Preprint of: Qiang Luo, Przemysław Gnatowski, Maryam Ansariaghmiuni, Edyta Piłat, Maryam Poostchi, Justyna Kucińska-Lipka, Mohsen Khodadadiyazdi, Jacek Ryl, Milad Ashrafizadeh, Fatemeh Mottaghitalab, Mehdi Farokhi, Mohammad Saeb, Tomasz Baczek, Chu Chen (2025). Hydrogel membranes in organ-on-a-chip devices: A review. COLLOIDS AND SURFACES B: BIOINTERFACES, vol. 251, 114591. **https://doi.org/10.1016/j.colsurfb.2025.114591**

Hydrogel Membranes in Organ-on-a-Chip Devices: Soft Material Systems for Mimicking Human Tissue Microenvironments

Przemysław Gnatowski[1,2,#], Maryam Ansari[3,#], Edyta Piłat[2], Maryam Poostchi[2], Justyna Kucińska-Lipka[2], Mohsen Khodadadi Yazdi[4,5], Jacek Ryl[4,5], Milad Ashrafizadeh[6], Fatemeh Mottaghitalab[8], Mehdi Farokhi[7], Mohammad Reza Saeb[9,*], Tomasz Bączek[9,*], Chu Chen[10], Qi Lu[10,*]

[1] Department of Environmental Toxicology, Faculty of Health Sciences, Medical University of Gdańsk, Dębowa 23A, 80-204 Gdańsk, Poland
[2] Department of Polymer Technology, Faculty of Chemistry, Gdańsk University of Technology, Narutowicza St. 11/12, 80-233 Gdańsk, Poland
[3] Polymer Research Laboratory, Department of Chemistry, Sharif University of Technology, Tehran 11365-9516, Iran
[4] Division of Electrochemistry and Surface Physical Chemistry, Faculty of Applied Physics and Mathematics, Gdańsk University of Technology, Narutowicza 11/12, Gdańsk, 80-233, Poland
[5] Advanced Materials Center, Gdańsk University of Technology, Narutowicza 11/12, 80-233 Gdańsk, Poland
[6] Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, 200032, China
[7] Nanotechnology Research Centre, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[8] National Cell Bank of Iran, Pasteur Institute of Iran, Tehran, Iran
[9] Department of Pharmaceutical Chemistry, Medical University of Gdańsk, J. Hallera 107, 80-416 Gdańsk, Poland
[10] Department of Cardiology, Affiliated Hospital of Nantong University, No. 568 Minle Middle Road, 226200, Qidong City, Nantong City, Jiangsu Province, China

# These authors contributed equally to this work.

* Correspondence to be addressed to:

M.R.S. (mrsaeb2008@gmail.com & mr.saeb@gumed.edu.pl), T.B. (tomasz.baczek@gumed.edu.pl) & Q. Lu (luqint@sina.com)

Abstract

Organ-on-a-chip (OoC) devices represent advanced *in vitro* models that enable mimicking the human tissue architecture function and physiology, offering a promising alternative to traditional animal testing methods. These devices combine the microfluidics with soft materials, specifically hydrogel membranes (HMs) for mimicking the extracellular matrix (ECM) and biological barriers, such as the blood-brain barrier (BBB). Hydrogels are ideal biomaterials for OoC systems because of their tunable properties, comprising biocompatibility, biodegradability, and microscale self-assembly. The integration of HMs with OoC devices gives an effective means to create dynamic, biologically relevant environments supporting living cells for applications like drug discovery, disease modeling, and personalized medicine. Recent advancements in 3D printing, photolithography, and bioprinting fabrication technologies have additionally developed such systems. This review surveys the role of HMs in OoC platforms, highlighting their material properties, self-assembly behavior, and challenges in fabrication. Additionally, we discuss the progress made in the past five years in utilizing HMs for applications in tissue engineering, drug development, and biosensing, with a focus on their interface dynamics and structural self-organization. The future perspective on OoC technology has also been patterned to provide a broader image on integration of OoC with personalized medicine and advanced drug delivery systems.

Keywords: Organs-on-a-chip; Hydrogel membrane; Tissue engineering; Bioprinting; Microfluidics

1. Introduction

Biomaterials design, engineering, and implementation methodologies are experiencing an era of maturity nowadays, so that broader innovation windows are showcased to revolutionize the materials and devices of higher performance enabling quicker detection, more precise analysis, and translationally suitable for clinics. Along with such technological evolutions, attention and regulations have been targeted at ethical aspects of biomaterials testing protocols and guidelines of animal experimentation [1]. Organ-on-a-chip (OoC) is a concept recently born to widen biomaterials commercialization by which novel generations of advanced functional biomaterials and testing methods are developed. It also facilitates biological research, modeling diseases, as well as single and multi-organ tissue functions [2]. For instance, OoC has revolutionized drug discovery and clinical approval, which was conventionally expensive, time-consuming, and a cumbersome in view of difficulties in getting approval by the US Food and Drug Administration (FDA). Some further technical difficulties are also associated with clinical implantation, where toxicity limits the efficacy of drugs [3]. Typically, possible interactions between a model drug and human cells remain mysterious and exclusive until drug commercialization. In the light of above example, the ability to mimic human organs *in vitro* takes deep roots in biology and a kind of state of the art [4]. Typical *in vitro* models used in biological research include two-dimensional (2D) cell cultures [5], three-dimensional (3D) models [6], and organoids [7] each requiring different animal models [8]. Although each test itself has a niche, none of them may necessarily allow for accurately predicting the performance of drugs in the human body during clinical studies as genetics of humans [9] and animals differ principally [10, 11]. It is promising that recent breakthroughs in cell biology, microfabrication techniques, and microfluidics have enabled the creation of micro physiological

systems to simulate the normal function of human organs [12]. Such OoC devices enabled faster yet cheaper identification of effective drugs for patients, allowing for the personalization of the model with an unprecedented level of accuracy (**Fig. 1 (a))** [10]. On the other hands, the use of OoC eliminates or at least decreases the need for animal experimentation. In line with such ethical recommendations, European parliament acted, dictating the EU to accelerate the transition to research systems not relying on animals [13]. Likewise, the US Environmental Protection Agency (EPA) decided, to reduce fundings and animal testing methods by 30% by 2025, keeping eyes at a brighter horizon targeted at elimination of animal tests by 2035 [14].

