and straightforward.

Paper is also suitable for biochemical, pharmaceutical, and forensic analysis and analyte detection (colorimetric, electrochemical, chemiluminescence, and electro-chemiluminescence). Dungchai et al. used electrochemical sensing in paper-based microfluidic devices to measure glucose, lactate, and uric acid in human serum samples.[129] Liu and Crooks presented a single-origami paper-based microfluidic system that could detect glucose and bovine serum albumin using fluorescence as well as colorimetry.[130] Derda and colleagues demonstrated a technique for seeding cells on stacking layers of sheets for 3D operations and culture.[131] As illustrated in Figure 14a, the cell-loaded sheets were arranged in a 3D hierarchy. Because of nutrition and oxygen consumption, cells on various paper layers were exposed to nutrient and oxygen concentrations that varied. Then, without optical or histological sectioning, the sheets were destacked and cell activities were observed. This approach was used to examine cancer cell chemotaxis with different oxygen concentrations.[132] Moreover, a 3D tumor culture by tissue roll for analyzing the cellular environment and response (TRACER) has been proposed.[133] Different cell types were seeded on the paper in designated areas,

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

Figure 15. Properties of chip materials for OoC developments.

and the biocomposite strips were subsequently rolled using a custom-built aluminum mandrel.

The oxygen and culture medium concentration gradients were simulated inside this setup. After unrolling and dismantling the strip, the bioactivities of cells that were exposed to hypoxic gradients were examined. Concentration gradients of nutrients and metabolic wastes can be simply created by stacking or rolling the sheets, and assessment can be quickly performed via destacking or unwrapping. Microfluidic device creation with paper has many advantages:

- It can act as a pumpless microfluidic device, since the microchannel operates as a passive pump dispenser
- It can have a high surface-to-volume ratio
- It is easy to create multilayer microfluidic devices
- These technologies, however, come with some drawbacks
- The fabric matrix of the channel can block internal signals and dilute the sample during transportation; sensitivity is generally insufficient
- As a result of hydrophobicity, liquid surface tension may not be good in the channels
- Small-sized valves can be integrated
- Vaporization can also be an issue in these devices

3.1.5.2. Silicon. Silicon was the very first material used in microfluidics, although that was shortly supplanted by glasses and, subsequently, polymers.[111,112] Silicon was initially chosen for its resistance toward various solvents, its convenient deposition process, excellent thermoconductive properties, relatively higher elastic modulus (130−180 GPa), and steady electro-osmotic mobility. In a typical fabrication process, subtractive methods (wet and dry etching) or additive methods (metal/dielectric/insulating deposition) are used to fabricate microfluidic devices.[113] The surface chemistry of Si is defined by the silanol group (−Si−OH); hence, a possible approach for reducing nonspecific adsorption or promoting cellular development would be chemical modification of the silicon substrate.[114−116] Droplet-based polymerase chain reaction,[116,117] cell culture, and nanowires for label-free cardiac biomarker detection[118] are some of the silicon-based biomed applications that have been studied, as shown in Figure 14b. Although this technology is difficult to work with, because of its stiffness and hard-to-design components, like valves and pumps in microfluidic devices. It involves the use of harmful chemicals during its fabrication process. It is an opaque material and while transparent to infrared light, this makes it difficult for use in devices for optical measurement. Silicon's many drawbacks, especially its expensiveness, further reduce its desirability for constructing microfluidic OoC devices. The initial silicon-based organ-on-chip devices were reported by Shuler and co-workers in 2004.[25] Their study demonstrated a cell culture analog system (μCCA), utilized for mammalian cell cultured in interconnected chambers to represent physiologically based pharmacokinetic models.[343] It involves three chambers (lung-liver-other) μCCA device fabricated on 2.54 cm square silicon chip shown in literature.[25] Furthermore, they implemented an oxygen sensor onto the μCCA device, which showed the ability of integrating sensors in the μCCA device.

3.1.5.3. Glass. Following an early focus on silica, glass was chosen as medium manufacturing microfluidic organ on chip devices. It is an amorphous substance that is optically transparent and shows resistance toward electricity. Usually, these are processed using conventional photolithography or wet/dry etching techniques.[133] It has a low background fluorescence and high resistance toward chemicals. On the other hand, it is less expensive and it easy to construct organ-on-chip devices on a glass substrate instead of creating molds for replication using polymer-based technologies.[119] In addition, it is absolutely suitable for biological specimens; it is a substance that is impermeable to gas and has a low nonspecific adsorption capacity. Because of the fact that oxygen cannot enter via glass chips, often channels and chambers are closed; this makes it incompatible for long-term cell-culture usage. Capillary electrophoresis (CE) is a significant application of glass chips.[120,121] This less-expensive technology is much more efficient to conventional CE because it allows for faster parallel analysis setup and electro-osmotic flow. Glass has a dependent elastic modulus that is used in the valves and pumps.[122,123] For applications that demand high pressure, glass is preferred. Finally, glass microchannels deliver improved action, in comparison to other materials, because of their thermoconductivity and electro-osmotic mobility. Glass-based devices are used for precise

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

cell-based assays to assess hydrophobic molecules. A study revealed that glass devices have high cell adhesiveness and low absorption, and therefore, should be useful in the cell-based assay for small hydrophobic molecules.[124] Because of hardness and the fabrication costs, the use of glass in microfluidics is limited,[125] which gives further opportunity for the development other low-cost chip materials.

3.2. Properties of OoC Materials. Various materials are reported for the development of OoC devices. Some of the most essential properties that the materials should possess are shown in Figure 15.[48] Furthermore, these materials must sustain their functional characteristics over a longer period. Several materials bear specific characteristics, including optical transparency, elasticity, gas permeability, biocompatibility, etc. for devices.[49−52] Animal models are costly, time-consuming, analytical but not correct for human conclusions, and are troubled with ethical burdens from society. Therefore, because of the resemblance of OoC performance with the physiology of the human body, the properties of OoC materials provide a way to examine biochemical gradients, active mechanical services, and tissue interfaces. The potential properties in physiological and pharmacological investigations are inclusive in cost-effective approach. The organ-on-a-chip can be relevant to micro(patho)physiological processes for immune system. To date, most of inflammation-on-a-chip devices have used a gradient of proinflammatory cytokines to study migration patterns and mostly been studied to evaluate drugs or for immunotherapy.[149] The interaction of the chip system with the human immune system or their compatibility have not been studied extensively.[149] Study shows that immunomodulatory OoCs use inflammatory biomolecules, i.e., pro- and anti-inflammatory cytokines, to modulate the cells to obtain the desired immune response and focus shifted toward the purpose of new generations of biomaterials (for example, synthetic peptide structures and cell-responsive polymers).[150] The tumor-on-a-chip is helpful to comprehend the physiological function of the goal organ, in terms of the cell types, structures, etc. Ex vivo platforms are effective to study the influence of the tumor microenvironment on immune cell recruitment.[151,152]

4. BIOINSPIRED ORGAN-ON-A-CHIP (OOC)TECHNOLOGY

The new pledges of healthcare technology have resulted in the growing demand for alternative physiological procedures. The global needs push the translational research and related market, different dynamics of the healthcare industry, digital and engineering technologies, manufacturer strategies, biomarkers research, nanomaterials compatibility, and aspects that are playing a substantial role in the upcoming marketplace. The breakthrough biomedical research and materials progress will help the key players to shape a roadmap of key segments, understand the trends, and drive the focus to develop holistic organ-specific application devices for global demands. However, understanding the limitations of technology, trends of bioinspired technology, and their utilization is must to frame the potential prospect.

5. TRANSLATIONAL AND MARKET POTENTIAL

Noteworthy, OoC technology requires multidisciplinary translational research and trials to become commercially accessible and applicable. In the past few years, several firms and startups have released OoC-based products for tissue/organ modeling (see Table 4). Mimetas OrganoPlate has demonstrated many different applications in this industry. Vulto and Joore improved the microfluidic channels by creating hydrogel−liquid interfaces.[361−363] The system involves meniscus pinning barriers, which utilize the Phaseguides technology, and is used to get precise, barrier-free defined cultured matrices and 3D cells.[296] Culturing of biological cells (neurons, hepatocytes, endothelial, kidney, cancer, etc.) has been accomplished in the

Table 4. Major Companies and Startups Working on the Advancements of Organ-on-a-Chip Technology

sample	company	technology	characteristics	services	products	website
1	human biological tissue company (Germany, 2010)	on-chip pump, constructs that closely simulates the activity	dynamic circulation with vascular perfusion, variable physiological shear stress application	custom chip designing and organ attachment	HUMIMIC chip, HUMIMIC starter, HUMIMIC AutoLab, HUMIMIC AutoPlant	https://www.tissuse.com/en/
2	microfluidic 3D tissue and organ culture company (Dutch, 2013)	capture stunning biology in the most versatile and user-friendly 3D tissue culture platform ever; OrganoPlate enables you to study relevant 3D tissue biology by incorporating perfused tubules, coculture, and full control over the tissue microenvironment	OrganoPlate is a microfluidic 3D tissue culture plate, supporting up to 96 tissue models on a single plate; its unique PhaseGuide technology enables cells to interact and migrate freely between channels	compound profiling/screening on a 3D tissue model, custom model-assay development	OrganoPlate PhaseGuide, OrganoPlate 2-lane, OrganoPlate 3-lane, OrganoPlate Graft, OrganoPlate Caco-2, OrganoTEER, OrganoFlow L	https://www.mimetas.com/en/home/
3	multiorgan culture chip-lab company (United States, 2013)	human emulation system for multiorgan culture chip-lab equipment interfacing	flexible plastic chip with a porous membrane allows organ chips to be transported and placed on standard microscopes for imaging up to 12 organ chip combinations	toxicity analysis, drug−drug interaction, inflammation services	Organ-Chips Pod Portable Module Zoë Culture Module Orb Hub Module Biokit for kidney, liver and intestine	https://emulatebio.com/
4	microfluidic device for 3D cell culture based company (Singapore, 2012)	microfluidic device for 3D cell culture, hydrogel-injectable, gas-permeable, multicellular co-culture	compatible with all polymerizable gels, enables the control of interstitial flow across the 3D gel region, rapid media exchange through vacuum aspiration	to design custom assays to deliver clinically relevant results	microscope slide format chips	https://aimbiotech.com/

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

Mimetas system. Marx and colleagues (from the Technische Universität Berlin) developed a multiorgan platform known as "TissUse". TissUse introduced gravity-driven media flow facilitated to achieve a pumpless fluid flow system. Furthermore, the company produced some products, such as HUMIMIC Chips for various in vitro modeling objectives. In this, microfluidic channel connects the organ models, which are sealed with human-dermal-microvascular-endothelial-cells.[297] With the main goal being a better understanding of diseases/drug models and the effect of food on our health, a new U.S.-based startup called Emulate devised the first commercialized organ-on-chip models. Ingber's group at the Wyss Institute for Biologically Inspired Engineering in Harvard, which designed a lung on a chip system in 2010, that reproduces the functionality of the lung-alveolus, such as the breathing mechanism. AIM Biotech has provided another fascinating OoC chip, which consists of a gel region with adjacent media platforms isolated from gel channels by trapezoidal posts.

The chip is used to cultivate cells in 3D, and to support the circulation of immune cells, e.g., T-cells in the channels that are immediately close to the gel channel. The primary objective of OoC devices is to replicate human organs and, subsequently, the modeling of drug interactions with the human physiology. The biomedical industry involves numerous procedures, several of which are demanding, and compose a highly competitive market. Thus, switching to a modern innovation may lead to potential losses in the production of drugs. Another way to view OoC is to examine it as a new technology with much of the related research still in the early stages of exploration and, thus, not mature enough to be incorporated into ongoing drug development projects. Even though several start-ups throughout the world have invested considerable effort in developing OoC device prototypes, despite all this effort, introducing OoC technology into the industrial scale is encountering numerous scientific, technical, and industrial obstacles. The manufacturer must ensure that OoC devices are consistent, cost-effective, ascendable, and produced at large scale. Quality OoC systems require skilled scientific personnel, equipment and model characterization during the cell culture process. The production of OoC devices for commercial processes is a key challenge to the OoC technology as it originates and extends from university laboratories with the established manufacturing procedures. OoC manufacturing calls for a multidisciplinary approach for engineers, manufacturing experts, materials researchers, and biologists.

Many firms are building OoC devices, such as those included in Table 4. These companies are making considerable strides toward offering exploratory platforms for feasibility studies with intriguing developments at a rising rate. As a result, many big pharmaceutical firms are engaged in OoC R&D feasibility studies (for instance, Emulate, Inc.'s medication candidate screening partnership with Johnson & Johnson (NJ, USA)). To study the potential of OoC models in drug screening, TissUse GmbH is partnering with Bayer AG (Leverkusen, Germany) with AstraZeneca.[298] Several other firms have also announced similar collaborations with unannounced partners in the industry.

6. TRENDING RESEARCH, FOCUSED TECHNOLOGY, AND LIMITATIONS

The concept of organ-on-chip is still in its early stages, and it has gained a significant amount of interest among researchers in academia. Yet, to transfer this technology from the laboratories to an industrial scale, a massive effort is required. Although remarkable progress have been made in materials field over recent decades, some clinical limitations restrict them from being widely adopted in the human body. A road map study shows that tuning of the following components may require special focus before the successful adaptation of OoCs technologies for users and developers:[299,300]

- Materials utilization—substrates, cells, and perfusion media
- Devices—size, footprint, functionality, and accessibility
- Interfaces—cross-compatibility, with laboratory instrumentation and workflows
- Bioassays—cell culture study, phenotypic and genotypic characterization, etc.
- Data validation—formatting, analysis, archiving, and sharing

The engineering of advanced biomaterials has found striking applications, such as biosensors, point-of-care diagnostics, cellular differentiation, stem-cell, resonance imaging, drug delivery, etc.[303−311] The extensive biocompatibility research and clinical trials may be helpful for adopting technology widely. However, tangible support from government funding and business partners, particularly, the pharmaceutical companies, has provided an immense boost in the development of OoCs. OoC materials are considered to be the top emerging technologies delivering services for precision medicine. Studies show that the structural and functional characteristics of human tissue are mimicked by OoCs and are responsible for the construction of physiological models, drug development, and toxicology from the viewpoint of different organs.[300]

Identification of suitable biomarkers, their sensitivity and specificity for the physiological consequences, and clinical validity through trials is challenging. Same way identification of suitable alternative materials, their cost of manufacturing and experimental implementation, reusability, suitable sensors are required for the technology.[301] Emerging materials play a diverse role, because of their architecture, design, and constituents, and deliver functionality of bioactivity with compatibility.[312−314]

Trending translational research shows that OoCs technology offers an excellent platform for disease modeling for various issues and organs such as pulmonary edema, protein-induced lung inflammation, central nervous system disease, type 2 diabetes, chronic obstructive pulmonary disease, inflammation sensing, etc.[302] Potential usage in a range of healthcare applications, advanced biomaterials, and nanomaterials play role in functional therapeutics, diagnostic device, DNA extraction, gene targeting, translational materials, engineering devices, tissue engineering, and organ regeneration.[311]

The bioprinting technology suitable for lung cancer research under a controlled microenvironment in a 3D tumor model, while therapeutical in anticancer drug screens in a breast ductal carcinoma and blood−brain barrier (BBB)-on-chip systems, is studied for a better understanding of disease progression.[303] CRISPR-Associated microfluidic channels and chips provide services in a cost-effective and high-throughput manner.[351]