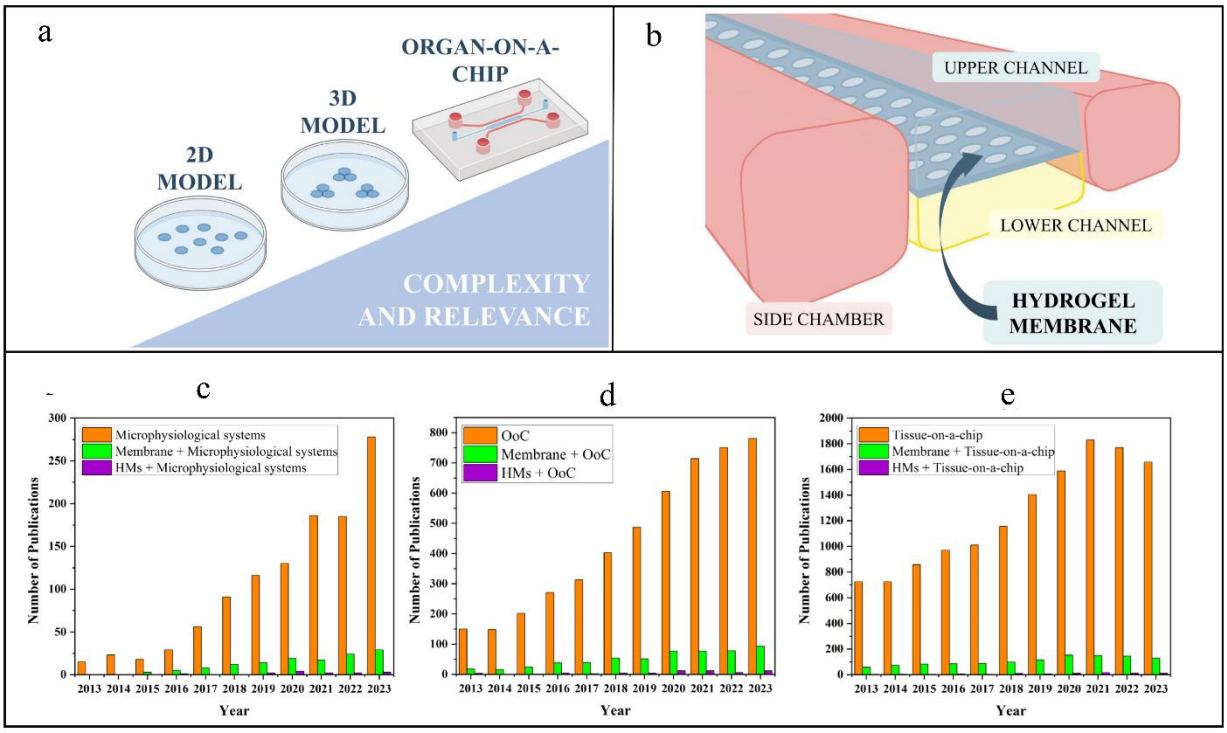

Figure 1. ***The brief summary of organ-on-a-chip related statistics, model relevance and structure***. **a)** The differences in complexity and relevance of individual models. OoC provides the highest relevance to real-life behavior, while 2D models are the simplest and cheapest way to screen e.g. drugs. *Created with BioRender.com.* **b)** The scheme of OoC structure**.** This device can be usually divided into four main parts: side chambers, usually used as fluid transport routes,

upper and lower channels simulating specific tissues and the membrane simulating the barriers inside the human body e.g., blood-brain barrier or air-blood barrier in lungs. Own elaboration based on [15]. *Created with BioRender.com.* **c-e)** Statistics on organ-on-a-chip related papers. The similar growth trends in interest for both OoC and membranes are observed with four to five times increase in articles number during the last 10 years. Looking at the number of articles, the interest in hydrogel membranes is not yet exposed, but slowly growing. *Data based on Scopus database; accessed February2024;* **c)** *Search within title and abstract: (hydrogel AND membrane AND ((organ AND on AND chip) OR OoC OR organ-on-chip OR organ-on-a-chip)).* OoC is also known as microphysiological systems in addition to being called organ/tissue chips. Part **d)** *Search within title and abstract: (hydrogel AND membrane AND (michrophysiological systems)) and* **e)** *Search within title and abstract: (hydrogel AND membrane AND (tissue AND on AND chip)).*

Materials type and fabrication strategies are key factors affecting the successful manufacturing and operation of OoC devices. Accordingly, materials selection for each part of OoC platforms plays a crucial role in their development. In general, the OoC devices could be structurally divided into three main parts as shown in **Figure 1 (b)**, including side channels that direct fluids flow, main chamber that may include 3D cultured cells or organoids, and the porous membrane that separates the main chamber into upper and lower channels. Appropriate materials should be non-toxic to cells, gas permeable, optically transparent to microscopic imaging, affordable, enable easy and scalable fabrication of microchannels, and closely mimic the physicochemical and biomechanical behavior of target organs [16]. Polydimethylsiloxane (PDMS) is the most popular material and has been widely used as a constructing material for tissue chips because of its affordable cost, ease of use, transparency, appropriate mechanical properties, and biocompatibility [17, 18]. However, PDMS has several shortcomings including absorption of small hydrophobic molecules, such as therapeutic agents [19], slow rate of prototyping [20], and lack of potential for cell ingrowth [21]. As a result, researchers have been looking for alternative materials

[20]. Recently, emerging materials like polymeric hydrogels, thermoplastic polymers, and inorganic materials, have been developed and utilized in the fabrication of OoC devices [19].

Since their discovery in the 1960s, hydrogels have impacted the health conditions of millions of individuals who suffer from many diseases such as trauma and cancer [22]. Hydrogels are cross-linked networks of hydrophilic polymers capable of retaining large amounts of aqueous fluids in their 3D structure [23]. They are used for a variety of applications such as tissue engineering [24], drug delivery [25], and bioelectronics [26]. Their inherent merits, such as appealing physicochemical and mechanical properties, interconnected porous structure, biocompatibility, and water retention capability have resulted in hydrogels' ability to closely mimic the features of extracellular matrix (ECM) of cells [27, 28]. Accordingly, the hydrogel demands for various biomedical engineering applications have tremendously increased [29, 30]. Hydrogels also allow for the exchange of metabolites and signaling molecules between neighboring cells similar to the native ECM. Moreover, special types of hydrogels, known as smart hydrogels, provide further control over the cellular microenvironment thanks to their capability to respond to exo- and/or endogenous stimuli (e.g., temperature, pH, light, electric and magnetic field). They may undergo a phase transition (i.e., between a swollen and a shrunken state) or mechanical properties alternation (e.g., because of partial degradation), upon application of stimulus [31]. This property makes hydrogels advantageous as a major constituent of OoC devices to simulate tissue/organ models. Generally speaking, the properties of hydrogels largely depend on the constructing materials [32], crosslinking methods [33], and fabrication strategies [34].

A variety of hydrogels have been employed over the years, in the form of scaffolds [35], injectable hydrogels [29], nanogels (i.e. hydrogel nanoparticles) [36], microgels and microspheres

(e.g. for encapsulation of cells or therapeutic agents) [37], nanofibers [38], and relatively thin, permeable films known as hydrogel membranes (HMs) [39]. HMs are one of the most attractive forms of hydrogel in OoC devices because they could facilitate to create a controlled microenvironment to study physiological processes, cell behavior, drug testing, and disease modeling [40]. HM could mimic the ECM of tissue which provides a versatile platform for cell growth. Furthermore, they have controlled permeability, which resembles biological barriers with mechanical behavior similar to native tissue [41]. Such porous structures separate two different microchannels and enable cell culture in each channel by providing nutrients and gas exchange. It is possible to instruct cellular behaviors via tuning the chemistry of hydrogels (e.g., finely tuning of monomers' functionalities) or surface modification of HMs using bioactive molecules or cell-instructive materials. Tuning the chemistry and chemical makeup of HMs enables them to make a variety of hydrogels with diverse physicochemical and mechanical properties [42]. Moreover, flexible and stretchable hydrogels can be used for simulating special tissues such as lung and blood vessels in which there are large and frequent mechanical deformations [43].

Some review papers appropriately investigate utilization of various hydrogels and organoids in OoC devices. They summarized their construction [44], applications [45], fabrication methods, and challenges [44]. Despite the high attention to this field, there is a lack of a comprehensive review that systematically reviews HMs in OoC devices. In this perspective, we visualize the state of the art for developing hydrogels especially in the membrane form for OoC devices, including the complete pathway starting from selecting materials, choosing the correct fabrication method, and discussing their limitations, potential applications, and future direction.

2. Hydrogel membrane for Organ-on-a-chips

2.1. Current trends in membranes in OoC devices

Organoids have been the state of art models for human organ simulation since the 1980s. These 3D structures typically arise from stem cells or organ-specific progenitor cells and possess the intrinsic capability to replicate the structure and function of original organs or tissues [46]. Despite their usefulness, organoids typically mimic only specific organs' behaviors and lack the crucial interorgan communications present in the tissue microenvironment, which limits their ability to fully replicate the complexity and function of their corresponding organs. These limitations can be addressed by integrating these 3D cell cultures with a microfluidic platform, leading to the development of OoC devices [46, 47]. OoC devices can replicate physiological and biomechanical conditions inside the human body by integrating microfluidics with living cell biology. These microfluidic devices, which contain microscale channel compartments, can mimic the 3D architecture of structures such as coronary arteries. This advanced design allows researchers to observe and manipulate the cellular behavior under physiological flow rate and shear stress [48]. In other words, flexible membranes can not only capable of mimic the features of biological barriers, but also offer a more accurate simulation of cellular microenvironment due to their soft, hydrated, and three-dimensional porous structure.

During the past decade, there has been a significant increase in the use of OoC to make tissue-mimicking organs, such as the lung [49], liver [50], heart [51], and kidney [52]. According to Yole's analysts, the global OoC market has reached US$29.6 million by 2018 and it is predicted to continue to grow at a high pace during the next years [53]. Additionally, interest in performing

academic research on OoC devices continues to grow steadily. The number of articles regarding OoC has increased nearly 4-fold during the last decade. Furthermore, number of publications related to HMs in OoC has been gradually growing during the last 5 years as shown in **Fig.1 (c)**. OoC is also referred to as a microphysiological system in addition to being called organ/tissue chips; hence, the number of publications related to these keywords is shown in **Fig. 1 (d) and (e)**.

Bibliographic analysis is also a powerful tool used to quantitatively assess the scientific publications. It would provide a scientific map representing the relationships among the different authors, institutions, and countries and valuable insight to uncover trends, future direction, frequency of keywords, citation analysis, funding, and policy-making of a particular field of study. In this study, we used the Scopus database to collect data and the analysis was done with the VOS viewer and Microsoft Excel. In the Scopus database, the query used was (hydrogel membrane AND organ-on-a-chip) in the (article title-abstract-keyword) part between 2013-2023. **Fig. 2 a)** The most common keyword related to OoC devices was shown. **Fig. 2 b)** The most common keywords related to membrane AND organ-on-a-chip and their relationship were demonstrated. **Fig. 2 c)** Network of keywords in HMs in OoC devices in the last decade. **Fig. 2 d)** Worldwide research related to HMs in OoC devices and their distribution by countries was shown.

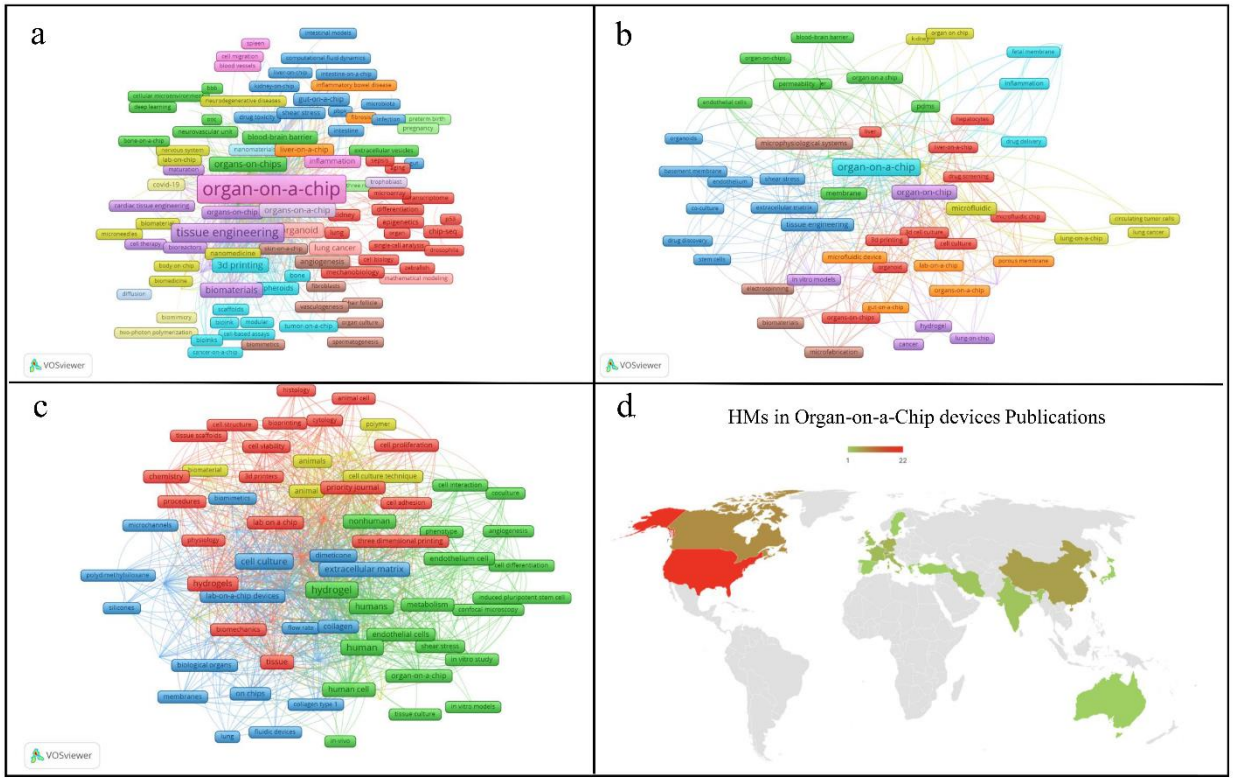

Figure 2. ***Bibliometrics analysis for future direction***. **a)** Network of keywords related to organ-on-a-chip in last decade. **b)** Network of keywords related to membrane AND organ-on-a-chip last decade. **c)** Network of keywords in HMs in OoC devices in last decade. **d)** Distribution of publications by countries on HMs in OoC devices.

OoC membranes have deepened our understanding of physiological processes. They provide a controlled microenvironment for exchanging gases, nutrients, drugs, and metabolites through membrane pores. These membranes can resemble some human tissue barriers *in vitro* and are considered as an alternative to animal testing. Membrane topographical characteristics, such as stiffness and pore size, should be precisely controlled as they could affect cell communication, tissue adhesion, and proliferation [21]. In OoC devices, HMs are usually used to provide a biomimetic interface between two different environments and should be compatible with both cells and fluids used in such systems [54, 55]. There are some considerations for designing HMs,

including porosity, hydrophilicity, tunable mechanical properties, thickness, and surface roughness [44]. Porosity is the most important characteristic of the HMs for OoC devices to provide suitable permeability. In addition, the porous and hydrated structure of hydrogel enables crosstalk among adjacent cells through the diffusion of signaling molecules, such as growth factors and cytokines [56]. Furthermore, microporous hydrogels provide a favorable microenvironment for cells' adhesion, growth, proliferation, and migration [57]. Nutrients that are carried through fluids flow in microchannels (i.e., convection mass transfer) can penetrate throughout the interconnected porous structure of HMs (i.e., diffusion mass transfer) to reach the living cells. Moreover, metabolic wastes can diffuse out through a microporous network, followed by entering the exiting fluids flow. In such systems, laminar flow creates medium perfusion through microchannels, which is usually created by a micropump, mimics heart function in the systemic blood flow. In addition, HMs based on natural materials have similar topography and surface chemistry to native ECM, promoting cell scaffold interactions. Accordingly, OoC systems closely simulate the real microenvironment of a native tissue with either similar dimension or properties. Furthermore, cell behaviors under physiologically relevant conditions can be adjusted via manipulation of physicochemical, and mechanical properties of HMs or through immobilization of bioactive molecules into HMs [10, 58].

2.2. Constructing materials for HMs

To fabricate OoC devices, constructing materials, such as PDMS, should be selected appropriately as discussed before. However, to create an appropriate cellular microenvironment, hydrogels with different architectures including 3D matrices and membrane forms are frequently integrated into microchambers and microchannels of OoC platforms. They provide cells, spheroids,

and organoids with an ECM-like microenvironment that favors cellular functions. In this section, hydrogel-based OoC devices are briefly discussed. **Table 1** presents an overview of materials utilized in the fabrication of HMs for OoC devices along with their advantages and disadvantages which are classified into three general categories: naturally derived materials, synthetic materials, and semi-synthetic materials [59].

Table 1. ***Classification of hydrogel materials used for the preparation of HM for OoC devices depends on the material origin***. Three main categories can be distinguished: natural, synthetic, and semi-synthetic materials. Although synthetic materials offer unparalleled mechanical properties, they often lack appropriate biocompatibility and biodegradability, contrary to natural materials. Semi-synthetic materials are chemically modified naturally-derived macromolecules and they combine the benefits of both groups. PEG: polyethylene glycol, PVA: polyvinyl alcohol, PHEMA: poly(2-hydroxyethyl methacrylate), PU: polyurethane, PAA: polyacrylic acid, PAAm: polyacrylamide, PNIPAAm: poly(N-isopropylacrylamide), Gel-MA: gelatin methacrylate, HA-MA: methacrylated hyaluronic acid, PEG-DA: PEG- diacrylate.