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

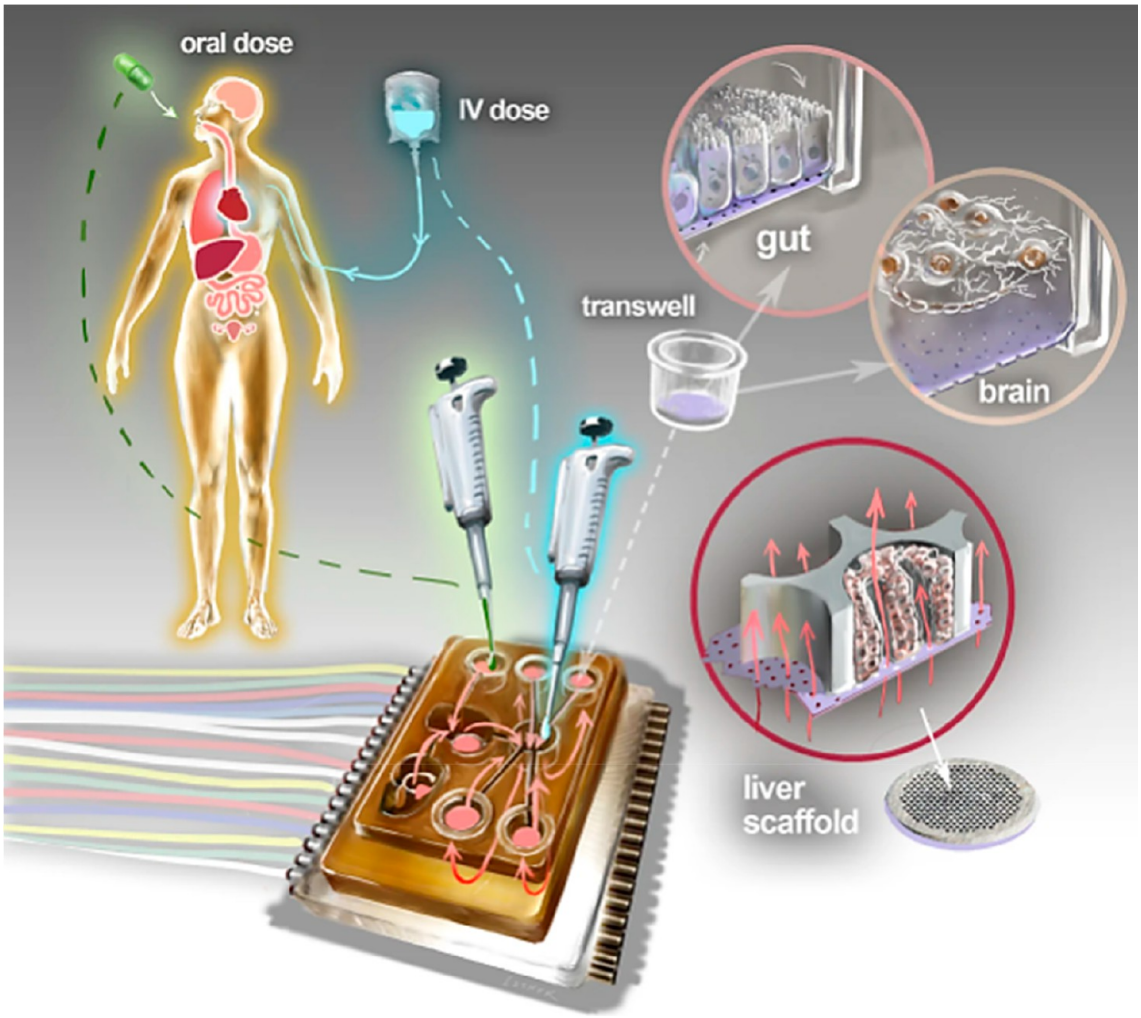


Figure 16. Schematic overview of Physiome-on-a-chip approach. The Physiome-on-a-Chip consists of bioengineered devices that nurture many interconnected 3D MPSs, representing specified functional behaviors of each organ of interest, designed to capture essential features of in vivo physiology based on quantitative systems models tailored for individual applications such as drug fate or disease modeling. (Illustration by Victor O. Leshyk.) [Reproduced with permission from ref 360. Copyright 2018. Nature Publications.]

Digital technology such as deep learning for image digitization, data analysis, and automation contribute in OoC extensively.[352] The digital organ-on-a-chip platform provides high-parallelism and a low-variability analytical tool for toxicity assessment to combat cancer.[353] High-tech technologies such as biofabrication, artificial intelligence (AI), robotics, and automation benefits the OoC technology regularly.[354] Edington et al. defined the interconnected microphysiological systems for quantitative biology and pharmacology studies.[360] This study illustrates several generalizable design and operational principles for implementing multi-MPS "physiome-on-a-chip" and potentially providing better prediction of human responses at lower financial and ethical costs as compared to current methods of drug development. Schematic overview of Physiome-on-a-chip approach is demonstrated in Figure 16, where bio-engineered devices that nurture many interconnected organ of interest for specific functional behaviors is illustrated. This kind of models is useful for drug fate or disease modeling.

Although OoC technology has excellent potential to adopt and implement the functionality; however, data analysis, clinical mechanisms, and medicine strategy still need to be optimized for specific biological conditions. Therefore, for the expansion of an automatic OoC structure to require a reliable, clinical platform for medical professionals, it should be adopted through medical policy, ethical guidelines, and a standard clinical practice model to avoid complex clinical challenges.

7. FUTURE PROSPECTS AND UTILIZATION

A revolution in scientific approaches to studying various diseases, ranging from pathophysiology to drug discovery, has taken place with the development of organ-on-a-chip (OoC) devices. More importantly, recent studies utilize human-induced pluripotent stem cells (hiPSCs) to develop personalized tissue or organ models. These integrated multiple organs on the single chip produce the best options for absorption, distribution, metabolism, excretion, and toxicity (ADMET) processes to predict drug efficacy and safety.[330] Applications for the neurodegenerative diseases and their relevance in translational personalized medicine lie in the study of the brain-on-a-chip, blood−brain barrier (BBB)-on-a-chip, and neurovascular unit (NVU)-on-a-chip, which provide testing platforms for high-throughput pharmacological screening.[331] A perspective on the future clinical applications lies in the feto-maternal interface OOC (FM−OOC) models, in obstetrics research, or in integrated multiple organ systems to make our

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

understanding for toxicity and therapeutic strategies.[332] Application of the clinical research, for patient benefit, lies in the functional testing for precision medicine.[333]

Choosing the proper type of chips is the first and most critical step to the successful application of OoC devices. Nanomaterials-based immunosensors and biosensor research are extensively used for biomedical application of diagnosis and therapeutics and can be used to transform the information at technology readiness levels (TRLs) to facilitate the device formulation for various diseases.[317−321] A stimuli-responsive interface based on responsive material is helpful to generate controlled and programmable bioelectronics.[322]

Many materials have been modified to build microphysiological processes capable of emulating the function of human tissues and organs to a large extent over the past many years.[34,334−341] These ideas are useful for clinical trials because they are inexpensive, easy to perform, and relevant to the human body. OoC technology, which focuses on microscopic research and inexpensive, portable tests, has helped drive the rapid advancement of chip materials. In general, choosing materials for laboratory research should allow for a good balance between the simplicity of the prototype and the overall performance of the device, whereas for commercial applications, the biggest challenges are the cost of production and how easy and reliable the product is to use. It seems that the current trends are to use glass, silicon, and PDMS in research laboratories, and plastic and paper in commercial products. Many materials have benefits and drawbacks. Teflon, glass, and silicon are the most inert materials when it comes to chemicals and solvents; PDMS is a good candidate for complex microfluidic circuits, while thermoplastic materials are good for commercialization and mass production of standard microfluidic devices.

Furthermore, numerous types of biocompatible materials suitable for 3D bioprinting have been developed, making 3D bioprinting a practical approach for creating complex chip structures. OoCs have benefited from these advancements in materials and construction techniques. However, these OoC devices are able to handle only a few obstacles. Even while simulated microenvironments are highly developed, they do not quite mimic the natural ECM microenvironments. In addition, the natural microenvironment is dynamic and ever-changing. Finally, constituents of integrated system, such as suitable materials for chip, sensitive biomarkers, and important fabrication techniques, are important for future organ-on-chip research to develop compatible microfluidic skills which precisely report and mimic the in vivo niche of the human body.

8. CONCLUSIONS

Imperative utilization of OoC materials has attained dominance in the translational biomedical field of physiology, diagnosis, and healthcare monitoring. The precise analytical device uses biocompatible materials for biological sensing. Thus, it can be said that the recent advances in the development of cell-encapsulating materials have provided significant understandings in microphysiological systems that, earlier, were challenging to achieve in the OoC. The current understanding of disease progression is based on structural engineering, sensor technology, biomarker research, clinical validation and softwares used on OoC materials, which offers deeper insights about human health and disease. In the foreseeable future, integration of technological inputs at various extents, such as emerging materials, digitalization, AI, ML and advanced genomics, make it possible to spread and adopt massively at an affordable cost. Moreover, the adoption of such systems is revealed, through policies and protocols, to be more effective (for example, cheaper healthcare system more specifically for emerging infectious and challenges of chronical disease. Remarkable advances have widespread application of materials with advanced technologies to led to future transformation of biomedical field through wearable, implantable and automated devices for healthcare monitoring with preprognosis strategies.

AUTHOR INFORMATION

Corresponding Author

Ashutosh Tiwari − *Institute of Advanced Materials, IAAM, Ulrika 59053, Sweden;* orcid.org/0000-0001-5634-7749; Phone: (+46) 1313-2424; Email: director@iaam.se

Authors

Bishal Kumar Nahak − *Institute of Advanced Materials, IAAM, Ulrika 59053, Sweden*

Anshuman Mishra − *Institute of Advanced Materials, IAAM, Ulrika 59053, Sweden*

Subham Preetam − *Institute of Advanced Materials, IAAM, Ulrika 59053, Sweden*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsabm.2c00041

Author Contributions

[▽]These authors made equal contributions to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

A.M. is thankful for a Prof. Herbert Gleiter Fellowship from International Association of Advanced Materials, Sweden.

ABBREVIATIONS

PDMS, polydimethylsiloxane; MPS, microphysiological systems; FDA, Food and Development Administration; OoC, organ-on-a-chip; LoC, lab-on-a-chip; μTAS, microscale total analysis systems; PBPK, physiologically based pharmacokinetic; ADME, absorption, distribution, metabolism, and excretion; IVIVE, in vitro to in vivo extrapolation; ECM, extracellular matrices; dECMS, decellularized extracellular matrices; PU, polyurethane; FEMP, tetrafluoroethylene propylene; PPS, poly(polyol sebacate); PGS, poly(glycerol sebacate); POMaC, poly(octamethylene maleate (anhydride) citrate); PICO, poly(itaconate-co-citrate-co-octanediol); P-(OCS), poly(octanediol-co-(citric acid)-co-sebacic acid); PLGA, poly(lactic-co-glycolic acid); μCCA, cell culture analog system; CE, capillary electrophoresis; TRACER, tissue roll for analyzing the cellular environment and response; MEMS, microelectro mechanical systems; PMMA, poly(methyl methacrylate); PTFE, polyethylene terephthalate; COC/COP, cyclic olefin polymer/copolymer; PS, polystyrene; PC, polycarbonate; PFPE, perfluoropolyether; PEGDA, poly-(ethylene glycol) diacrylate; PEEK, polyether ether ketone; PTFE, poly(tetrafluoroethylene); PEO, poly(ethylene oxide); PET, poly(ethylene terephthalate); GelMA, gelatin methacrylate; TME, tumor microenvironment; HA, hyaluronic acid;

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

PEG, poly(ethylene glycol); PLA, polylactic acid; CS, cardiac spheroid

REFERENCES

(1) Harrison, D. C.; Winkle, R.; Sami, M.; Mason, J. Encainide: a new and potent antiarrhythmic agent. *Am. Heart J.* **1980**, *100*, 1046−1054.

(2) Lai, W.; Chang, Y.-F.; Chou, F.-N.; Yang, D.-M. Portable FRET-Based Biosensor Device for On-Site Lead Detection. *Biosensors* **2022**, *12* (3), 157.

(3) Mi, F.; Hu, C.; Wang, Y.; Wang, L.; Peng, F.; Geng, P. F.; Guan, M. Recent advancements in microfluidic chip biosensor detection of foodborne pathogenic bacteria: a review. *Anal. Bioanal. Chem.* **2022**, *414*, 2883−2902.

(4) Huang, F.; Zhang, Y.; Lin, J.; Liu, Y. Biosensors Coupled with Signal Amplification Technology for the Detection of Pathogenic Bacteria: A Review. *Biosensors (Basel).* **2021**, *11* (6), 190.

(5) Mo, T.; Liu, X.; Luo, Y.; Zhong, L.; Zhang, Z.; Li, T.; Gan, L.; Liu, X.; Li, L.; Wang, H.; Sun, X.; Fan, D.; Qian, Z.; Wu, P.; Chen, X. Aptamer-based biosensors and application in tumor theranostics. *Cancer Sci.* **2022**, *113* (1), 7−16.

(6) Wang, G.; Jiang, G.; Zhu, Y.; Cheng, W.; Cao, K.; Zhou, J.; Lei, H.; Xu, G.; Zhao, D. Developing cellulosic functional materials from multi-scale strategy and applications in flexible bioelectronic devices. *Carbohydr. Polym.* **2022**, *283*, 119160.

(7) Echt, D. S.; Liebson, P. R.; Mitchell, L. B.; Peters, R. W.; Obias-Manno, D.; Barker, A. H.; Arensberg, D.; Baker, A.; Friedman, L.; Greene, H. L.; et al. CAST Investigators. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: The Cardiac Arrhythmia Suppression Trial. *N. Engl. J. Med.* **1991**, *324*, 781−788.

(8) Plenge, R. M. Disciplined approach to drug discovery and early development. *Sci. Transl. Med.* **2016**, *8* (349), 349ps15.

(9) Capulli, A. K.; Tian, K.; Mehandru, N.; Bukhta, A.; Choudhury, S. F.; Suchyta, M.; Parker, K. K. Approaching the in vitro clinical trial: engineering organs on chips. *Lab Chip* **2014**, *14*, 3181−3186.

(10) Hooijmans, C. R.; Ritskes-Hoitinga, M. Progress in using systematic reviews of animal studies to improve translational research. *PLoS med.* **2013**, *10*, No. e1001482.

(11) Benam, K. H.; Novak, R.; Nawroth, J.; Hirano-Kobayashi, M.; Ferrante, T. C.; Choe, Y.; Prantil-Baun, R.; Weaver, J. C.; Bahinski, A.; Parker, K. K.; Ingber, D. E. Matched-comparative modeling of normal and diseased human airway responses using a microengineered breathing lung chip. *Cell Syst.* **2016**, *3*, 456−466.

(12) Huh, D.; Matthews, B. D.; Mammoto, A.; Montoya-Zavala, M.; Hsin, H. Y.; Ingber, D. E. Reconstituting organ-level lung functions on a chip. *Science* **2010**, *328*, 1662−1668.

(13) Kilic, O.; Pamies, D.; Lavell, E.; Schiapparelli, P.; Feng, Y.; Hartung, T.; Bal-Price, A.; Hogberg, H. T.; Quinones-Hinojosa, A.; Guerrero-Cazares, H.; Levchenko, A. Brain-on-a-chip model enables analysis of human neuronal differentiation and chemotaxis. *Lab Chip* **2016**, *16*, 4152−4162.

(14) Park, J.; Lee, B. K.; Jeong, G. S.; Hyun, J. K.; Lee, C. J.; Lee, S. H. Three-dimensional brain-on-a-chip with an interstitial level of flow and its application as an in vitro model of Alzheimer's disease. *Lab Chip* **2015**, *15*, 141−150.

(15) Jastrzebska, E.; Tomecka, E.; Jesion, I. Heart-on-a-chip based on stem cell biology. *Biosens. Bioelectron.* **2016**, *75*, 67−81.