Source		Hydrogel	Advantages	Disadvantages	Refs.
Natural	**Proteins**	Collagen Fibrin Gelatin Elastin Collagen- Elastin Matrigel Silk	- Highly biocompatible - Stimulate cell adhesion, migration and proliferation - Similar structure to the ECM - Biodegradable - Available from renewable resources - Low immunogenicity - Cost effective	- Poor mechanical properties - Difficult reproducibility - Poor processability	[60-66]
	Polysaccharides	HA Agarose Chitosan			

	Collagen- Alginate			
	Collagen-Chitosan			
Synthetic	PEG PVA PHEMA PU PAA PAAM PNIPAAM	- Easily tuned properties - Enhanced mechanical properties - High transparency - More reproducible physical and chemical properties	- Lack of cell-specific bioactivities, such as cell adhesion, migration and proliferation - Biodegradation adjustment - Limited biocompatibility - Potential toxicity	[62, 67-70]
Semi-synthetics	GEL-MA HA-MA Dopamine-modified alginate PEG-fibrinogen Gel-MA-PEG-DA	- High biocompatibility - Tunable mechanical properties - Biodegradable - Long-term durable	- Complex production process - Highly expensive	[69, 71-76]

2.2.1. Naturally derived biomaterials

Green biomaterials have attracted lots of attention and launched promising horizons to shape the future landscape of public health and biomedical engineering in recent years. The emergence of new manufacturing methods combined with the fundamental principle of green chemistry and biomaterials has played a pivotal role in the development and evolution of green biomaterials [77]. Naturally derived hydrogels are considered as green biomaterials. Natural polymers are extracted from natural resources, such as animals' (e.g., collagen) or plants' (e.g., cellulose) tissues, and microorganisms (e.g., exopolysaccharide) [78]. Typically, these materials possess high biocompatibility, show bio-adhesion, and benefit from biodegradability and nontoxicity, which make them a promising constituent of HMs for various OoC applications [20]. Naturally derived HMs based on proteins (e.g., collagen, elastin, and silk fibroin) and polysaccharides (e.g., chitosan, alginate, and HA) are common in OoC devices [79, 80]. Collagen-based HMs are biocompatible, biodegradable, stretchable, and can easily mimic the chemical composition and structure of the ECM [65]. Zamprogno et al. [49] developed collagen–elastin (CE) hydrogel in the form of suspended thin HMs for the lung-on-a-chip platform, which outperformed traditional PDMS membrane in the simplicity of modification and resistance to rhodamine-B as shown in **Fig. 3**. Moreover, the CE hydrogel membrane showed the ability to finely adjust thickness to as low as 4.5 microns by manipulating the CE solution pipetted onto the mesh. Arik et al. [81] developed a semipermeable HM based on collagen that was incorporated into an OoC device to model the basement membrane and separate the culturing chambers. Collagen Type I was used there as being main component of the basal membrane, which acts as a barrier between different tissue compartments. Collagen contributes to the membrane's strength, stability, elasticity, and facilitates nutrient/waste exchange. Overall collagen is one of the most promising hydrogel components for an

application in OoCs. **Fig. 4** describes collagen membrane fiber structure and shows collagen compatibility for cell *culture*. Despite of mentioned advantages, natural biomaterials have several limitations such as poor mechanical properties and low stiffness compared to synthetic materials like PDMS [82] as shown in **Fig. 5**. Accordingly, researchers have looked for alternative materials for making HMs for OoCs.

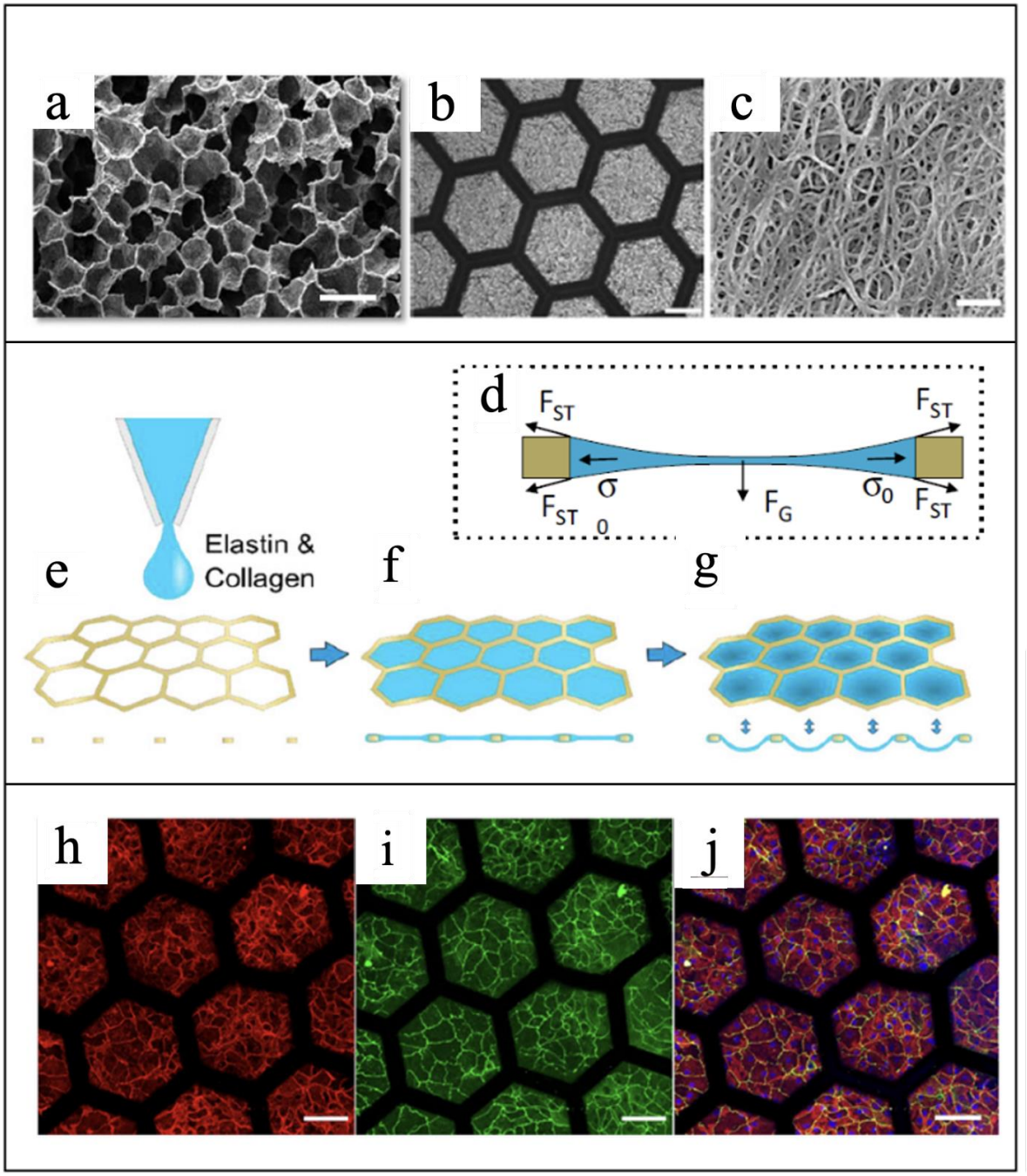

Figure 3. ***Representative of hydrogels utilized in lung-on-a-chip: creation of the lung alveoli array***. SEM picture of **a)** a slice of human lung parenchyma with tiny lung alveoli and their ultrathin air–blood barrier, **b)** an array of several hexagons with a CE membrane. Scale bar: 100 μm, **c)** the collagen and elastin fibers of the CE membrane. Scale bar: 500 nm, **d)** Schematic of the force balance during the drying of the membrane. FST, FG and σo stand for surface tension force, gravity and residual stress, respectively, **e-g)** Schematic of the production of the CE membrane used in the lung-on-a-chip. A thin gold mesh with an array of hexagonal pores of about 260 μm is used

as a scaffold, on which a drop of collagen–elastin solution is pipetted, **h-j)** hAEpC cultured on the hexagonal mesh with the CE membrane after 4 days and at the air–liquid interface for 2 days with expression of adherent junction markers (E-Cadherin, red), tight junctions with zonula occludens-1 (ZO-1, green) and merged (Hoechst, blue; E-Cadherin, red; ZO-1, green), Scale bar: 100 μm [49].

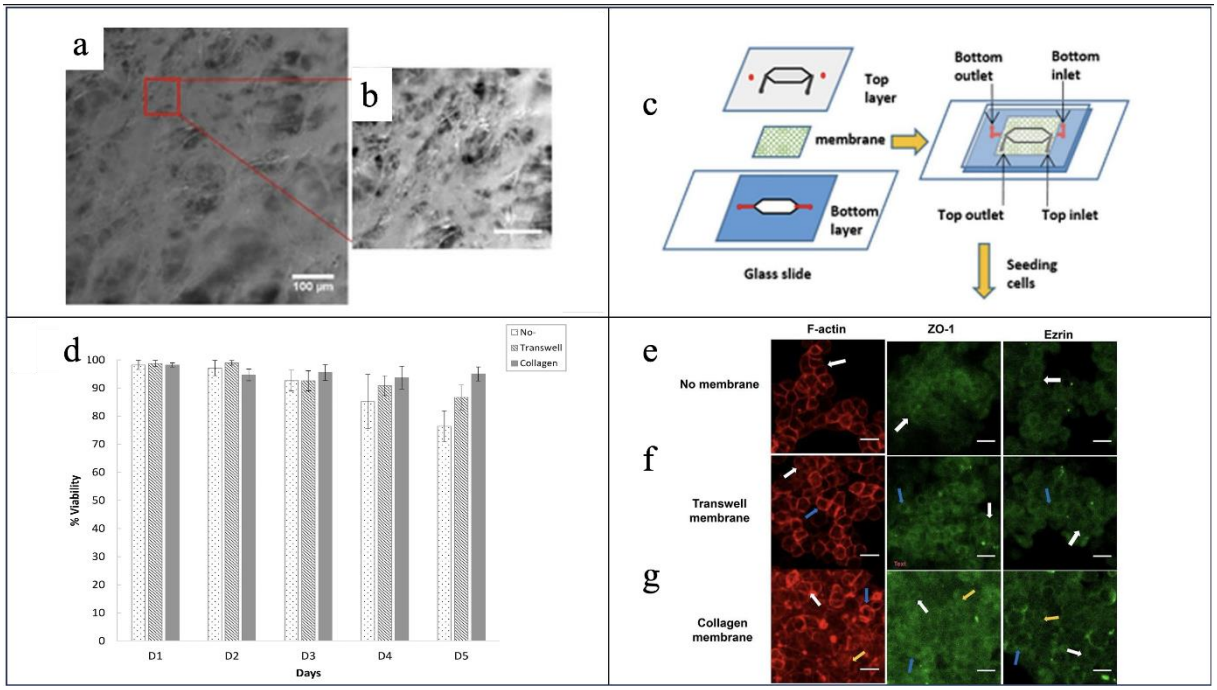

Figure 4. ***Collagen membrane fiber structure***. **a)** Confocal microscopy (scale bar, 100 μm), **b)** Magnified picture shows detailed clustered fibers and pores of the collagen membrane (scale bar, 20 μm), **c)** Schematic of a microfluidic devices with a membrane, **d)** Comparison viability of caco 2 cells in the microfluidic devices with 3 condition (no, Transwell, or collagen membrane) for 5 days (n > 6), **e to g)** Immunofluorescent images of caco 2 cells in devices with no, Transwell, or collagen membranes. F-actin, tight junction, and ezrin in caco 2 cells were stained by Phalloidin, ZO-1, and Ezrin (scale bar, 20 um). Three different cell morphologies were marked as squamous, white arrows; round, blue arrows; and cells that appeared integrated with collagen fibers, orange arrows [60].

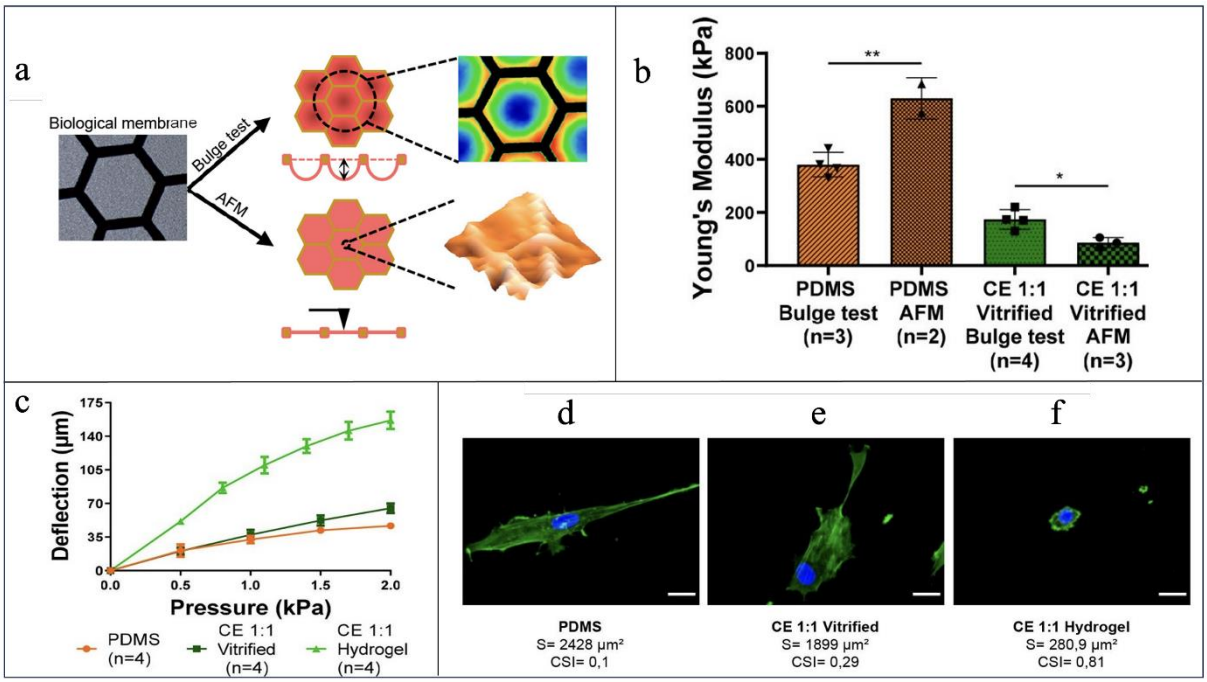

Figure 5. ***Mechanical properties of a natural HMs in a OoC device***. **a)** Mechanical properties were investigated by AFM and Bulge test, **b**) Comparison the Young's modulus obtain from AFM and Bulge test, **c)** Deflection diagram of collagen- elastin hydrogel membrane, and **d-f)** Different substrates stiffness (PDMS or hydrogel membrane) will affect cell spreading. Scale bar: 20 µm [65].

2.2.2. Synthetic materials

Since natural polymers often suffer from drawbacks such as poor mechanical properties, modern organic chemistry achievements can be used to address this challenge. This can be achieved by adjusting the physiochemical and mechanical properties of hydrogels through the selection and/or modification of constructing materials [20]. HMs based on purely synthetic polymers can be used in the construction of OoC platforms. One of the most used polymers in this regard is PEG due to its unique chemistry allowing various modifications [83]. Thus, this polymer can be modified to produce various derivatives such as diacrylate, dithiol, or diepoxy [44]. These modifications allow hydrogels to be enriched with bioactive molecules, such as peptides [84], or to enhance the reactivity of gel, improving adhesion and making it more

suitable for applications like 3D printing. For example, Kuo et al. [67] developed a photocurable resin based on low molecular weight PEG-DA, that can be used for stereolithography to fabricate high-resolution microfluidic and OoC devices. They found that the hydrogel formed from polymerized PEG-DA is transparent and biocompatible, making it suitable for these applications. Accordingly, it can be used to culture mammalian cells in OoC platforms. Another commonly used synthetic material for HM fabrication is polyacrylamide, thanks to the ability to tune its mechanical properties with stiffness ranging from less than one kPa to a few MPa [68]. Additionally, synthetic copolymers are also employed as HMs in OoC. Shen et al. [85] used a commercial hydrogel, Pluronic F-127 (poloxamer 407), modified with acrylates to simulate human alveoli for the development of a lung-on-a-chip device. This material is a copolymer with alternating units of ethylene oxide and propylene oxide. The Pluronic F-127 hydrogel effectively reconstructed both the mechanical and biological behaviors of the alveoli ECM. This makes it a valuable model for simulating lung tissue in lung-on-a-chip devices, particularly in the fields of drug testing, lung diseases research, and precision medicine [86].