(16) Marsano, A.; Conficconi, C.; Lemme, M.; Occhetta, P.; Gaudiello, E.; Votta, E.; Cerino, G.; Redaelli, A.; Rasponi, M. Beating heart on a chip: a novel microfluidic platform to generate functional 3D cardiac microtissues. *Lab Chip* **2016**, *16*, 599−610.

(17) Musah, S.; Mammoto, A.; Ferrante, T. C.; Jeanty, S. S.; Hirano-Kobayashi, M.; Mammoto, T.; Roberts, K.; Chung, S.; Novak, R.; Ingram, M.; et al. Mature induced-pluripotent-stem-cell-derived human podocytes reconstitute kidney glomerular-capillary-wall function on a chip. *Nat. Biomed. Eng.* **2017**, *1*, 1−12.

(18) Wilmer, M. J.; Ng, C. P.; Lanz, H. L.; Vulto, P.; Suter-Dick, L.; Masereeuw, R. Kidney-on-a-chip technology for drug-induced nephrotoxicity screening. *Trends Biotechnol.* **2016**, *34*, 156−170.

(19) Bhise, N. S.; Manoharan, V.; Massa, S.; Tamayol, A.; Ghaderi, M.; Miscuglio, M.; Lang, Q.; Zhang, Y. S.; Shin, S. R.; Calzone, G.; et al. A liver-on-a-chip platform with bioprinted hepatic spheroids. *Biofabrication* **2016**, *8*, 014101.

(20) Gori, M.; Simonelli, M. C.; Giannitelli, S. M.; Businaro, L.; Trombetta, M.; Rainer, A. Investigating nonalcoholic fatty liver disease in a liver-on-a-chip microfluidic device. *PLoS One* **2016**, *11*, No. e0159729.

(21) Kim, H. J.; Huh, D.; Hamilton, G.; Ingber, D. E. Human gut-on-a-chip inhabited by microbial flora that experiences intestinal peristalsis-like motions and flow. *Lab Chip* **2012**, *12*, 2165−2174.

(22) Tiwari, A.; Tiwari, A. *Nanomaterials in Drug Delivery, Imaging, and Tissue Engineering*; John Wiley Sons, 2013.

(23) Rohr, S.; Schölly, D. M.; Kleber, A. G. Patterned growth of neonatal rat heart cells in culture. Morphological and electrophysiological characterization. *Circ. Res.* **1991**, *68*, 114−130.

(24) Duffy, D. C.; McDonald, J. C.; Schueller, O. J.; Whitesides, G. M. Rapid prototyping of microfluidic systems in poly dimethylsiloxane. *Anal. Chem.* **1998**, *70*, 4974−4984.

(25) Sin, A.; Chin, K. C.; Jamil, M. F.; Kostov, Y.; Rao, G.; Shuler, M. L. The design and fabrication of three-chamber microscale cell culture analog devices with integrated dissolved oxygen sensors. *Biotechnol. Prog.* **2004**, *20*, 338−345.

(26) Ho, C. T.; Lin, R. Z.; Chang, W. Y.; Chang, H. Y.; Liu, C. H. Rapid heterogeneous liver-cell on-chip patterning via the enhanced field-induced dielectrophoresis trap. *Lab Chip* **2006**, *6*, 724−734.

(27) Huh, D.; Fujioka, H.; Tung, Y. C.; Futai, N.; Paine, R.; Grotberg, J. B.; Takayama, S. Acoustically detectable cellular-level lung injury induced by fluid mechanical stresses in microfluidic airway systems. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 18886−18891.

(28) Kimura, H.; Yamamoto, T.; Sakai, H.; Sakai, Y.; Fujii, T. An integrated microfluidic system for long-term perfusion culture and on-line monitoring of intestinal tissue models. *Lab Chip* **2008**, *8*, 741−746.

(29) Wang, J.; Bettinger, C. J.; Langer, R. S.; Borenstein, J. T. Biodegradable microfluidic scaffolds for tissue engineering from amino alcohol-based poly ester amide) elastomers. *Organogenesis* **2010**, *6*, 212−216.

(30) Domansky, K.; Leslie, D. C.; McKinney, J.; Fraser, J. P.; Sliz, J. D.; Hamkins-Indik, T.; Hamilton, G. A.; Bahinski, A.; Ingber, D. E. Clear castable polyurethane elastomer for fabrication of microfluidic devices. *Lab Chip* **2013**, *13*, 3956−3964.

(31) Ng, K.; Gao, B.; Yong, K. W.; Li, Y.; Shi, M.; Zhao, X.; Li, Z.; Zhang, X.; Pingguan-Murphy, B.; Yang, H.; Xu, F. based cell culture platform and its emerging biomedical applications. *Mater. Today* **2017**, *20*, 32−44.

(32) Nguyen, T.; Jung, S. H.; Lee, M. S.; Park, T. E.; Ahn, S. K.; Kang, J. H. Robust chemical bonding of PMMA microfluidic devices to porous PETE membranes for reliable cytotoxicity testing of drugs. *Lab Chip* **2019**, *19*, 3706−3713.

(33) Ongaro, A. E.; Di Giuseppe, D.; Kermanizadeh, A.; Miguelez Crespo, A.; Mencattini, A.; Ghibelli, L.; Mancini, V.; Wlodarczyk, K. L.; Hand, D. P.; Martinelli, E.; et al. Polylactic is a sustainable, low absorption, low autofluorescence alternative to other plastics for microfluidic and organ-on-chip applications. *Anal. Chem.* **2020**, *92*, 6693−6701.

(34) Abaci, H. E.; Shuler, M. L. Human-on-a-chip design strategies and principles for physiologically based pharmacokinetics/pharmacodynamics modeling. *Integr. Biol.* **2015**, *7*, 383−391.

(35) Meyer, U.; Meyer, T.; Handschel, J.; Wiesmann, H. P. *Fundamentals of Tissue Engineering and Regenerative Medicine*; Springer Science Business Media, 2009, DOI: 10.1007/978-3-540-77755-7.

(36) Mahler, G. J.; Esch, M. B.; Glahn, R. P.; Shuler, M. L. Characterization of a gastrointestinal tract microscale cell culture analog used to predict drug toxicity. *Biotechnol. Bioeng.* **2009**, *104*, 193−205.

(37) Ataç, B.; Wagner, I.; Horland, R.; Lauster, R.; Marx, U.; Tonevitsky, A. G.; Azar, R. P.; Lindner, G. Skin and hair on-a-chip: in

vitro skin models versus ex vivo tissue maintenance with dynamic perfusion. *Lab Chip* **2013**, *13*, 3555−3561.
(38) Abaci, H. E.; Gledhill, K.; Guo, Z.; Christiano, A. M.; Shuler, M. L. Pumpless microfluidic platform for drug testing on human skin equivalents. *Lab Chip* **2015**, *15*, 882−888.
(39) Rostami-Hodjegan, A. Physiologically based pharmacokinetics joined with in vitro-in vivo extrapolation of ADME: a marriage under the arch of systems pharmacology. *Clin. Pharmacol. Ther.* **2012**, *92*, 50−61.
(40) Jang, K. J.; Mehr, A. P.; Hamilton, G. A.; McPartlin, L. A.; Chung, S.; Suh, K. Y.; Ingber, D. E. Human kidney proximal tubule-on-a-chip for drug transport and nephrotoxicity assessment. *Integr. Biol.* **2013**, *5*, 1119−1129.
(41) Christoffersson, J.; van Noort, D.; Mandenius, C. F. Developing organ-on-a-chip concepts using bio-mechatronic design methodology. *Biofabrication* **2017**, *9* (2), 025023.
(42) Mandenius, C. F. Conceptual Design of Micro-Bioreactors and Organ-on-Chips for Studies of Cell Cultures. *Bioengineering (Basel)* **2018**, *5* (3), 56.
(43) Tajeddin, A.; Mustafaoglu, N. Design and Fabrication of Organ-on-Chips: Promises and Challenges. *Micromachines (Basel).* **2021**, *12* (12), 1443.
(44) Baracu, A. M.; Gugoasa, L. A. D. Review—Recent Advances in Microfabrication, Design and Applications of Amperometric Sensors and Biosensors. *J. Electrochem. Soc.* **2021**, *168*, 037503.
(45) Nitsche, K. S.; Müller, I.; Malcomber, S.; Carmichael, P. L.; Bouwmeester, H. Implementing organ-on-chip in a next-generation risk assessment of chemicals: a review. *Arch. Toxicol.* **2022**, *96*, 711−741.
(46) McGinnity, D. F.; Grime, K. ADME optimization in drug discovery. In *Comprehensive Medicinal Chemistry III*; Elsevier, 2017; pp 34−44, DOI: 10.1016/B978-0-12-409547-2.12365-0.
(47) Kunze, A.; Huwyler, J.; Poller, B.; Gutmann, H.; Camenisch, G. In vitro-in vivo extrapolation method to predict human renal clearance of drugs. *J. Pharm. Sci.* **2014**, *103*, 994−1001.
(48) Ren, K.; Zhou, J.; Wu, H. Materials for microfluidic chip fabrication. *Acc. Chem. Res.* **2013**, *46*, 2396−2406.
(49) Patra, H. K.; Khaliq, N. U.; Romu, T.; Wiechec, E.; Borga, M.; Turner, A. P. F.; Tiwari, A. MRI-Visual Order−Disorder Micellar Nanostructures for Smart Cancer Theranostics. *Adv. Healthc. Mater.* **2014**, *3*, 526−535, DOI: 10.1002/adhm.201300225.
(50) Tiwari, A. *Polysaccharides: Development, Properties and Applications*; Nova Science Publishers, 2010.
(51) Tiwari, A.; Nordin, A. N. *Advanced Biomaterials and Biodevices*; John Wiley & Sons, 2014.
(52) Tiwari, A.; Ramalingam, M.; Kobayashi, H.; Turner, A. P. *Biomedical Materials and Diagnostic Devices*; John Wiley & Sons, 2012.
(53) Shukla, S. K.; Govender, P. P.; Tiwari, A. Polymeric micellar structures for biosensor technology. *Adv. Biomembr. Lipid Self-Assem.* **2016**, *24*, 143−161.
(54) Wei, G.; Jin, Q.; Giannobile, W. V.; Ma, P. X. The enhancement of osteogenesis by nano-fibrous scaffolds incorporating rhBMP-7 nanospheres. *Biomaterials* **2007**, *28*, 2087−2096.
(55) Dikovsky, D.; Bianco-Peled, H.; Seliktar, D. The effect of structural alterations of PEG-fibrinogen hydrogel scaffolds on 3-D cellular morphology and cellular migration. *Biomaterials* **2006**, *27*, 1496−1506.
(56) Morelli, S.; Salerno, S.; Mohamed Magdy Ahmed, H.; Piscioneri, A.; De Bartolo, L. Recent strategies combining biomaterials and stem cells for bone, liver and skin regeneration. *Curr. Stem Cell Res. Therapy* **2016**, *11*, 676−691.
(57) Shirosaki, Y.; Hirai, M.; Hayakawa, S.; Fujii, E.; Lopes, M. A.; Santos, J. D.; Osaka, A. Preparation and in vitro cytocompatibility of chitosan-siloxane hybrid hydrogels. *J. Biomed. Mater. Res., Part A* **2015**, *103*, 289−299.
(58) Connell, L. S.; Gabrielli, L.; Mahony, O.; Russo, L.; Cipolla, L.; Jones, J. R. Functionalizing natural polymers with alkoxysilane coupling agents: reacting 3-glycidoxypropyl trimethoxysilane with poly γ-glutamic acid) and gelatin. *Polym. Chem.* **2017**, *8*, 1095−1103.
(59) Xu, S.; Zhang, Y.; Jia, L.; Mathewson, K. E.; Jang, K. I.; Kim, J.; Fu, H.; Huang, X.; Chava, P.; Wang, R.; Bhole, S.; Wang, L.; Na, Y. J.; Guan, Y.; Flavin, M.; Han, Z.; Huang, Y.; Rogers, J. A. Soft microfluidic assemblies of sensors, circuits, and radios for the skin. *Science* **2014**, *344*, 70−74.
(60) Yuk, H.; Zhang, T.; Parada, G. A.; Liu, X.; Zhao, X. Skin-inspired hydrogel-elastomer hybrids with robust interfaces and functional microstructures. *Nat. Commun.* **2016**, *7*, 1−11.
(61) Wu, F.; Chen, S.; Chen, B.; Wang, M.; Min, L.; Alvarenga, J.; Ju, J.; Khademhosseini, A.; Yao, Y.; Zhang, Y. S.; et al. Bioinspired universal flexible elastomer-based microchannels. *Small* **2018**, *14*, 1702170.
(62) Tiwari, A. Synthesis and characterization of pH switching electrical conducting biopolymer hybrids for sensor applications. *J. Polym. Res.* **2008**, *15*, 337−342.
(63) Harink, B.; Le Gac, S.; Truckenmüller, R.; van Blitterswijk, C.; Habibovic, P. Regeneration-on-a-chip? The perspectives on use of microfluidics in regenerative medicine. *Lab Chip* **2013**, *13*, 3512−3528.
(64) Bhatia, S. N.; Ingber, D. E. Microfluidic organs-on-chips. *Nat. Biotechnol.* **2014**, *32*, 760−772.
(65) Zhang, B.; Montgomery, M.; Chamberlain, M. D.; Ogawa, S.; Korolj, A.; Pahnke, A.; Wells, L. A.; Massé, S.; Kim, J.; Reis, L.; et al. Biodegradable scaffold with built-in vasculature for organ-on-a-chip engineering and direct surgical anastomosis. *Nat. Mater.* **2016**, *15*, 669−678.
(66) Davenport Huyer, L.; Zhang, B.; Korolj, A.; Montgomery, M.; Drecun, S.; Conant, G.; Zhao, Y.; Reis, L.; Radisic, M. Highly elastic and moldable polyester biomaterial for cardiac tissue engineering applications. *ACS Biomater. Sci. Eng.* **2016**, *2*, 780−788.
(67) Toepke, M. W.; Beebe, D. J. PDMS absorption of small molecules and consequences in microfluidic applications. *Lab Chip* **2006**, *6*, 1484−1486.
(68) Su, X.; Young, E. W.; Underkofler, H. A.; Kamp, T. J.; January, C. T.; Beebe, D. J. Microfluidic cell culture and its application in high-throughput drug screening: cardiotoxicity assay for hERG channels. *SLAS Discovery* **2011**, *16*, 101−111.
(69) Regehr, K. J.; Domenech, M.; Koepsel, J. T.; Carver, K. C.; Ellison-Zelski, S. J.; Murphy, W. L.; Schuler, L. A.; Alarid, E. T.; Beebe, D. J. Biological implications of polydimethylsiloxane-based microfluidic cell culture. *Lab Chip* **2009**, *9*, 2132−2139.
(70) Eddington, D. T.; Puccinelli, J. P.; Beebe, D. J. Thermal aging and reduced hydrophobic recovery of polydimethylsiloxane. *Sens. Actuators B Chem.* **2006**, *114*, 170−172.
(71) Lee, J. N.; Park, C.; Whitesides, G. M. Solvent compatibility of poly dimethylsiloxane)-based microfluidic devices. *Anal. Chem.* **2003**, *75*, 6544−6554.
(72) Conradie, E. H.; Moore, D. F. SU-8 thick photoresist processing as a functional material for MEMS applications. *J. Micromech. Microeng.* **2002**, *12*, 368.
(73) Fikar, P.; Lissorgues, G.; Rousseau, L.; Francais, O.; Le Pioufle, B.; Hamdi, F. S.; Georgiev, V.; Georgiev, D. SU-8 microchannels for live cell dielectrophoresis improvements. *Microsyst. Technol.* **2017**, *23*, 3901−3908.
(74) Daunton, R.; Gallant, A. J.; Wood, D. Manipulation of exposure dose parameters to improve production of high aspect ratio structures using SU-8. *J. Micromech. Microeng.* **2012**, *22*, 075016.
(75) Thompson, B. L.; Ouyang, Y.; Duarte, G. R.; Carrilho, E.; Krauss, S. T.; Landers, J. P. Inexpensive, rapid prototyping of microfluidic devices using overhead transparencies and a laser print, cut and laminate fabrication method. *Nat. Protoc.* **2015**, *10*, 875−886.
(76) Urbaczek, A. C.; Leão, P. A. G. C.; de Souza, F. Z. R.; Afonso, A.; Alberice, J. V.; Cappelini, L. T. D.; Carlos, I. Z.; Carrilho, E. Endothelial cell culture under perfusion on a polyester-toner microfluidic device. *Sci. Rep.* **2017**, *7*, 1−12.
(77) Moraes, C.; Kagoma, Y. K.; Beca, B. M.; Tonelli-Zasarsky, R. L.; Sun, Y.; Simmons, C. A. Integrating polyurethane culture substrates into poly dimethylsiloxane) microdevices. *Biomaterials* **2009**, *30*, 5241−5250.