2.2.3. Semi-synthetic materials

Hydrogels based on semi-synthetic materials have been developed to address the limitations of naturally derived hydrogels, such as poor mechanical strength and rapid degradation while preserving their superior biological properties. For instance, HA–PEG hydrogels are chemically-modified naturally-derived macromolecules [87]. By incorporating functional groups or cross-linkers, the structure of HA–PEG hydrogels can be tailored to enhance their mechanical properties and biocompatibility, achieving more desirable characteristics. In the semi-synthetic approach, the properties of naturally-derived macromolecules are usually improved by installing special types of chemical functionalities. One of the most intriguing examples is the GelMA-based hydrogels [88]. This photo-

crosslinkable polymer with high biocompatibility and tunable properties can be used in advanced manufacturing techniques such as 3D bioprinting [71, 72]. Massa et al. [89] used GelMA as an HM in a vascularized liver on-chip model to assess the drug toxicity. Other notable examples include methacrylated HA [90], thiolated hyaluronic acid (HA-SH) [91] or PEG-fibrinogen [92]. Semi-synthetic hydrogels will continue to push the boundaries of biomimicry by allowing researchers to finely tune the mechanical, chemical, and structural properties of the membranes. This will enable the recreation of organ-specific microenvironments with greater precision, leading to more accurate disease modeling and drug testing. Also, combining different semi-synthetic hydrogel materials or incorporating them with other supporting materials (such as synthetic polymers or nanoparticles) could lead to the development of hybrid systems that offer enhanced mechanical strength, stability, tunability, and biofunctionality. This approach could enable the creation of more robust OoC devices capable of withstanding physiological conditions over longer periods.

2.2.4. Hybrid materials

In order to benefit from the advantages of both natural and synthetic materials, hybrid materials can be used to make HMs for OoC applications. Hydrogels based on hybrid materials utilize a combination of both (semi) synthetic and natural materials. They benefit from the biodegradability and biocompatibility of naturally derived biomaterials and the appropriate mechanical properties of their synthetic counterparts [73]. Hybrid hydrogels can be classified into two categories: simple blending of two or more synthetic and natural polymers or an interpenetrating polymer network (IPN) or semi-IPN of a natural polymer and a synthetic polymer.

Pradhan et al. [74] developed a cancer-on-a-chip platform using an HM based on PEG-fibrinogen and PEG-DA to investigate anti-cancer drug efficiency. The hydrogel mimicking the ECM of tumor microenvironment was used for long-term 3D co-culture retaining high cell viability (>90%) during the study span. They investigated tumor-endothelial interactions and tumor cell migration under different flow conditions. The results demonstrated that the mechanical properties including the stiffness and Young's modulus could be modulated by the ratio between substrates. The stiffness could be changed by addition 1% or 2% w/v of PEG-DA within the polymer precursor prior to crosslinking. As a result, crosslinking density and Young's moduli of the bulk matrix would be increased.

Bhusal et al. [75] used a hydrogel bioink based on GelMA and PEG-DA to produce tissue chips using bioprinting technique. They used digital-light-processing (DLP) method for the bioprinting of cell-laden composite hydrogel. This biofabrication method provides a valuable tool for quickly integrating micro-tissue models into OoC devices. Human-derived tumor cells were embedded in the hydrogel to assess the biocompatibility of the device. They changed ratios of PEG-DA:GelMA to get tunable mechanical properties that are promising for making micro-tissue models. By increasing the concentration of GelMA from 0% to 3% w/v, the stiffness of PEG-DA/GelMA hydrogel would increase. Nie et al. [93] used three different hydrogel compositions: gelatin-alginate, alginate-GelMA, and gelatin-GelMA for fabrication of vessel-on-a-chip devices. HMs were produced using a process consisting of casting, demolding, and bonding of the gels. The microfluidic Gelatin-Gelma hydrogel showed enhanced attachment and spreading of HUVEC, making it a promising model for studying vessel function in both physiological and pathological conditions. **Table 2** provides examples of hydrogels used in OoC fabrication, along with a brief description of their fabrication methods.

Table 2. ***Examples of hydrogel membranes characteristics and applications in specific organ-on-a-chip devices***. Researchers are still exploring new materials combinations and different architectures of membranes to better simulate human organs.

Hydrogel Materials	Mimicked tissue	Description	Membrane thickness	Method of fabrication	Refs.
Collagen-Elastin (1:1)	Lung	A biological membrane made of proteins of the lung ECM mimicking the central aspects of the air–blood barrier.	4.5 ± 0.8 μm	Hydrogel pipetted on the thin gold meshed surface with an array of hexagonal pores.	[49]
Collagen	Barrier model	Membrane treated with proteases which fiber thickness can be changed.	2 μm	3D print	[81]
Pluronic F127 diacrylate (F127-DA)	Lung	A thin, biocompatible, soft, and stretchable hydrogel membrane reflecting stiffness of extracellular matrix in human alveoli for construction of lung-on-a-chip.	40-120 μm	soft lithography	[85]
PEG-fibrinogen	Tumor tissue	a microfluidics-based tumor-mimetic chip system for the long-term 3D co-culture of cancer cells and fibroblasts within an ECM-mimic hydrogel matrix.	600 μm	photolithography	[74]

Gelatin-alginate; Alginate-GelMA; Gelatin-GelMA	Vessel	Hydrogel allowed HUVEC attachment, spreading and realization of vascular function.	1,2.5,5,10 mm	3D print	[93]
Collagen I and Matrigel	Lung	Membrane provides air–liquid interface and allows cyclic breathing motions mimicking the primary human alveolar epithelial cell's function.	500 µm	Hydrogel pipetted to the middle channel.	[94]
Collagen I	Gut	Gut-on-a-chip model for investigating hallmarks of inflammatory bowel disease.	400 µm	Collagen I gel loaded on organoplate	[95]
Matrigel	Brain	Membrane embedded with human induced pluripotent stem cell allowed to simulate blood-brain barrier and analyze the neurotoxicity of Organophosphates exposure.	Not given	Hydrogel pipetted on the chip.	[96]
Poly(ethylene glycol) diacrylate modified with photo absorbers	Vessel	Different architectures of hydrogel membranes provided an environment to explore the oxygenation and flow of human red blood cells during tidal ventilation and distension.	Not given	stereolithography	[97]

3. Fabrication methods of Hydrogel Membranes

Several manufacturing processes can be used in the creation of microfluidic channels for OoC devices, including photolithography, soft lithography, injection molding, hot embossing process, or etching technique [98, 99]. However, in line with recent technology improvements, 3D printing and 3D bioprinting are becoming more prevalent to incorporate HMs in OoC devices, mostly due to unique abilities for personalization and manufacturing troublesome, physiological shapes [100].

3D printing is a layer-by-layer fabrication process that is the most promising technique in recent decades for the fabrication of complex 3D structures in OoC devices [101, 102]. This technique extends the concept of manufacturing by enabling the production of various cells and porous hydrogels within a single-step process, resulting in intricate 3D microfluidic devices [103, 104]. 3D bioprinting techniques including laser-based systems (such as stereolithography and soft lithography) and nozzle-based systems (such as inkjet printing and extrusion) can be chosen for developing 3D precisely controlled construction of hydrogel-based devices [98], as presented in **Table 3**. 3D bioprinters usually used bioink to create the 3D structure of HMs. Bioink could provide an ECM-like structure that mimics the tissue environment to support cell culture [105].

Table 3. ***3D print based-fabrication methods for preparation of hydrogel membranes suitable for OoC devices***.

Method		Description	Advantages	Limitations	Used materials	Refs.
Nozzle-based	**Inkjet**	Deposition of tiny droplets, ejected by thermal or piezoelectric force	- Fabricate complex structures - High speed (up to 10000 drops/s) - Low cost - High resolution (up to 50 μm) - Desirable to print thin construct	-Low droplet directionality -Unreliable cell encapsulation -Low viscosity of ink -Non-uniform droplet size -Nozzle clogging -Low viscosity of ink(3.5–12 mPa·s) -Poor cell viability	Sodium Alginate hydrogel	[106-111]
	Extrusion	Deposition of hydrogels through the forces exerted by pneumatic pressure	- The ink could have wide range of viscosity - Print complex structures - Good structure integrity	-Low resolution (up to 100 μm) -Poor cell viability -High shear stress -Hydrogel could be deformed	Gelatin and liver dECM bioinks (collagen type 1)	[107, 108, 112, 113]

Laser-assisted	**Stereo-lithography**	Layer by layer solidification of a prepolymer solution using light source	- Support printing of complex structures - High accuracy - Low surface roughness -High resolution (up to 6 μm)	- Limited to photopolymers - Post processing is required - Using a clean room for machine operation is required - Poor cell viability - Cytotoxicity of the photoinitiators - High cost -Slow, complex and time-consuming process	PEG-DA	[108, 114, 115]
	Soft-lithography	Production of membranes utilizing stamps, molds and photo masks	- Low cost - One step patterning - High resolution (up to 100 nm)	- Requires a lot of manual operations - High number of defects	PEG-DA and GelMA	[75, 116-120]

		- Use for wide range of biomaterials - Desirable to print HMs and modify their surface			
Sacrificial bioprinting	Production of a lumen area using a sacrificial hydrogel	-Enhanced mechanical properties	- Low resolution - Complex and long fabrication process - Low precision	GelMA	[121, 122]

3.1. Nozzle based bioprinting

Nozzle-based techniques of bioprinting utilize very small size of droplets to build a structure. The size of droplets highly depends on nozzle diameter and applied condition generated by mechanical or heating pressure which respectively called inkjet and extrusion printing [109].

In inkjet bioprinting, a piezoelectric actuator or a heater forces the bioink through the nozzle, creating droplets that are deposited onto the surface. This technique enables to control of small values of low-viscosity bioink (~0.1 Pa·s) with high resolution, enabling the fabrication of complex structures, such as multiple organ tissue [123]. Although, the ink-based method can fabricate complex shapes on hydrogels at high speed (up to 10000 drops per second) and resolution (50-300 um), besides it's a low-cost method [110, 112], the shear and thermal stress that applies to cells limits the use of this method for hydrogel bioprinting. Extrusion technique, another nozzle-based bioprinting, produces large-scale biomimetic structures by extruding bioink onto a surface using pneumatic pressure or a piston at high speeds. The printing heads move in the x, y, and z directions to rapidly create 3D structures. Although the resolution of extrusion printing is generally lower than that of other techniques, it is versatile and can accommodate a wide range of bioink viscosities (0.008–22 Pa·s) without adversely affecting cell structures [123].

3.2. Laser-based bioprinting

Laser-assisted bioprinting is an innovative technique used to deposit biomaterials onto a surface through the controlled use of a pulsed laser beam as an energy source. Stereolithography (SL) and soft lithography are the main methods that can fabricate 3D structures through laser-assisted bioprinting [106, 110, 114]. The SL technique involves layer by layer solidification of a

photosensitive resin, typically through radical photopolymerization to create 3D constructs [108]. Photosensitive resin must be biocompatible to fabricate an OoC device. This technology enables high-resolution patterning of hydrogels containing cells while maintaining their viability. The accuracy of the SL could be controlled by adjusting the laser position and intensity [124]. As a non-contact technology, SL eliminates the risk of contamination because there is no direct contact between the dispenser and the bioink. Additionally, cells are not subjected to mechanical forces such as shear stress during printing. These advantages contribute to achieving high cell density and viability (greater than 95%), making SL suitable for constructing hydrogels used in OoC devices [110, 125, 126]. However, the complexity of the manufacturing process, the need for a clean room, and the high costs have limited the use of this method for constructing hydrogels. Additionally, the technique is slow and time-consuming due to its point-by-point photopolymerization process.

Soft lithographic technique, another laser-assisted bioprinting method, is an improved version of photolithography. It produces 3D constructs with complex structures on nano and micro scales from soft materials, using stamps, molds, and photo masks. Soft lithography is the most commonly used technique for production of the microfluidic devices on a large scale and creating porous membranes for OoC devices [117-119]. Compared to photolithography, soft lithography can be applied to a broader range of materials and is not limited to the photopolymers. This versatility allows for the faster fabrication of multiple OoC, making it a more cost-effective method that involves fewer and simpler steps [127].

3.3. Sacrificial bioprinting

Creating tubular structures in OoC devices presents a significant challenge. These structures are essential for mimicking the architecture and function of blood vessels [128], airways [129], and other tubular organs [130]. The complexity lies in replicating the precise geometry, mechanical properties, and cellular environments of natural tissues within a microscale platform [131]. Bioinks, based on natural materials, are highly biocompatible with cell culture; however, they have insufficient mechanical properties to support and maintain shape of tubular structure under physiological condition [106]. Direct bioprinting methods of bioinks could not effectively create complex hollow structures. Recently, indirect bioprinting methods could provide an opportunity to precisely produce tubular structures in microfluidic models [132, 133]. This method is required to remove the initial bioink that was printed at first stage. First, a temporary sacrificial biomaterial is printed layer by layer to form desired tubular structure. Next, the sacrificial biomaterial is surrounded by a hydrogel matrix to support the tubular structure. The HM would be solidify using UV light or a crosslinker. Finally, the sacrificial bioink is dissolved or melted by changing the temperature without affecting the surrounding matrix [134]. For example, Pan et al. [134] have developed a sacrificial template to fabricate a hydrogel based vascular chip. They used water-soluble PVA as sacrificial templates, first printing the templates and then covering them with GelMA, which was cured using UV light. The sacrificial templates were subsequently dissolved to create channel networks. In another study, researchers developed a 3D vascularized perusable structure by using sacrificial agarose fibers surrounded by photocrosslinkable, cell-laden GelMA hydrogel. This approach was employed to study drug toxicity in a liver-on-a-chip model [89].

4. Applications

Microfluidic devices can be considered as one of the rapidly developing fields of science and technology and are increasingly used in many research areas ranging from material science to biology [135]. Nowadays, more and more applications of OoC can be found in the fields of tissue engineering, drug discovery and testing, toxicity studies, cell culture, biosensors, and separation [16, 136, 137] as presented in **Figure 6**.

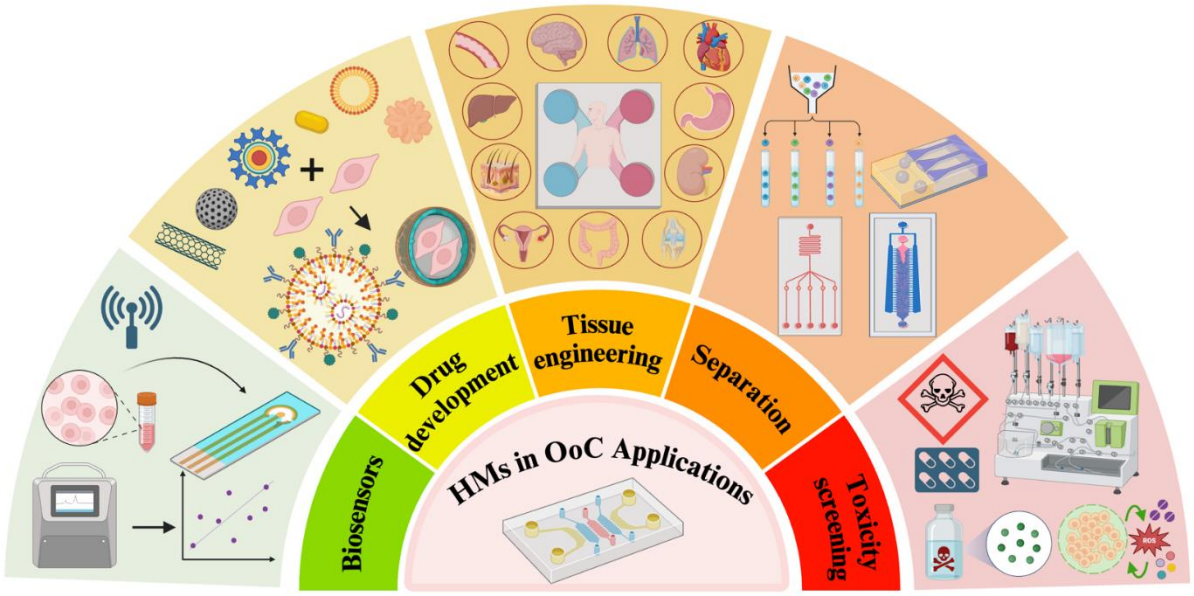

Figure 6. ***HMs in Organ-on-a-chip (OoC) applications***. HMs in OoC devices could provide a 3D scaffold that resemble natural ECM and tissue environment. This feature could be useful in tissue engineering, drug development, and toxicity screening. Moreover, HMs could create barriers in OoC devices that mimic the selective permeability of biological membrane and could be useful in separation and biosensor studies.