(78) Mehta, G.; Lee, J.; Cha, W.; Tung, Y. C.; Linderman, J. J.; Takayama, S. Hard top soft bottom microfluidic devices for cell culture and chemical analysis. *Anal. Chem.* **2009**, *81*, 3714−3722.
(79) Sano, E.; Mori, C.; Matsuoka, N.; Ozaki, Y.; Yagi, K.; Wada, A.; Tashima, K.; Yamasaki, S.; Tanabe, K.; Yano, K.; Torisawa, Y. S. Tetrafluoroethylene-propylene elastomer for fabrication of microfluidic organs-on-chips resistant to drug absorption. *Micromachines* **2019**, *10*, 793.
(80) Laurenson, L.; Dennis, N. T. M. Permeability of common elastomers for gases over a range of temperatures. *J. Vac. Sci. Technol.* **1985**, *3*, 1707−1710.
(81) Wang, Y.; Ameer, G. A.; Sheppard, B. J.; Langer, R. A tough biodegradable elastomer. *Nat. Biotechnol.* **2002**, *20*, 602−606.
(82) Bettinger, C. J.; Weinberg, E. J.; Kulig, K. M.; Vacanti, J. P.; Wang, Y.; Borenstein, J. T.; Langer, R. Three-dimensional microfluidic tissue-engineering scaffolds using a flexible biodegradable polymer. *Adv. Mater.* **2006**, *18*, 165−169.
(83) Göpferich, A. Mechanisms of polymer degradation and erosion. *Biomaterials* **1996**, *17*, 103−114.
(84) Chen, Q. Z.; Ishii, H.; Thouas, G. A.; Lyon, A. R.; Wright, J. S.; Blaker, J. J.; Chrzanowski, W.; Boccaccini, N. N.; Ali, N. N.; Knowles, J. C.; Harding, S. E. An elastomeric patch derived from poly glycerol sebacate) for delivery of embryonic stem cells to the heart. *Biomaterials* **2010**, *31*, 3885−3893.
(85) Tran, R. T.; Thevenot, P.; Gyawali, D.; Chiao, J. C.; Tang, L.; Yang, J. Synthesis and characterization of a biodegradable elastomer featuring a dual crosslinking mechanism. *Soft Matter* **2010**, *6*, 2449−2461.
(86) Zhao, Y.; Rafatian, N.; Feric, N. T.; Cox, B. J.; Aschar-Sobbi, R.; Wang, E. Y.; Aggarwal, P.; Zhang, B.; Conant, G.; Ronaldson-Bouchard, K.; et al. A platform for generation of chamber-specific cardiac tissues and disease modeling. *Cell* **2019**, *176*, 913−927.
(87) Lai, B. F. L.; Huyer, L. D.; Lu, R. X. Z.; Drecun, S.; Radisic, M.; Zhang, B. InVADE: integrated vasculature for assessing dynamic events. *Funct. Mater.* **2017**, *27*, 1703524.
(88) Motlagh, D.; Allen, J.; Hoshi, R.; Yang, J.; Lui, K.; Ameer, G. Hemocompatibility evaluation of poly diol citrate) in vitro for vascular tissue engineering. *J. Biomed. Mater. Res., Part A* **2007**, *82A*, 907−916.
(89) Yang, J.; Webb, A. R.; Ameer, G. A. Novel citric acid-based biodegradable elastomers for tissue engineering. *Adv. Mater.* **2004**, *16*, 511−516.
(90) Gao, J.; Ensley, A. E.; Nerem, R. M.; Wang, Y. Poly glycerol sebacate) supports the proliferation and phenotypic protein expression of primary baboon vascular cells. *J. Biomed. Mater. Res., Part A* **2007**, *83A*, 1070−1075.
(91) Qiu, H.; Yang, J.; Kodali, P.; Koh, J.; Ameer, G. A. A citric acid-based hydroxyapatite composite for orthopedic implants. *Biomaterials* **2006**, *27*, 5845−5854.
(92) Yang, J.; Webb, A. R.; Pickerill, S. J.; Hageman, G.; Ameer, G. A. Synthesis and evaluation of poly diol citrate) biodegradable elastomers. *Biomaterials* **2006**, *27*, 1889−1898.
(93) Webb, A. R.; Kumar, V. A.; Ameer, G. A. Biodegradable poly diol citrate) nanocomposite elastomers for soft tissue engineering. *J. Mater. Chem. A* **2007**, *17*, 900−906.
(94) Djordjevic, I.; Choudhury, N. R.; Dutta, N. K.; Kumar, S. Poly [octanediol-co-(citric acid)-co-(sebacic acid)] elastomers: novel bioelastomers for tissue engineering. *Polym. Int.* **2011**, *60*, 333−343.
(95) Davenport Huyer, L.; Bannerman, A. D.; Wang, Y.; Savoji, H.; Knee-Walden, E. J.; Brissenden, A.; Yee, B.; Shoaib, M.; Bobicki, E.; Amsden, B. G.; Radisic, M. One-Pot Synthesis of Unsaturated Polyester Bioelastomer with Controllable Material Curing for Microscale Designs. *Adv. Healthc. Mater.* **2019**, *8*, 1900245.
(96) Yang, X.; Li, K.; Zhang, X.; Liu, C.; Guo, B.; Wen, W.; Gao, X. Nanofiber membrane supported lung-on-a-chip microdevice for anticancer drug testing. *Lab Chip* **2018**, *18*, 486−495.
(97) Shrestha, J.; Razavi Bazaz, S.; Aboulkheyr Es, H.; Yaghobian Azari, D.; Thierry, B.; Ebrahimi Warkiani, M.; Ghadiri, M. Lung-on-a-chip: the future of respiratory disease models and pharmacological studies. *Crit. Rev. Biotechnol.* **2020**, *40*, 213−230.
(98) Carter, S. S. D.; Atif, A. R.; Kadekar, S.; Lanekoff, I.; Engqvist, H.; Varghese, O. P.; Tenje, M.; Mestres, G. PDMS leaching and its implications for on-chip studies focusing on bone regeneration applications. *Organs-on-a-Chip* **2020**, *2*, 100004.
(99) Li, W.; Sun, X.; Ji, B.; Yang, X.; Zhou, B.; Lu, Z.; Gao, X. PLGA nanofiber/PDMS microporous composite membrane-sandwiched microchip for drug testing. *Micromachines* **2020**, *11*, 1054.
(100) Ferrari, E.; Rasponi, M. Liver-Heart on chip models for drug safety. *APL Bioeng.* **2021**, *5*, 031505.
(101) Guo, Y.; Luo, R.; Wang, Y.; Deng, P.; Song, T.; Zhang, M.; Wang, P.; Zhang, X.; Cui, K.; Tao, T. SARS-CoV-2 induced intestinal responses with a biomimetic human gut-on-chip. *Sci. Bull.* **2021**, *66*, 783−793.
(102) Essaouiba, A.; Okitsu, T.; Kinoshita, R.; Jellali, R.; Shinohara, M.; Danoy, M.; Legallais, C.; Sakai, Y.; Leclerc, E. Development of a pancreas-liver organ-on-chip coculture model for organ-to-organ interaction studies. *Biochem. Eng. J.* **2020**, *164*, 107783.
(103) Zakharova, M.; Palma do Carmo, M. A.; van der Helm, M. W.; Le-The, H.; de Graaf, M. N. S.; Orlova, V.; van den Berg, A.; van der Meer, A. D.; Broersen, K.; Segerink, L. I. Multiplexed blood-brain barrier organ-on-chip. *Lab Chip* **2020**, *20*, 3132−3143.
(104) Polidoro, M. A.; Ferrari, E.; Marzorati, S.; Lleo, A.; Rasponi, M. Experimental liver models: From cell culture techniques to microfluidic organs-on-chip. *Liver Int.* **2021**, *41* (8), 1744−1761.
(105) Bossink, E.; Slob, J. V. M.; Wasserberg, D.; Segerink, L. I.; Odijk, M. Versatile fabrication and integration method of optical oxygen sensors in organ-on-chips. *IEEE Sensors* **2020**, 1−4.
(106) Paoli, R.; Di Giuseppe, D.; Badiola-Mateos, M.; Martinelli, E.; Lopez-Martinez, M. J.; Samitier, J. Rapid Manufacturing of Multilayered Microfluidic Devices for Organ on a Chip Applications. *Sensors* **2021**, *21*, 1382.
(107) Onbas, R.; Bilginer, R.; Yildiz, A. A. On-Chip Drug Screening Technologies for Nanopharmaceutical and Nanomedicine Applications. In *Nanopharmaceuticals: Principles and Applications*, Vol. *1*; Springer, 2021; pp 311−346, DOI: 10.1007/978-3-030-44925-4_8.
(108) Liu, Y.; Sakolish, C.; Chen, Z.; Phan, D. T.; Bender, R. H. F.; Hughes, C. C.; Rusyn, I. Human in vitro vascularized micro-organ and micro-tumor models are reproducible organ-on-a-chip platforms for studies of anticancer drugs. *Toxicology* **2020**, *445*, 152601.
(109) Hammel, J. H.; Cook, S. R.; Belanger, M. C.; Munson, J. M.; Pompano, R. R. Modeling Immunity In Vitro: Slices, Chips, and Engineered Tissues. *Annu. Rev. Biomed. Eng.* **2021**, *23*, 461−491.
(110) Steinway, S. N.; Saleh, J.; Koo, B. K.; Delacour, D.; Kim, D. H. Human microphysiological models of intestinal tissue and gut microbiome. *Front. Bioeng. Biotechnol.* **2020**, *8*, 725.
(111) Washburn, A. L.; Gunn, L. C.; Bailey, R. C. Label-free quantitation of a cancer biomarker in complex media using silicon photonic microring resonators. *Anal. Chem.* **2009**, *81*, 9499−9506.
(112) Anderson, R. R.; Hu, W.; Noh, J. W.; Dahlquist, W. C.; Ness, S. J.; Gustafson, T. M.; Richards, D. C.; Kim, S.; Mazzeo, B. A.; Woolley, A. T.; Nordin, G. P. Transient deflection response in microcantilever array integrated with polydimethylsiloxane PDMS) microfluidics. *Lab Chip* **2011**, *11*, 2088−2096.
(113) Iliescu, C.; Taylor, H.; Avram, M.; Miao, J.; Franssila, S. A practical guide for the fabrication of microfluidic devices using glass and silicon. *Biomicrofluidics* **2012**, *6*, 016505.
(114) Wu, Z.; Chen, H.; Liu, X.; Zhang, Y.; Li, D.; Huang, H. Protein adsorption on poly N-vinylpyrrolidone)-modified silicon surfaces prepared by surface-initiated atom transfer radical polymerization. *Langmuir* **2009**, *25*, 2900−2906.
(115) Li, L.; Marchant, R. E.; Dubnisheva, A.; Roy, S.; Fissell, W. H. Anti-biofouling sulfobetaine polymer thin films on silicon and silicon nanopore membranes. *J. Biomater. Sci. Polym. Ed.* **2011**, *22*, 91−106.
(116) Wang, F.; Burns, M. A. Performance of nanoliter-sized droplet-based microfluidic PCR. *Biomed. Microdevices* **2009**, *11*, 1071−1080.
(117) Sung, J. H.; Shuler, M. L. A micro cell culture analog μCCA) with 3-D hydrogel culture of multiple cell lines to assess metabolism-

dependent cytotoxicity of anti-cancer drugs. *Lab Chip* **2009**, *9*, 1385−1394.
(118) Chua, J. H.; Chee, R. E.; Agarwal, A.; Wong, S. M.; Zhang, G. J. Label-free electrical detection of cardiac biomarker with complementary metal-oxide semiconductor-compatible silicon nanowire sensor arrays. *Anal. Chem.* **2009**, *81*, 6266−6271.
(119) Roy, E.; Pallandre, A.; Zribi, B.; Horny, M. C.; Delapierre, F. D.; Cattoni, A.; Gamby, J.; Haghiri-Gosnet, A. M. Overview of materials for microfluidic applications. In *Advances in Microfluidics—New Applications in Biology, Energy, and Materials Sciences*, 2016, DOI: 10.5772/65773.
(120) Mellors, J. S.; Gorbounov, V.; Ramsey, R. S.; Ramsey, J. M. Fully integrated glass microfluidic device for performing high-efficiency capillary electrophoresis and electrospray ionization mass spectrometry. *Anal. Chem.* **2008**, *80*, 6881−6887.
(121) Mellors, J. S.; Jorabchi, K.; Smith, L. M.; Ramsey, J. M. Integrated microfluidic device for automated single cell analysis using electrophoretic separation and electrospray ionization mass spectrometry. *Anal. Chem.* **2010**, *82*, 967−973.
(122) Grover, W. H.; Skelley, A. M.; Liu, C. N.; Lagally, E. T.; Mathies, R. A. Monolithic membrane valves and diaphragm pumps for practical large-scale integration into glass microfluidic devices. Sens. *Actuators B: Chem.* **2003**, *89*, 315−323.
(123) Grover, W. H.; Ivester, R. H.; Jensen, E. C.; Mathies, R. A. Development and multiplexed control of latching pneumatic valves using microfluidic logical structures. *Lab Chip* **2006**, *6*, 623−631.
(124) Hirama, H.; Satoh, T.; Sugiura, S.; Shin, K.; Onuki-Nagasaki, R.; Kanamori, T.; Inoue, T. Glass-based organ-on-a-chip device for restricting small molecular absorption. *J. Biosci. Bioeng.* **2019**, *127*, 641−646.
(125) Mu, X.; Liang, Q.; Hu, P.; Ren, K.; Wang, Y.; Luo, G. Laminar flow used as "liquid etch mask" in wet chemical etching to generate glass microstructures with an improved aspect ratio. *Lab Chip* **2009**, *9*, 1994−1996.
(126) Martinez, A. W.; Phillips, S. T.; Butte, M. J.; Whitesides, G. M. Patterned paper as a platform for inexpensive, low-volume, portable bioassays. *Angew. Chem.* **2007**, *119*, 1340−1342.
(127) Martinez, A. W.; Phillips, S. T.; Whitesides, G. M.; Carrilho, E. Diagnostics for the developing world: microfluidic paper-based analytical devices. *Anal. Chem.* **2010**, *82*, 3−10.
(128) Pelton, R. Bioactive paper provides a low-cost platform for diagnostics. *Trends Anal. Chem.* **2009**, *28*, 925−942.
(129) Dungchai, W.; Chailapakul, O.; Henry, C. S. Electrochemical detection for paper-based microfluidics. *Anal. Chem.* **2009**, *81*, 5821−5826.
(130) Liu, H.; Crooks, R. M. Three-dimensional paper microfluidic devices assembled using the principles of origami. *J. Am. Chem. Soc.* **2011**, *133*, 17564−17566.
(131) Derda, R.; Laromaine, A.; Mammoto, A.; Tang, S. K.; Mammoto, T.; Ingber, D. E.; Whitesides, G. M. supported 3D cell culture for tissue-based bioassays. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 18457−18462.
(132) Mosadegh, B.; Lockett, M. R.; Minn, K. T.; Simon, K. A.; Gilbert, K.; Hillier, S.; Newsome, D.; Li, H.; Hall, A. B.; Boucher, D. M.; et al. A paper-based invasion assay: Assessing chemotaxis of cancer cells in gradients of oxygen. *Biomaterials* **2015**, *52*, 262−271.
(133) Rodenhizer, D.; Cojocari, D.; Wouters, B. G.; McGuigan, A. P. Development of TRACER: tissue roll for analysis of cellular environment and response. *Biofabrication* **2016**, *8*, 045008.
(134) Piruska, A.; Nikcevic, I.; Lee, S. H.; Ahn, C.; Heineman, W. R.; Limbach, P. A.; Seliskar, C. J. The autofluorescence of plastic materials and chips measured under laser irradiation. *Lab Chip* **2005**, *5*, 1348−1354.
(135) Abdel-Wahab, A. A.; Ataya, S.; Silberschmidt, V. V. Temperature-dependent mechanical behavior of PMMA: Experimental analysis and modelling. *Polym. Test.* **2017**, *58*, 86−95.
(136) Becker, H.; Gärtner, C. Polymer microfabrication methods for microfluidic analytical applications. *Electrophoresis* **2000**, *21*, 12−26.
(137) Wan, A. M.; Devadas, D.; Young, E. W. Recycled polymethylmethacrylate PMMA) microfluidic devices. *Sens. Actuators B: Chem.* **2017**, *253*, 738−744.
(138) Humayun, M.; Chow, C. W.; Young, E. W. Microfluidic lung airway-on-a-chip with arrayable suspended gels for studying epithelial and smooth muscle cell interactions. *Lab Chip* **2018**, *18*, 1298−1309.
(139) Mathur, A.; Roy, S. S.; Tweedie, M.; Mukhopadhyay, S.; Mitra, S. K.; McLaughlin, J. A. Characterisation of PMMA microfluidic channels and devices fabricated by hot embossing and sealed by direct bonding. *Curr. Appl. Phys.* **2009**, *9*, 1199−1202.
(140) Tennico, Y. H.; Koesdjojo, M. T.; Kondo, S.; Mandrell, D. T.; Remcho, V. T. Surface modification-assisted bonding of polymer-based microfluidic devices. *Sens. Actuators B: Chem.* **2010**, *143*, 799−804.
(141) Song, I. H.; Park, T. PMMA solution assisted room temperature bonding for PMMA-PC hybrid devices. *Micromachines* **2017**, *8*, 284.
(142) Trinh, K. T. L.; Thai, D. A.; Chae, W. R.; Lee, N. Y. Rapid Fabrication of Poly methyl methacrylate) Devices for Lab-on-a-Chip Applications Using Acetic Acid and UV Treatment. *ACS Omega* **2020**, *5*, 17396−17404.
(143) Yamazaki, M. Industrialization and application development of cyclo-olefin polymer. *J. Mol. Catal. A Chem.* **2004**, *213*, 81−87.
(144) Cooper, M.; Charest, J. L.; Coppeta, J. Design principles for dynamic microphysiological systems. In *Microfluidic Cell Culture Systems*, 2019; pp 1−29, .
(145) Jena, R. K.; Yue, C. Y. Cyclic olefin copolymer based microfluidic devices for biochip applications: Ultraviolet surface grafting using 2-methacryloyloxyethyl phosphorylcholine. *Biomicrofluidics* **2012**, *6*, 012822.
(146) Liu, J.; Lee, M. L. Permanent surface modification of polymeric capillary electrophoresis microchips for protein and peptide analysis. *Electrophoresis* **2006**, *27*, 3533−3546.
(147) Dolník, V. Wall coating for capillary electrophoresis on microchips. *Electrophoresis* **2004**, *25*, 3589−3601.
(148) Belder, D.; Ludwig, M. Surface modification in microchip electrophoresis. *Electrophoresis* **2003**, *24*, 3595−3606.
(149) Morsink, M. A. J.; Willemen, N. G. A.; Leijten, J.; Bansal, R.; Shin, S. R. Immune Organs and Immune Cells on a Chip: An Overview of Biomedical Applications. *Micromachines (Basel)* **2020**, *11* (9), 849.
(150) Kou, P. M.; Pallassana, N.; Bowden, R.; Cunningham, B.; Joy, A.; Kohn, J.; Babensee, J. E. Predicting biomaterial property-dendritic cell phenotype relationships from the multivariate analysis of responses to polymethacrylates. *Biomaterials* **2012**, *33*, 1699−1713.
(151) Liu, X.; Fang, J.; Huang, S.; Wu, X.; Xie, X.; Wang, J.; Liu, F.; Zhang, M.; Peng, Z.; Hu, N. Tumor-on-a-chip: from bioinspired design to biomedical application. *Microsyst. Nanoeng.* **2021**, *7*, 50.
(152) Aung, A.; Kumar, V.; Theprungsirikul, J.; Davey, S. K.; Varghese, S. An Engineered Tumor-on-a-Chip Device with Breast Cancer-Immune Cell Interactions for Assessing T-cell Recruitment. *Cancer Res.* **2020**, *80* (2), 263−275.
(153) Rohr, T.; Ogletree, D. F.; Svec, F.; Fréchet, J. M. Surface functionalization of thermoplastic polymers for the fabrication of microfluidic devices by photoinitiated grafting. *Adv. Funct. Mater.* **2003**, *13*, 264−270.
(154) Lin, R.; Burns, M. A. Surface-modified polyolefin microfluidic devices for liquid handling. *J. Micromech. Microeng.* **2005**, *15*, 2156.
(155) Theobald, J.; Ghanem, A.; Wallisch, P.; Banaeiyan, A. A.; Andrade-Navarro, M. A.; Taškova, K.; Haltmeier, M.; Kurtz, A.; Becker, H.; Reuter, S.; et al. Liver-kidney-on-chip to study toxicity of drug metabolites. *ACS Biomater. Sci. Eng.* **2018**, *4*, 78−89.
(156) Bruijns, B.; Veciana, A.; Tiggelaar, R.; Gardeniers, H. Cyclic olefin copolymer microfluidic devices for forensic applications. *Biosensors* **2019**, *9*, 85.
(157) Wen, X.; Yamanaka, M.; Terada, S.; Kamei, K. I. In vitro nonalcoholic fatty liver disease model with cycloolefin-polymer-based microphysiological systems. *bioRxiv*, **2020**, DOI: 10.1101/2020.12.28.424535.

(158) Aghvami, S. A.; Opathalage, A.; Zhang, Z. K.; Ludwig, M.; Heymann, M.; Norton, M.; Wilkins, N.; Fraden, S. Rapid prototyping of cyclic olefin copolymer COC) microfluidic devices. *Sens. Actuators B: Chem.* **2017**, *247*, 940−949.
(159) Khanarian, G. Optical properties of cyclic olefin copolymers. *Opt. Eng.* **2001**, *40*, 1024−1029.
(160) Li, C.; Yang, Y.; Craighead, H. G.; Lee, K. H. Isoelectric focusing in cyclic olefin copolymer microfluidic channels coated by polyacrylamide using a UV photografting method. *Electrophoresis* **2005**, *26*, 1800−1806.
(161) Ren, K.; Zhou, J.; Wu, H. Materials for microfluidic chip fabrication. *Acc. Chem. Res.* **2013**, *46*, 2396−2406.
(162) Nge, P. N.; Rogers, C. I.; Woolley, A. T. Advances in microfluidic materials, functions, integration, and applications. *Chem. Rev.* **2013**, *113*, 2550−2583.
(163) Chen, C. S.; Breslauer, D. N.; Luna, J. I.; Grimes, A.; Chin, W. C.; Lee, L. P.; Khine, M. Shrinky-Dink microfluidics: 3D polystyrene chips. *Lab Chip* **2008**, *8*, 622−624.
(164) Quirós-Solano, W. F.; Gaio, N.; Silvestri, C.; Pandraud, G.; Sarro, P. M. PEDOT: PSS: a conductive and flexible polymer for sensor integration in organ-on-chip platforms. *Procedia Eng.* **2016**, *168*, 1184−1187.
(165) Delon, L. C.; Nilghaz, A.; Cheah, E.; Prestidge, C.; Thierry, B. Unlocking the Potential of Organ-on-Chip Models through Pumpless and Tubeless Microfluidics. *Adv. Healthc. Mater.* **2020**, *9*, 1901784.
(166) Young, E. W.; Berthier, E.; Guckenberger, D. J.; Sackmann, E.; Lamers, C.; Meyvantsson, I.; Huttenlocher, A.; Beebe, D. J. Rapid prototyping of arrayed microfluidic systems in polystyrene for cell-based assays. *Anal. Chem.* **2011**, *83*, 1408−1417.
(167) Ogonczyk, D.; Węgrzyn, J.; Jankowski, P.; Dąbrowski, B.; Garstecki, P. Bonding of microfluidic devices fabricated in polycarbonate. *Lab Chip* **2010**, *10*, 1324−1327.
(168) Rahimi, R.; Htwe, S. S.; Ochoa, M.; Donaldson, A.; Zieger, M.; Sood, R.; Tamayol, A.; Khademhosseini, A.; Ghaemmaghami, A. M.; Ziaie, B. *Lab Chip* **2016**, *16*, 4319.
(169) Liu, C. C.; Wang, Y. N.; Fu, L. M.; Chen, K. L. Microfluidic paper-based chip platform for benzoic acid detection in food. *Food Chem.* **2018**, *249*, 162−167.
(170) Fu, H.; Song, P.; Wu, Q.; Zhao, C.; Pan, P.; Li, X.; Li-Jessen, N. Y. K.; Liu, X. A paper-based microfluidic platform with shape-memory-polymer-actuated fluid valves for automated multi-step immunoassays. *Microsyst. Nanoeng.* **2019**, *5*, 50.
(171) Wang, Y.; He, Q.; Dong, Y.; Chen, H. In-channel modification of biosensor electrodes integrated on a polycarbonate microfluidic chip for micro flow-injection amperometric determination of glucose. *Sens. Actuators B: Chem.* **2010**, *145*, 553−560.
(172) Miller, P. G.; Shuler, M. L. Design and demonstration of a pumpless 14 compartment microphysiological system. *Biotechnol. Bioeng.* **2016**, *113*, 2213−2227.
(173) Ahadian, S.; Civitarese, R.; Bannerman, D.; Mohammadi, M. H.; Lu, R.; Wang, E.; Davenport-Huyer, L.; Lai, B.; Zhang, B.; Zhao, Y.; et al. Organ-on-a-chip platforms: a convergence of advanced materials, cells, and microscale technologies. *Adv. Healthc. Mater.* **2018**, *7*, 1700506.
(174) Bale, S. S.; Manoppo, A.; Thompson, R.; Markoski, A.; Coppeta, J.; Cain, B.; Haroutunian, N.; Newlin, V.; Spencer, A.; Azizgolshani, H.; et al. A thermoplastic microfluidic microphysiological system to recapitulate hepatic function and multicellular interactions. *Biotechnol. Bioeng.* **2019**, *116*, 3409−3420.
(175) Shah, P.; Fritz, J. V.; Glaab, E.; Desai, M. S.; Greenhalgh, K.; Frachet, A.; Niegowska, M.; Estes, M.; Jager, C.; Seguin-Devaux, C.; Zenhausern, F.; Wilmes, P. A microfluidics-based in vitro model of the gastrointestinal human-microbe interface. *Nat. Commun.* **2016**, *7*, 1−15.
(176) Magno, M. H. R.; Kim, J.; Srinivasan, A.; McBride, S.; Bolikal, D.; Darr, A.; Hollinger, J. O.; Kohn, J. Synthesis, degradation and biocompatibility of tyrosine-derived polycarbonate scaffolds. *J. Mater. Chem. A* **2010**, *20*, 8885−8893.
(177) Rolland, J. P.; Van Dam, R. M.; Schorzman, D. A.; Quake, S. R.; DeSimone, J. M. Solvent-resistant photocurable "liquid teflon" for microfluidic device fabrication. *J. Am. Chem. Soc.* **2004**, *126*, 2322−2323.
(178) Vitale, A.; Quaglio, M.; Marasso, S. L.; Chiodoni, A.; Cocuzza, M.; Bongiovanni, R. Direct photolithography of perfluoropolyethers for solvent-resistant microfluidics. *Langmuir* **2013**, *29*, 15711−15718.
(179) Jellali, R.; Paullier, P.; Fleury, M. J.; Leclerc, E. Liver and kidney cells cultures in a new perfluoropolyether biochip. *Sens. Actuators B: Chem.* **2016**, *229*, 396−407.
(180) Rogers, C. I.; Pagaduan, J. V.; Nordin, G. P.; Woolley, A. T. Single-monomer formulation of polymerized polyethylene glycol diacrylate as a nonadsorptive material for microfluidics. *Anal. Chem.* **2011**, *83*, 6418−6425.
(181) Chung, S.; Sudo, R.; Mack, P. J.; Wan, C. R.; Vickerman, V.; Kamm, R. D. Cell migration into scaffolds under co-culture conditions in a microfluidic platform. *Lab Chip* **2009**, *9*, 269−275.
(182) Wong, A. P.; Perez-Castillejos, R.; Love, J. C.; Whitesides, G. M. Partitioning microfluidic channels with hydrogel to construct tunable 3-D cellular microenvironments. *Biomaterials* **2008**, *29*, 1853−1861.
(183) Cuchiara, M. P.; Allen, A. C.; Chen, T. M.; Miller, J. S.; West, J. L. Multilayer microfluidic PEGDA hydrogels. *Biomaterials* **2010**, *31*, 5491−5497.
(184) Temiz, Y.; Lovchik, R. D.; Kaigala, G. V.; Delamarche, E. Lab-on-a-chip devices: How to close and plug the lab? *Microelectron. Eng.* **2015**, *132*, 156−175.
(185) Díez-Pascual, A. M.; Naffakh, M.; Marco, C.; Ellis, G.; Gómez-Fatou, M. A. High-performance nanocomposites based on polyetherketones. *Prog. Mater. Sci.* **2012**, *57*, 1106−1190.
(186) Arayanarakool, R.; Le Gac, S.; van den Berg, A. Low-temperature, simple and fast integration technique of microfluidic chips by using a UV-curable adhesive. *Lab Chip* **2010**, *10*, 2115−2121.
(187) Bartolo, D.; Degré, G.; Nghe, P.; Studer, V. Microfluidic stickers. *Lab Chip* **2008**, *8*, 274−279.
(188) Dupont, E. P.; Luisier, R.; Gijs, M. A. NOA 63 as a UV-curable material for fabrication of microfluidic channels with native hydrophilicity. *Microelectron. Eng.* **2010**, *87*, 1253−1255.
(189) Awaja, F.; Wong, T. T.; Arhatari, B. Lab-on-a-chip device made by autohesion-bonded polymers. Biomed. *Microdevices* **2018**, *20*, 1−9.
(190) Ozdil, D.; Aydin, H. M. Polymers for medical and tissue engineering applications. *J. Chem. Technol. Biotechnol.* **2014**, *89*, 1793−1810.
(191) Zhang, Y.; Sun, H.; Song, X.; Gu, X.; Sun, C. Biomaterials for periodontal tissue regeneration. *Rev. Adv. Mater. Sci.* **2015**, *40*, 209−214.
(192) Tan, L.; Yu, X.; Wan, P.; Yang, K. Biodegradable materials for bone repairs: a review. *J. Mater. Sci. Technol.* **2013**, *29*, 503−513.
(193) Van de Velde, K.; Kiekens, P. Biopolymers: overview of several properties and consequences on their applications. *Polym. Test.* **2002**, *21*, 433−442.
(194) Cheung, H. Y.; Lau, K. T.; Lu, T. P.; Hui, D. A critical review on polymer-based bio-engineered materials for scaffold development. *Composites B: Eng.* **2007**, *38*, 291−300.
(195) Lehtonen, T. J.; Tuominen, J. U.; Hiekkanen, E. Resorbable composites with bioresorbable glass fibers for load-bearing applications. In vitro degradation and degradation mechanism. *Acta Biomater.* **2013**, *9*, 4868−4877.
(196) Shuai, C.; Wu, P.; Zhong, Y.; Feng, P.; Gao, C.; Huang, W.; Zhou, Z.; Chen, L.; Shuai, C. Polyetheretherketone/poly glycolic acid) blend scaffolds with biodegradable properties. *J. Biomater. Sci. Polym. Ed.* **2016**, *27*, 1434−1446.
(197) Evans, N. T. S.; Quinton, T. H. Permeability and diffusion coefficient of oxygen in membranes for oxygen electrodes. *Respir. Physiol.* **1978**, *35*, 89−99.

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

(198) Grover, W. H.; von Muhlen, M. G.; Manalis, S. R. Teflon films for chemically-inert microfluidic valves and pumps. *Lab Chip* **2008**, *8*, 913−918.
(199) Yang, M. K.; French, R. H.; Tokarsky, E. W. Optical properties of Teflon® AF amorphous fluoropolymers. *J. Micro Nanolitho. MEMS MOEMS* **2008**, *7*, 033010.
(200) Cho, S. H.; Godin, J.; Lo, Y. H. Optofluidic waveguides in Teflon AF-coated PDMS microfluidic channels. *IEEE Photon. Technol. Lett.* **2009**, *21*, 1057−1059.
(201) Planchon, S.; Gaillard-Martinie, B.; Dordet-Frisoni, E.; Bellon-Fontaine, M. N.; Leroy, S.; Labadie, J.; Hébraud, M.; Talon, R. Formation of biofilm by Staphylococcus xylosus. *Int. J. Food Microbiol.* **2006**, *109*, 88−96.
(202) Katzer, A.; Marquardt, H.; Westendorf, J.; Wening, J. V.; Von Foerster, G. Polyetheretherketone—cytotoxicity and mutagenicity in vitro. *Biomaterials* **2002**, *23*, 1749−1759.
(203) Sagomonyants, K. B.; Jarman-Smith, M. L.; Devine, J. N.; Aronow, M. S.; Gronowicz, G. A. The in vitro response of human osteoblasts to polyetheretherketone PEEK) substrates compared to commercially pure titanium. *Biomaterials* **2008**, *29*, 1563−1572.
(204) Harsha, A. P.; Tewari, U. S. The effect of fibre reinforcement and solid lubricants on abrasive wear behavior of polyetheretherketone composites. *J. Reinf. Plast. Compos.* **2003**, *22*, 751−767.
(205) Hwang, W.; Mühlberger, H.; Hoffmann, W.; Guber, A. E.; Saile, V. Polyether ether ketone microstructures for chemical analytics. *Microsyst. Technol.* **2008**, *14*, 1699−1700.
(206) Muhlberger, H.; Hwang, W.; Guber, A. E.; Saile, V.; Hoffmann, W. Polymer lab-on-a-chip system with electrical detection. *IEEE Sens. J.* **2008**, *8*, 572−579.
(207) Hansen, T. S.; Selmeczi, D.; Larsen, N. B. Fast prototyping of injection molded polymer microfluidic chips. *J. Micromech. Microeng.* **2010**, *20*, 015020.
(208) Canullo, L.; Malagnino, V. A., Vertical ridge augmentation around implants by e-PTFE titanium-reinforced membrane and bovine bone matrix: A 24-to 54-month study of 10 consecutive cases. **2008**, *Int. J. Oral Maxillofac. Implants 23*, 858−866.
(209) Gentile, P.; Chiono, V.; Tonda-Turo, C.; Ferreira, A. M.; Ciardelli, G. Polymeric membranes for guided bone regeneration. *Biotechnol. J.* **2011**, *6*, 1187−1197.
(210) Hoshi, R. A.; Van Lith, R.; Jen, M. C.; Allen, J. B.; Lapidos, K. A.; Ameer, G. The blood and vascular cell compatibility of heparin-modified ePTFE vascular grafts. *Biomaterials* **2013**, *34*, 30−41.
(211) Ranjbarzadeh-Dibazar, A.; Barzin, J.; Shokrollahi, P. Microstructure crystalline domains disorder critically controls formation of nano-porous/long fibrillar morphology of ePTFE membranes. *Polymer* **2017**, *121*, 75−87.
(212) Ju, J.; Kang, W.; Li, L.; He, H.; Qiao, C.; Cheng, B. Preparation of poly tetrafluoroethylene) nanofiber film by electro-blown spinning method. *Mater. Lett.* **2016**, *171*, 236−239.
(213) Park, J. Y.; Lee, J. H.; Kim, C. H.; Kim, Y. J. Fabrication of polytetrafluoroethylene nanofibrous membranes for guided bone regeneration. *RSC Adv.* **2018**, *8*, 34359−34369.
(214) Hegde, M.; Jindal, R.; Bhushan, A.; Bale, S. S.; McCarty, W. J.; Golberg, I.; Usta, O. B.; Yarmush, M. L. Dynamic interplay of flow and collagen stabilizes primary hepatocytes culture in a microfluidic platform. *Lab Chip* **2014**, *14*, 2033−2039.
(215) Shim, K. Y.; Lee, D.; Han, J.; Nguyen, N. T.; Park, S.; Sung, J. H. Microfluidic gut-on-a-chip with three-dimensional villi structure. *Biomed. Microdevices* **2017**, *19*, 37.
(216) Palacio-Castañeda, V.; Kooijman, L.; Venzac, B.; Verdurmen, W. P.; Le Gac, S. Metabolic switching of tumor cells under hypoxic conditions in a tumor-on-a-chip model. *Micromachines* **2020**, *11*, 382.
(217) Le, N. X. T.; Trinh, K. T. L.; Lee, N. Y. Poly acrylic acid) as an adhesion promoter for UV-assisted thermoplastic bonding: Application for the in vitro construction of human blood vessels. *Mater. Sci. Eng., C* **2021**, *122*, 111874.
(218) Shrestha, J.; Razavi Bazaz, S.; Aboulkheyr Es, H.; Yaghobian Azari, D.; Thierry, B.; Ebrahimi Warkiani, M.; Ghadiri, M. Lung-on-a-chip: the future of respiratory disease models and pharmacological studies. *Crit. Rev. Biotechnol.* **2020**, *40*, 213−230.
(219) Arık, Y. B.; Buijsman, W.; Loessberg-Zahl, J.; Cuartas-Velez, C.; Veenstra, C.; Logtenberg, S.; Grobbink, A. M.; Bergveld, P.; Gagliardi, G.; den Hollander, A. I.; Bosschaart, N.; van den Berg, A.; Passier, R.; van der Meer, A. D. Microfluidic organ-on-a-chip model of the outer blood-retinal barrier with clinically relevant read-outs for tissue permeability and vascular structure. *Lab Chip* **2021**, *21*, 272−283.
(220) Wang, Y.; Wu, D.; Wu, G.; Wu, J.; Lu, S.; Lo, J.; He, Y.; Zhao, C.; Zhao, X.; Zhang, H.; Wang, S. Metastasis-on-a-chip mimicking the progression of kidney cancer in the liver for predicting treatment efficacy. *Theranostics* **2020**, *10*, 300−311.
(221) Paoli, R.; Di Giuseppe, D.; Badiola-Mateos, M.; Martinelli, E.; Lopez-Martinez, M. J.; Samitier, J. Rapid Manufacturing of Multi-layered Microfluidic Devices for Organ on a Chip Applications. *Sensors* **2021**, *21*, 1382.
(222) Azizgolshani, H.; Coppeta, J. R.; Vedula, E. M.; Marr, E. E.; Cain, B. P.; Luu, R. J.; Lech, M. P.; Kann, S. H.; Mulhern, T. J.; Tandon, V.; et al. High-throughput organ-on-chip platform with integrated programmable fluid flow and real-time sensing for complex tissue models in drug development workflows. *Lab Chip* **2021**, *21*, 1454−1474.
(223) Jia, Z.; Guo, Z.; Yang, C. T.; Prestidge, C.; Thierry, B. Mucus-on-Chip": A new tool to study the dynamic penetration of nanoparticulate drug carriers into mucus. *Int. J. Pharm.* **2021**, *598*, 120391.
(224) Inbody, S. C.; Sinquefield, B. E.; Lewis, J. P.; Horton, R. E. Biomimetic Microsystems for Cardiovascular studies. *Am. J. Physiol.-Cell Physiol.* **2021**, *320*, C850−C872.
(225) Pauline, Z.; Wüthrich, S.; Sven, A.; Giuditta, T.; Stucki, J. D.; Nina, H.; Schneider-Daum, N.; Claus-Michael, L.; Hanno, H.; Geiser, T.; Schmid, R. A. Second-generation lung-on-a-chip with an array of stretchable alveoli made with a biological membrane. *Commun. Biol.* **2021**, *4*, 168.
(226) Essaouiba, A.; Okitsu, T.; Kinoshita, R.; Jellali, R.; Shinohara, M.; Danoy, M.; Legallais, C.; Sakai, Y.; Leclerc, E. Development of a pancreas-liver organ-on-chip coculture model for organ-to-organ interaction studies. *Biochem. Eng. J.* **2020**, *164*, 107783.
(227) Nejatian, M. Design of a System with a 3D Biomimetic Stretchable Substrate for Maintenance and Study of Alveolar Epithelial Cells; Doctoral dissertation; University of Toronto, Toronto, Canada, 2020.
(228) Fajstavrová, K.; Rimpelová, S.; Fajstavr, D.; Švorčík, V.; Slepička, P. Cell Behavior of Primary Fibroblasts and Osteoblasts on Plasma-Treated Fluorinated Polymer Coated with Honeycomb Polystyrene. *Materials* **2021**, *14*, 889.
(229) Zhang, J.; Chen, Z. Z.; Zhang, Y. Y.; Wang, X. C.; Ouyang, J.; Zhu, J. F.; Yan, Y. C.; Sun, X. W.; Wang, F.; Li, X. R. Construction of a High Fidelity Epidermis-on-a-Chip for Scalable in vitro Irritation Evaluation. *Lab Chip.* **2021**, *21*, 3804−3818.
(230) Artzy-Schnirman, A.; Lehr, C. M.; Sznitman, J. Advancing human in vitro pulmonary disease models in preclinical research: opportunities for lung-on-chips. *Expert Opin. Drug Delivery* **2020**, *17*, 621−625.
(231) Loenen, A. C.; Peters, M. J.; Bevers, R. T.; Schaffrath, C.; van Haver, E.; Cuijpers, V. M.; Rademakers, T.; van Rietbergen, B.; Willems, P. C.; Arts, J. J. Early bone ingrowth and segmental stability of a trussed titanium cage versus a polyether ether ketone cage in an ovine lumbar interbody fusion model. *Spine J.* **2022**, *22*, 174−182.
(232) Kulthong, K.; Duivenvoorde, L.; Sun, H.; Confederat, S.; Wu, J.; Spenkelink, B.; de Haan, L.; Marin, V.; van der Zande, M.; Bouwmeester, H. Microfluidic chip for culturing intestinal epithelial cell layers: Characterization and comparison of drug transport between dynamic and static models. *Toxicol. In Vitro* **2020**, *65*, 104815.
(233) Gelse, K.; Pöschl, E.; Aigner, T. Collagens—structure, function, and biosynthesis. *Adv. Drug Delivery Rev.* **2003**, *55*, 1531−1546.

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

(234) Lee, C. H.; Singla, A.; Lee, Y. Biomedical applications of collagen. *Int. J. Pharm.* **2001**, *221*, 1−22.
(235) Chattopadhyay, S.; Raines, R. T. Collagen-based biomaterials for wound healing. *Biopolymers* **2014**, *101*, 821−833.
(236) Yue, K.; Trujillo-de Santiago, G.; Alvarez, M. M.; Tamayol, A.; Annabi, N.; Khademhosseini, A. Synthesis, properties, and biomedical applications of gelatin methacryloyl GelMA) hydrogels. *Biomaterials* **2015**, *73*, 254−271.
(237) Arık, Y. B.; de Sa Vivas, A.; Laarveld, D.; Van Laar, N.; Gemser, J.; Visscher, T.; Van Den Berg, A.; Passier, R.; Van Der Meer, A. D. Collagen I Based Enzymatically Degradable Membranes for Organ-on-a-Chip Barrier Models. *ACS Biomater. Sci. Eng.* **2021**, *7*, 2998−3005.
(238) Zhao, Y.; Rafatian, N.; Wang, E. Y.; Feric, N. T.; Lai, B. F.; Knee-Walden, E. J.; Backx, P. H.; Radisic, M. Engineering microenvironment for human cardiac tissue assembly in heart-on-a-chip platform. *Matrix Biol.* **2020**, *85*, 189−204.
(239) Zamprogno, P.; Wuthrich, S.; Achenbach, S.; Thoma, G.; Stucki, J. D.; Hobi, N.; Schneider-Daum, N.; Lehr, C.-M.; Huwer, H.; Geiser, T.; Schmid, R. A.; Guenat, O. T. Second-generation lung-on-a-chip with an array of stretchable alveoli made with a biological membrane. *Commun. Biol.* **2021**, *4*, 1−10.
(240) Verhulsel, M.; Simon, A.; Bernheim-Dennery, M.; Gannavarapu, V. R.; Gérémie, L.; Ferraro, D.; Krndija, D.; Talini, L.; Viovy, J. L.; Vignjevic, D. M.; Descroix, S. Developing an advanced gut on chip model enabling the study of epithelial cell/fibroblast interactions. *Lab Chip* **2021**, *21*, 365−377.
(241) Xiao, Y.; Zhang, B.; Liu, H.; Miklas, J. W.; Gagliardi, M.; Pahnke, A.; Thavandiran, N.; Sun, Y.; Simmons, C.; Keller, G.; Radisic, M. Microfabricated perfusable cardiac biowire: a platform that mimics native cardiac bundle. *Lab Chip* **2014**, *14*, 869−882.
(242) Koide, T. Designed triple-helical peptides as tools for collagen biochemistry and matrix engineering. Philos. Trans. R. Soc. Lond., B. *Biol. Sci.* **2007**, *362*, 1281−1291.
(243) Badylak, S. F.; Gilbert, T. W. Immune response to biologic scaffold materials. *Semin. Immunol.* **2008**, *20*, 109−116.
(244) Ghasemi-Mobarakeh, L.; Prabhakaran, M. P.; Morshed, M.; Nasr-Esfahani, M. H.; Ramakrishna, S. Electrospun poly ε-caprolactone)/gelatin nanofibrous scaffolds for nerve tissue engineering. *Biomaterials* **2008**, *29*, 4532−4539.
(245) Burke, C. J.; Hsu, T. A.; Volkin, D. B. Formulation, stability, and delivery of live attenuated vaccines for human use. *Crit. Rev. Ther. Drug Carrier Syst.* **1999**, *16*, 1−83.
(246) Gou, Y.; Miao, D.; Zhou, M.; Wang, L.; Zhou, H.; Su, G. Bio-inspired protein-based nanoformulations for cancer theranostics. *Front. Pharmacol.* **2018**, *9*, 421.
(247) Saddler, J. M.; Horsey, P. J. The new generation gelatins: a review of their history, manufacture and properties. *Anaesthesia* **1987**, *42*, 998−1004.
(248) Gevaert, E.; Billiet, T.; Declercq, H.; Dubruel, P.; Cornelissen, R. Galactose-F unctionalized Gelatin Hydrogels Improve the Functionality of Encapsulated Hepg2 Cells. *Macromol. Biosci.* **2014**, *14*, 419−427.
(249) McCain, M. L.; Agarwal, A.; Nesmith, H. W.; Nesmith, A. P.; Parker, K. K. Micromolded gelatin hydrogels for extended culture of engineered cardiac tissues. *Biomaterials* **2014**, *35*, 5462−5471.
(250) Yang, L.; Shridhar, S. V.; Gerwitz, M.; Soman, P. An in vitro vascular chip using 3D printing-enabled hydrogel casting. *Biofabrication* **2016**, *8*, 035015.
(251) Zhang, J.; Zhao, X.; Liang, L.; Li, J.; Demirci, U.; Wang, S. A decade of progress in liver regenerative medicine. *Biomaterials* **2018**, *157*, 161−176.
(252) Wu, G.; Wu, D.; Lo, J.; Wang, Y.; Wu, J.; Lu, S.; Xu, H.; Zhao, X.; He, Y.; Li, J.; Demirci, U.; Wang, S. A bioartificial liver support system integrated with a DLM/GelMA-based bioengineered whole liver for prevention of hepatic encephalopathy via enhanced ammonia reduction. *Biomater. Sci.* **2020**, *8*, 2814−2824.
(253) Lu, S.; Cuzzucoli, F.; Jiang, J.; Liang, L. G.; Wang, Y.; Kong, M.; Zhao, X.; Cui, W.; Li, J.; Wang, S. Development of a biomimetic liver tumor-on-a-chip model based on decellularized liver matrix for toxicity testing. *Lab Chip* **2018**, *18*, 3379−3392.
(254) Karim, A. A.; Bhat, R. Fish gelatin: properties, challenges, and prospects as an alternative to mammalian gelatins. *Food Hydrocoll.* **2009**, *23*, 563−576.
(255) Bigi, A.; Cojazzi, G.; Panzavolta, S.; Roveri, N.; Rubini, K. Stabilization of gelatin films by crosslinking with genipin. *Biomaterials* **2002**, *23*, 4827−4832.
(256) Kaminski, M.; McDonagh, J. Studies on the mechanism of thrombin. Interaction with fibrin. *J. Biol. Chem.* **1983**, *258*, 10530−10535.
(257) Ahmed, T. A.; Dare, E. V.; Hincke, M. Fibrin: a versatile scaffold for tissue engineering applications. *Tissue Eng. Part B Rev.* **2008**, *14*, 199−215.
(258) Briganti, E.; Spiller, D.; Mirtelli, C.; Kull, S.; Counoupas, C.; Losi, P.; Senesi, S.; Di Stefano, R.; Soldani, G. A composite fibrin-based scaffold for controlled delivery of bioactive pro-angiogenetic growth factors. *J. Controlled Release* **2010**, *142*, 14−21.
(259) Barsotti, M. C.; Magera, A.; Armani, C.; Chiellini, F.; Felice, F.; Dinucci, D.; Piras, A. M.; Minnocci, A.; Solaro, R.; Soldani, G.; Balbarini, A.; Di Stefano, R. Fibrin acts as biomimetic niche inducing both differentiation and stem cell marker expression of early human endothelial progenitor cells. *Cell Prolif.* **2011**, *44*, 33−48.
(260) de la Puente, P.; Ludeña, D.; López, M.; Ramos, J.; Iglesias, J. Differentiation within autologous fibrin scaffolds of porcine dermal cells with the mesenchymal stem cell phenotype. Exp. *Cell Res.* **2013**, *319*, 144−152.
(261) de la Puente, P.; Ludeña, D. Cell culture in autologous fibrin scaffolds for applications in tissue engineering. Exp. *Cell Res.* **2014**, *322*, 1−11.
(262) Pradeep, A. R.; Nagpal, K.; Karvekar, S.; Patnaik, K.; Naik, S. B.; Guruprasad, C. N. Platelet-rich fibrin with 1% metformin for the treatment of intrabony defects in chronic periodontitis: A randomized controlled clinical trial. *J. Periodontol.* **2015**, *86*, 729−737.
(263) Ajwani, H.; Shetty, S.; Gopalakrishnan, D.; Kathariya, R.; Kulloli, A.; Dolas, R. S.; Pradeep, A. R. Comparative evaluation of platelet-rich fibrin biomaterial and open flap debridement in the treatment of two and three wall intrabony defects. *J. Int. Oral Health* **2015**, *7*, 32−37.
(264) Bencherif, S. A., Synthesis, characterization, and evaluation of biodegradable polymers and biomimetic hydrogel scaffolds for biomedical applications. Doctoral dissertation, Carnegie Mellon University, Pittsburgh, PA, 2009, DOI: 10.1016/j.carbpol.2021.117832.
(265) Ahmann, K. A.; Weinbaum, J. S.; Johnson, S. L.; Tranquillo, R. T. Fibrin degradation enhances vascular smooth muscle cell proliferation and matrix deposition in fibrin-based tissue constructs fabricated in vitro. *Tissue Eng. Part A* **2010**, *16*, 3261−3270.
(266) Nagamine, K.; Kawashima, T.; Sekine, S.; Ido, Y.; Kanzaki, M.; Nishizawa, M. Spatiotemporally controlled contraction of micro-patterned skeletal muscle cells on a hydrogel sheet. *Lab Chip* **2011**, *11*, 513−517.
(267) Rajangam, T.; An, S. S. A. Fibrinogen and fibrin based micro and nano scaffolds incorporated with drugs, proteins, cells and genes for therapeutic biomedical applications. *Int. J. Nanomed.* **2013**, *8*, 3641−3662.
(268) Allison, D. D.; Grande-Allen, K. J. Hyaluronan: a powerful tissue engineering tool. *Tissue Eng.* **2006**, *12*, 2131−2140.
(269) Prestwich, G. D. Engineering a clinically-useful matrix for cell therapy. *Organogenesis* **2008**, *4*, 42−47.
(270) Burdick, J. A.; Prestwich, G. D. Hyaluronic acid hydrogels for biomedical applications. *Adv. Mater.* **2011**, *23*, H41−H56.
(271) Yu, A.; Niiyama, H.; Kondo, S.; Yamamoto, A.; Suzuki, R.; Kuroyanagi, Y. Wound dressing composed of hyaluronic acid and collagen containing EGF or bFGF: comparative culture study. *J. Biomater. Sci. Polym. Ed.* **2013**, *24*, 1015−1026.
(272) Niiyama, H.; Kuroyanagi, Y. Development of novel wound dressing composed of hyaluronic acid and collagen sponge containing

epidermal growth factor and vitamin C derivative. *Int. J. Artif. Organs* **2014**, *17*, 81−87.
(273) Prestwich, G. D. Hyaluronic acid-based clinical biomaterials derived for cell and molecule delivery in regenerative medicine. *J. Controlled Release* **2011**, *155*, 193−199.
(274) Skardal, A.; Devarasetty, M.; Forsythe, S.; Atala, A.; Soker, S. A reductionist metastasis-on-a-chip platform for in vitro tumor progression modeling drug screening. *Biotechnol. Bioeng.* **2016**, *113*, 2020−2032.
(275) Tavana, H.; Zamankhan, P.; Christensen, P. J.; Grotberg, J. B.; Takayama, S. Epithelium damage and protection during reopening of occluded airways in a physiologic microfluidic pulmonary airway model. *Biomed. Microdevices* **2011**, *13*, 731−742.
(276) Spearman, B. S.; Agrawal, N. K.; Rubiano, A.; Simmons, C. S.; Mobini, S.; Schmidt, C. E. Tunable methacrylated hyaluronic acid-based hydrogels as scaffolds for soft tissue engineering applications. *J. Biomed. Mater. Res., Part A* **2020**, *108*, 279−291.
(277) Narkhede, A. A.; Crenshaw, J. H.; Crossman, D. K.; Shevde, L. A.; Rao, S. S. An in vitro hyaluronic acid hydrogel-based platform to model dormancy in brain metastatic breast cancer cells. *Acta Biomater.* **2020**, *107*, 65−77.
(278) Singh, V.; Tiwari, A.; Tripathi, D. N.; Sanghi, R. Microwave enhanced synthesis of chitosan-graft-polyacrylamide. *Polymer* **2006**, *47*, 254−260.
(279) Kumar, M. R.; Muzzarelli, R.; Muzzarelli, C.; Sashiwa, H.; Domb, A. J. Chitosan chemistry and pharmaceutical perspectives. *Chem. Rev.* **2004**, *104*, 6017−6084.
(280) Kozen, B. G.; Kircher, S. J.; Henao, J.; Godinez, F. S.; Johnson, A. S. An alternative hemostatic dressing: comparison of CELOX, HemCon, and QuikClot. *Acad. Emerg. Med.* **2008**, *15*, 74−81.
(281) Ueno, H.; Mori, T.; Fujinaga, T. Topical formulations and wound healing applications of chitosan. *Adv. Drug Delivery Rev.* **2001**, *52*, 105−115.
(282) Mourya, V. K.; Inamdar, N. N.; Tiwari, A. Carboxymethyl chitosan and its applications. *Adv. Mater. Lett.* **2010**, *1*, 11−33.
(283) Ahsan, S. M.; Thomas, M.; Reddy, K. K.; Sooraparaju, S. G.; Asthana, A.; Bhatnagar, I. Chitosan as biomaterial in drug delivery and tissue engineering. *Int. J. Biol. Macromol.* **2018**, *110*, 97−109.
(284) Rosella, E.; Jia, N.; Mantovani, D.; Greener, J. A microfluidic approach for development of hybrid collagen-chitosan extracellular matrix-like membranes for on-chip cell cultures. *J. Mater. Sci. Technol.* **2021**, *63*, 54−61.
(285) Yuan, J.; Hou, Q.; Chen, D.; Zhong, L.; Dai, X.; Zhu, Z.; Li, M.; Fu, X. Chitosan/LiCl composite scaffolds promote skin regeneration in full-thickness loss. *Sci. China Life Sci.* **2020**, *63* (4), 552−562.
(286) Patil, P. S.; Fathollahipour, S.; Inmann, A.; Pant, A.; Amini, R.; Shriver, L. P.; Leipzig, N. D. Fluorinated methacrylamide chitosan hydrogel dressings improve regenerated wound tissue quality in diabetic wound healing. *Adv. Wound Care* **2019**, *8*, 374−385.
(287) Sashiwa, H.; Shigemasa, Y. Chemical modification of chitin and chitosan 2: preparation and water soluble property of N-acylated or N-alkylated partially deacetylated chitins. *Carbohydr. Polym.* **1999**, *39*, 127−138.
(288) Ruvinov, E.; Cohen, S. Alginate biomaterial for the treatment of myocardial infarction: progress, translational strategies, and clinical outlook: from ocean algae to patient bedside. *Adv. Drug Delivery Rev.* **2016**, *96*, 54−76.
(289) Venkatesan, J.; Bhatnagar, I.; Manivasagan, P.; Kang, K. H.; Kim, S. K. Alginate composites for bone tissue engineering: a review. *Int. J. Biol. Macromol.* **2015**, *72*, 269−281.
(290) Mørch, Ý.A.; Donati, I.; Strand, B. L.; Skjåk-Bræk, G. Molecular engineering as an approach to design new functional properties of alginate. *Biomacromolecules* **2007**, *8*, 2809−2814.
(291) Lee, K. Y.; Mooney, D. J. Alginate: properties and biomedical applications. *Prog. Polym. Sci.* **2012**, *37*, 106−126.
(292) Polonchuk, L.; Surija, L.; Lee, M. H.; Sharma, P.; Ming, C. L. C.; Richter, F.; Ben-Sefer, E.; Rad, M. A.; Sarmast, H. M. S.; Al Shamery, W.; et al. Towards engineering heart tissues from bioprinted cardiac spheroids. *Biofabrication* **2021**, *13*, 045009.
(293) Shao, F.; Yu, L.; Zhang, Y.; An, C.; Zhang, H.; Zhang, Y.; Xiong, Y.; Wang, H. Microfluidic encapsulation of single cells by alginate microgels using a trigger-gellified strategy. *Front. Bioeng. Biotechnol.* **2020**, *8*, 583065.
(294) Dai, G.; Wan, W.; Zhao, Y.; Wang, Z.; Li, W.; Shi, P.; Shen, Y. Controllable 3D alginate hydrogel patterning via visible-light induced electrodeposition. *Biofabrication* **2016**, *8*, 025004.
(295) Wang, X. Y.; Jin, Z. H.; Gan, B. W.; Lv, S. W.; Xie, M.; Huang, W. H. Engineering interconnected 3D vascular networks in hydrogels using molded sodium alginate lattice as the sacrificial template. *Lab Chip* **2014**, *14*, 2709−2716.
(296) Maguire, T. J.; Novik, E.; Chao, P.; Barminko, J.; Nahmias, Y.; Yarmush, M. L.; Cheng, K. C. Design and application of microfluidic systems for in vitro pharmacokinetic evaluation of drug candidates. *Curr. Drug Metab.* **2009**, *10*, 1192−1199.
(297) Schimek, K.; Frentzel, S.; Luettich, K.; Bovard, D.; Rutschle, I.; Boden, L.; Rambo, F.; Erfurth, H.; Dehne, E.-M.; Winter, A.; Marx, U.; Hoeng, J. Human multi-organ chip co-culture of bronchial lung culture and liver spheroids for substance exposure studies. *Sci. Rep.* **2020**, *10*, 1−13.
(298) Bauer, S.; Huldt, C. W.; Kanebratt, K. P.; Durieux, I.; Gunne, D.; Andersson, S.; Ewart, L.; Haynes, W. G.; Maschmeyer, I.; Winter, A.; et al. Functional coupling of human pancreatic islets and liver spheroids on-a-chip: Towards a novel human ex vivo type 2 diabetes model. *Sci. Rep.* **2017**, *7*, 1−11.
(299) Mastrangeli, M.; van den Eijnden-van Raaij, J. Organs-on-chip: The way forward. *Stem Cell Reports.* **2021**, *16* (9), 2037−2043.
(300) Wu, Q.; Liu, J.; Wang, X.; Feng, L.; Wu, J.; Zhu, X.; Wen, W.; Gong, X. Organ-on-a-chip: recent breakthroughs and future prospects. *BioMed. Eng. OnLine* **2020**, *19*, 9.
(301) Sosa-Hernandez, J. E.; Villalba-Rodriguez, A. M.; Romero-Castillo, K. D.; Aguilar-Aguila-Isaias, M. A.; Garcia-Reyes, I. E.; Hernandez-Antonio, A.; Ahmed, I.; Sharma, A.; Parra-Saldivar, R.; Iqbal, H. M. N. Organs-on-a-Chip Module: A Review from the Development and Applications Perspective. *Micromachines (Basel)* **2018**, *9* (10), 536.
(302) Quan, Y.; Sun, M.; Tan, Z.; Eijkel, J. C. T.; van den Berg, A.; van der Meer, A.; Xie, Y. Organ-on-a-chip: the next generation platform for risk assessment of radiobiology. *RSC Adv.* **2020**, *10*, 39521−39530.
(303) Tiwari, A., Tiwari, A., Eds. *Bioengineered Nanomaterials*, 1st Edition; CRC Press, 2013, DOI: 10.1201/b15403.
(304) Tiwari, A., Ramalingam, M., Kobayashi, H., Turner, A. P. F., Eds. *Biomedical Materials and Diagnostic Devices*; John Wiley & Sons, 2012.
(305) Tiwari, A., Turner, A. P. F., Eds. *Biosensors Nanotechnology*; John Wiley & Sons, 2014.
(306) Tiwari, A., Patra, H. K., Choi, J. W., Eds. *Advanced Theranostic Materials*; John Wiley & Sons, 2015.
(307) Tiwari, A., Mishra, Y. K., Kobayashi, H., Turner, A. P. F., Eds. *Intelligent Nanomaterials*; John Wiley & Sons, 2016.
(308) Tiwari, A., Garipcan, B., Uzun, L., Eds. *Advanced Surfaces for Stem Cell Research*; John Wiley & Sons, 2016.
(309) Tiwari, A., Patra, H. K., Wang, X, Eds. *Advanced Materials Interfaces*; John Wiley & Sons, 2016.
(310) Tiwari, A., Patra, H. K., Turner, A. P. F., Eds. *Advanced Bioelectronic Materials*; John Wiley & Sons, 2015.
(311) Tiwari, A., Ed. *Graphene Bioelectronics*; Elsevier, 2017.
(312) Tiwari, A.; Singh, V. Synthesis and characterization of electrical conducting chitosan-graft-polyaniline. *Express Polym. Lett.*, **2007**.
(313) Solanki, P. R.; Kaushik, A.; Ansari, A. A.; Tiwari, A.; Malhotra, B. D. Multi-walled carbon nanotubes/sol-gel-derived silica/chitosan nanobiocomposite for total cholesterol sensor. *Sens. Actuators, B* **2009**, *137* (2), 727−735.

https://doi.org/10.1021/acsabm.2c00041
ACS Appl. Bio Mater. 2022, 5, 3576−3607

(314) Tiwari, A. *Polysaccharides: Development, Properties and Applications*; Nova Science Publishers, Inc.: New York, 2010 (ISBN-10:160876544X).
(315) Singh, V.; Tripathi, D. N.; Tiwari, A.; Sanghi, R. Microwave promoted synthesis of chitosan-graft-poly(acrylonitrile). *J. Appl. Polym. Sci.* **2005**, *95*, 820−825.
(316) Ashaduzzaman, M.; Deshpande, S. R.; Murugan, N. A.; Mishra, Y. K.; Turner, A. P.; Tiwari, A. On/off-switchable LSPR nano-immunoassay for troponin-T. *Sci. Rep.* **2017**, *7* (1), DOI: 10.1038/srep44027.
(317) Parlak, O.; İncel, A.; Uzun, L.; Turner, A. P.; Tiwari, A. Structuring Au nanoparticles on two-dimensional MoS2 nanosheets for electrochemical glucose biosensors. *Biosens. Bioelectron.* **2017**, *89*, 545−50.
(318) Parlak, O.; Ashaduzzaman, M.; Kollipara, S. B.; Tiwari, A.; Turner, A. P. Switchable bioelectrocatalysis controlled by dual stimuli-responsive polymeric interface. *ACS Appl. Mater. Interfaces* **2015**, *7* (43), 23837−47.
(319) Parlak, O.; Turner, A. P.; Tiwari, A. On/Off-Switchable Zipper-Like Bioelectronics on a Graphene Interface. *Adv. Mater.* **2014**, *26* (3), 482−486.
(320) Tiwari, A., Kobayashi, H., Eds. *Responsive Materials and Methods: State-of-the-Art Stimuli-Responsive Materials and Their Applications*; John Wiley & Sons, 2013.
(321) Parlak, O.; Beyazit, S.; Tse-Sum-Bui, B.; Haupt, K.; Turner, A. P.; Tiwari, A. Programmable bioelectronics in a stimuli-encoded 3D graphene interface. *Nanoscale* **2016**, *8* (19), 9976−81.
(322) Tiwari, A., Mishra, Y. K., Kobayashi, H., Turner, A. P., Eds. *Intelligent Nanomaterials*; Wiley−Scrivener, 2016 (ISBN: 978-1-119-24248-2).
(323) Osikoya, A. O.; Tiwari, A. Recent advances in 2D bioelectronics. *Biosens. Bioelectron.* **2017**, *89*, 1−7.
(324) Tiwari, A., Ed. *Graphene Bioelectronics*; Elsevier, 2017.
(325) Parlak, O.; Beyazit, S.; Jafari, M. J.; Bui, B. T.; Haupt, K.; Tiwari, A.; Turner, A. P. Light-Triggered Switchable Graphene-Polymer Hybrid Bioelectronics. *Adv. Mater. Interfaces* **2016**, *3* (2), 1500353.
(326) Mishra, A.; Basumallick, S.; Lu, A.; Chiu, H.; Shah, M. A.; Shukla, Y.; Tiwari, A. The healthier healthcare management models for COVID-19. *J. Infect. Public Health* **2021**, *14* (7), 927−37.
(327) Mishra, A.; Choudhary, M.; Das, T. R.; Saren, P.; Bhattacherjee, P.; Thakur, N.; Tripathi, S. K.; Upadhaya, S.; Kim, H. S.; Murugan, A. N.; et al. Sustainable Chemical Preventive Models in COVID-19: Understanding, Innovation, Adaptations and Impact. Journal of the Indian Chemical Society. *J. Indian Chem. Soc.* **2021**, *98* (10), 100164.
(328) Preetam, S.; Nahak, B. K.; Patra, S.; Toncu, D. C.; Park, S.; Syväjärvi, M.; Orive, G.; Tiwari, A. Emergence of microfluidics for next generation biomedical devices. *Biosens. Bioelectron.: X* **2022**, *10*, 100106.
(329) Zhao, Y.; Kankala, R. K.; Wang, S. B.; Chen, A. Z. Multi-Organs-on-Chips: Towards Long-Term Biomedical Investigations. *Molecules* **2019**, *24* (4), 675.
(330) Jodat, Y. A.; Kang, M. G.; Kiaee, K.; Kim, G. J.; Martinez, A. F.H.; Rosenkranz, A.; Bae, H.; Shin, S. R. Human-Derived Organ-on-a-Chip for Personalized Drug Development. *Curr. Pharm. Des.* **2019**, *24* (45), 5471−5486.
(331) Staicu, C. E.; Jipa, F.; Axente, E.; Radu, M.; Radu, B. M.; Sima, F. Lab-on-a-Chip Platforms as Tools for Drug Screening in Neuropathologies Associated with Blood-Brain Barrier Alterations. *Biomolecules* **2021**, *11* (6), 916.
(332) Richardson, L.; Kim, S.; Menon, R.; Han, A. Organ-On-Chip Technology: The Future of Feto-Maternal Interface Research? *Front Physiol.* **2020**, *11*, 715.
(333) Van den Berg, A.; Mummery, C. L.; Passier, R.; van der Meer, A. D. Personalised Organs-On-Chips: Functional Testing for Precision Medicine. *Lab. Chip* **2019**, *19*, 198−205.
(334) Yang, X.; Li, K.; Zhang, X.; Liu, C.; Guo, B.; Wen, W.; Gao, X. Nanofiber membrane supported lung-on-a-chip microdevice for anti-cancer drug testing. *Lab Chip* **2018**, *18*, 486−495.
(335) Delon, L. C.; Nilghaz, A.; Cheah, E.; Prestidge, C.; Thierry, B. Unlocking the Potential of Organ-on-Chip Models through Pumpless and Tubeless Microfluidics. *Adv. Healthc Mater.* **2020**, *9* (11), No. 1901784.
(336) Conradie, E. H.; Moore, D. F. SU-8 thick photoresist processing as a functional material for MEMS applications. *J. Micromech. Microeng.* **2002**, *12*, 368−374.
(337) Sano, E.; Mori, C.; Matsuoka, N.; Ozaki, Y.; Yagi, K.; Wada, A.; Tashima, K.; Yamasaki, S.; Tanabe, K.; Yano, K.; Torisawa, Y. S. Tetrafluoroethylene-propylene elastomer for fabrication of microfluidic organs-on-chips resistant to drug absorption. *Micromachines* **2019**, *10* (11), 793.
(338) Park, J. Y.; Lee, J. H.; Kim, C. H.; Kim, Y. J. Fabrication of polytetrafluoroethylene nanofibrous membranes for guided bone regeneration. *RSC Adv.* **2018**, *8* (60), 34359−34369.
(339) Jellali, R.; Paullier, P.; Fleury, M. J.; Leclerc, E. Liver and kidney cells cultures in a new perfluoropolyether biochip. *Sens. Actuators, B* **2016**, *229*, 396−407.
(340) Cuchiara, M. P.; Allen, A. C.; Chen, T. M.; Miller, J. S.; West, J. L. Multilayer microfluidic PEGDA hydrogels. *Biomaterials* **2010**, *31* (21), 5491−5497.
(341) Wang, X. Y.; Jin, Z. H.; Gan, B. W.; Lv, S. W.; Xie, M.; Huang, W. H. Engineering interconnected 3D vascular networks in hydrogels using molded sodium alginate lattice as the sacrificial template. *Lab Chip* **2014**, *14* (15), 2709−2716.
(342) Bhise, N. S.; Manoharan, V.; Massa, S.; Tamayol, A.; Ghaderi, M.; Miscuglio, M.; Lang, Q.; Zhang, Y. S.; Shin, S. R.; Calzone, G.; et al. A liver-on-a-chip platform with bioprinted hepatic spheroids. *Biofabrication* **2016**, *8*, 014101.
(343) Sin, A.; Chin, K. C.; Jamil, M. F.; Kostov, Y.; Rao, G.; Shuler, M. L. The Design and Fabrication of Three-Chamber Microscale Cell Culture Analog Devices with Integrated Dissolved Oxygen Sensors. *Biotechnol. Prog.* **2004**, *20* (1), 338−345.
(344) Zhao, Y.; Rafatian, N.; Feric, N.; Cox, B.; Aschar-sobbi, R.; Wang, E.; Aggarwal, P.; Zhang, B.; Conant, G.; Ronaldson-Bouchard, K.; et al. A Platform for Generation of Chamber-Specific Cardiac Tissues and Disease Modeling. *Cell* **2019**, *176* (4), 913−927.
(345) Park, J. Y.; Lee, J. H.; Kim, C. H.; Kim, Y. J. Fabrication of polytetrafluoroethylene nanofibrous membranes for guided bone regeneration. *RSC Adv.* **2018**, *8*, 34359−34369.
(346) Jellali, R.; Paullier, P.; Fleury, M. J.; Leclerc, E. Liver and kidney cells cultures in a new perfluoropolyether biochip. *Sens. Actuators, B* **2016**, *229*, 396−407.
(347) Cuchiara, M. P.; Allen, A. C. B.; Chen, T. M.; Miller, J. S.; West, J. L. Multilayer microfluidic PEGDA hydrogels. *Biomaterials* **2010**, *31* (21), 5491−5497.
(348) Verhulsel, M.; Simon, A.; Bernheim-Dennery, M.; Gannavarapu, V. R.; Geremie, L.; Ferraro, D.; Krndija, D.; Talini, L.; Viovy, J.-L.; Vignjevic, D. M.; Descroix, S. Developing an advanced gut on chip model enabling the study of epithelial cell/fibroblast interactions. *Lab Chip* **2021**, *21*, 365−377.
(349) Wang, X.-Y.; Jin, Z.-H.; Gan, B.-W.; Lv, S.-W.; Xie, M.; Huang, W.-H. Engineering interconnected 3D vascular networks in hydrogels using molded sodium alginate lattice as the sacrificial template. *Lab Chip* **2014**, *14*, 2709−2716.
(350) Derda, R.; Laromaine, A.; Mammoto, A.; Tang, S. K. Y.; Mammoto, T.; Ingber, D. E.; Whitesides, G. M. Paper-supported 3D cell culture for tissue-based bioassays. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106* (44), 18457−18462.
(351) Peyravian, N.; Kebria, M. M.; Kiani, J.; Milan, P. B.; Mozafari, M. CRISPR-Associated (CAS) Effectors Delivery via Microfluidic Cell-Deformation Chip. *Materials* **2021**, *14* (12), 3164.
(352) Li, J.; Chen, J.; Bai, H.; Wang, H.; Hao, S.; Ding, Y.; Peng, B.; Zhang, J.; Li, L.; Huang, W. An Overview of Organs-on-Chips Based on Deep Learning. *Research* **2022**, *2022*, 9869518.

(353) Wu, G.; Wu, J.; Li, Z.; Shi, S.; Wu, D.; Wang, X.; Xu, H.; Liu, H.; Huang, Y.; Wang, R.; et al. Development of digital organ-on-a-chip to assess hepatotoxicity and extracellular vesicle-based anti-liver cancer immunotherapy. *Bio-Design. Manuf.* **2022**, DOI: 10.1007/s42242-022-00188-1.
(354) Polini, A.; Moroni, L. The convergence of high-tech emerging technologies into the next stage of organ-on-a-chips. *Biomater. Biosyst.* **2021**, *1*, 100012.
(355) Rhyou, J.; Youn, J.; Eom, S.; Kim, D. S. Facile Fabrication of Electrospun Nanofiber Membrane-Integrated PDMS Microfluidic Chip via Silver Nanowires-Uncured PDMS Adhesive Layer. *ACS Macro Lett.* **2021**, *10* (7), 965−970.
(356) Skardal, A.; Murphy, S. V.; Devarasetty, M.; Mead, I.; Kang, H.-W.; Seol, Y.-J.; Zhang, Y. S.; Shin, S.-R.; Zhao, L.; Aleman, J.; et al. Multi-tissue interactions in an integrated three-tissue organ-on-a-chip platform. *Sci. Rep.* **2017**, *7* (1), 8837.
(357) Li, T.; Hantusch, M.; Qu, J.; Bandari, V. K.; Knupfer, M.; Zhu, F.; Schmidt, O. G. On-chip integrated process-programmable sub-10 nm thick molecular devices switching between photomultiplication and memristive behaviour. *Nat. Commun.* **2022**, *13*, 2875.
(358) Adly, N.; Weidlich, S.; Seyock, S.; Brings, F.; Yakushenko, A.; Offenhäusser, A.; Wolfrum, B. Printed microelectrode arrays on soft materials: from PDMS to hydrogels. *npj Flex Electron* **2018**, *2*, 15.
(359) Glick, C. C.; Srimongkol, M. T.; Schwartz, A. J.; Zhuang, W. S.; Lin, J. C.; Warren, R. H.; Tekell, D. R.; Satamalee, P. A.; Lin, L. Rapid assembly of multilayer microfluidic structures via 3D-printed transfer molding and bonding. *Microsyst. Nanoeng.* **2016**, *2*, 16063.
(360) Edington, C. D.; Chen, W. L. K.; Geishecker, E.; Kassis, T.; Soenksen, L. R.; Bhushan, B. M.; Freake, D.; Kirschner, J.; Maass, C.; Tsamandouras, N.; Valdez, J.; Cook, C. D.; Parent, T.; Snyder, S.; Yu, J.; Suter, E.; Shockley, M.; Velazquez, J.; Velazquez, J. J.; Stockdale, L.; Papps, J. P.; Lee, I.; Vann, N.; Gamboa, N.; LaBarge, M. E.; Zhong, Z.; Wang, X.; Boyer, L. A.; Lauffenburger, D. A.; Carrier, R. L.; Communal, C.; Tannenbaum, S. R.; Stokes, C. L.; Hughes, D. J.; Rohatgi, G.; Trumper, D. L.; Cirit, M.; Griffith, L. G. Interconnected Microphysiological Systems for Quantitative Biology and Pharmacology Studies. *Sci. Rep.* **2018**, *8*, 4530.
(361) Zhang, B.; Radisic, M. Organ-on-a-chip devices advance to market. *Lab Chip* **2017**, *17*, 2395−2420.
(362) Vulto, P.; Dame, G.; Maier, U.; Makohliso, S.; Podszun, S.; Zahn, P.; Urban, G. A. A microfluidic approach for high efficiency extraction of low molecular weight RNA. *Lab Chip* **2010**, *10*, 610−616.
(363) Yildirim, E.; Trietsch, S. J.; Joore, J.; van den Berg, A.; Hankemeier, T.; Vulto, P. Phaseguides as tunable passive microvalves for liquid routing in complex microfluidic networks. *Lab Chip* **2014**, *14*, 3334−3340.