4.1. Tissue engineering

Microfluidic integrated with hydrogels and living cells offer an alternative method to traditional *in vitro* models to study human physiology. HMs contain up to 99% water, are highly permeable to biomolecules, and therefore mitigate the need for incorporating micropores to improve material permeability. Rosella et al. [138] developed a hybrid collagen-chitosan extracellular matrix-like membranes to study the viability of fibroblast cells in a microfluidic device as briefly discussed in **Figure 7 (a)**. To better simulate human physiology, the tissue chips are designed to control cell microenvironments and maintain tissue-specific functions by mimicking ECM-like membranes for on-chip cell cultures. As represented in **Table 2**, HMs in OoC devices are widely used to study various organs and tissues, including lung [85], liver [139], gut [95], kidney [140], brain [96], vessel [93], and multivascular networks [97]. **Figure 7 (b) and (c)** demonstrate a brain-on-a-chip platform consisting of human iPSC-derived GABAergic neurons and astrocytes. Integration of hydrogels in microfluidic devices is also summarized in **Figure 7 (d)** [54]. They could resemble many physiological tissue barrier's function, such as blood-brain barrier, [141] pulmonary epithelial barrier, renal glomerular barrier, and intestinal epithelial barrier.

HMs are the ideal candidate for mimicking the tissue barrier interface in OoC because of their porous structure and ability to provide a proper environment for cell culture by gas exchange and nutrient supply. The application of HMs in lung-on-a-chip research has gained significant attention compared to other platforms for disease modeling, toxicity study, and drug development. For example, researchers developed thin HMs made of collagen-elastin for the lung-on-a-chip platform. HMs in lung-on-a-chip platforms provide a unique capability to mimic the architecture and physiological function of the alveolar–capillary interface as shown in **Figure 7 (e)** [94, 142].

Gut-on-a-chip model offers a powerful platform to study the gut physiology and function under static culture condition as shown in **Figure 7 (f)**. This model involves two microchannels seeded with gut epithelial cells and the other channel is lined with vascular endothelial cells. These two microchannels are separated by a porous and flexible HM coated with ECM to mimic the barrier between the intestinal and lumen area. Membrane allows the transport of nutrients and gas exchange between the intestine and the blood vessel layers. In recent years more research used green biomaterials like collagen [143], for the membrane to increase the biocompatibility and facilitate cell proliferation and attachment.

Recently, there has also been growing interest in the development of multi-organs-on-chip and body-on-a-chip systems, which are more complex devices that can simulate the behavior of multiple organs or even the entire human body [144, 145]. These systems have the potential to revolutionize drug discovery and testing, as they can provide a more comprehensive understanding of how different organs and tissues interact with one another and respond to different treatments enabling many breakthroughs in the understanding of human cell biology, disease physiology, cancer treatment, while providing superior alternatives to animal models that often fail to predict clinical trial outcomes.

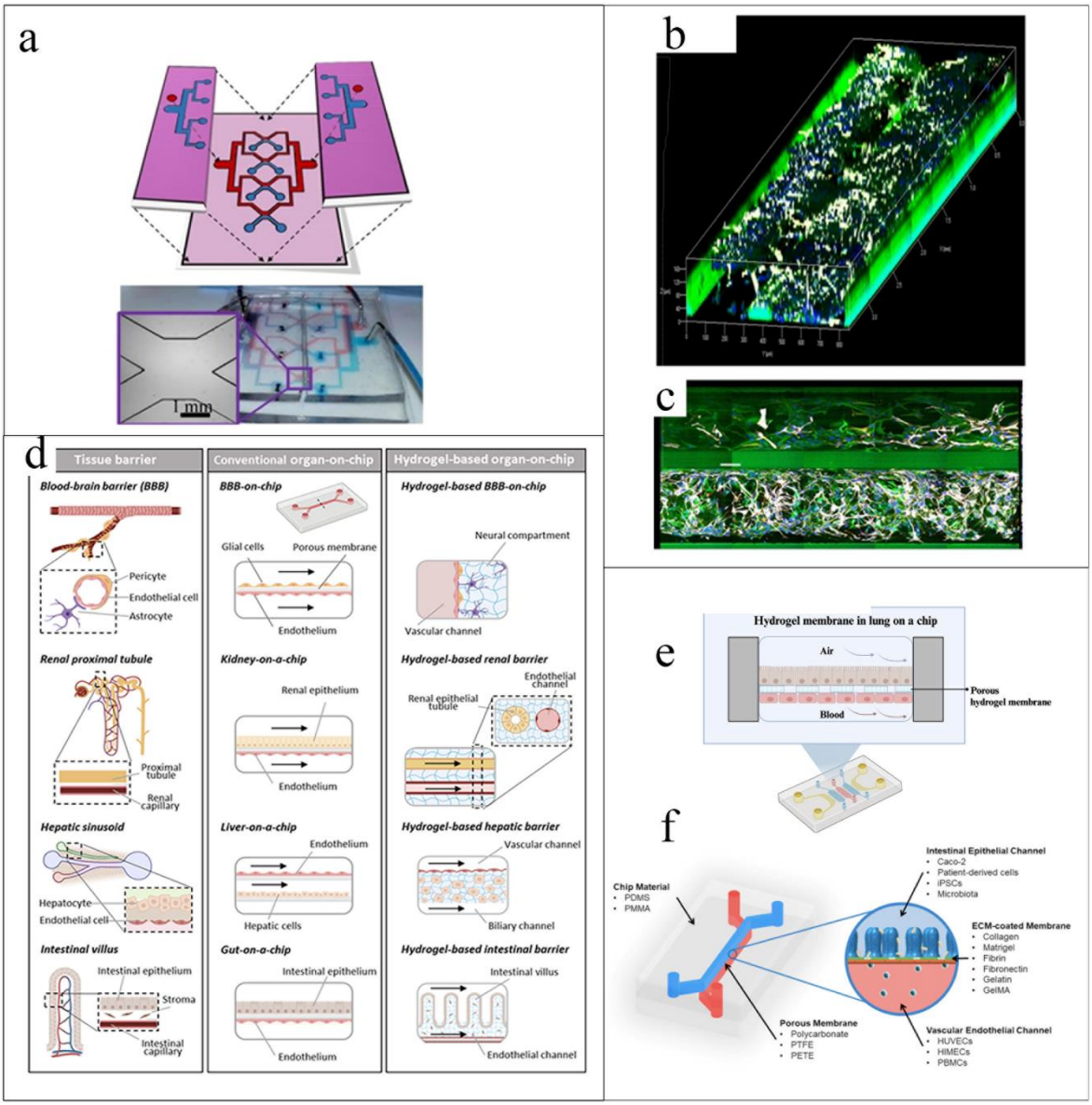

Figure 7. ***Applications of hydrogel membranes in organ-on-a-chip devices.*** **a)** Microfluidic platform for synthesis of collagen-chitosan matrix as an extracellular matrix support. On top: schematic representation of created platform with co-flowing solutions shown in blue (basic) and red (acidic) and on the bottom: photo of real device with dye solutions to mimic the scheme above [138]. **b and c)** Dynamic 3D brain tissue construct for brain-on-a-chip model with hydrogel matrix embedded with human neurons, astrocytes and a perfusion channel**. b)** Entire brain-on-a-chip construct as a 3D render and **c)** View from the top on brain construct with cell-gel matrix and perfusion line [96]. **d)** Summary integration

of hydrogels in microfluidic devices as a tissue barrier. **e)** HMs in lung-on-a-chip platform mimic physiological function of the alveolar–capillary interface and **f)** Gut on a chip model.

4.2. Drug development

In recent years, OoC devices have emerged as a convenient tool, facilitating faster drug development, cost-effective management, operative drug selection with low risk, as well as improved drug production in human models [127]. On the other hand, the COVID-19 pandemic has highlighted the urgent need for innovative approaches to accelerate drug repurposing and discovery during viral outbreaks. OoC technology has been successfully employed to address this challenge. “Ingber group” used airway-on-a-chip technology as a rapid method for identifying potential treatments for viral infections, including seasonal influenza and COVID-19 [146, 147]. These lung-on-a-chip models are capable of mimicking lung responses to viral infections. Additionally, they enable researchers to enhance existing drugs and expedite the development of new therapeutics. The airway microfluidic device comprises two microchannels separated by a porous membrane coated with ECM. Primary human lung bronchial airway basal stem cells are seeded on one side, while human lung endothelium is cultured on the opposite side. This model successfully confirmed the antiviral activity of several FDA-approved medications, including chloroquine, hydroxychloroquine, amodiaquine, toremifene, clomiphene, arbidol, verapamil, and amiodarone. In another study, Beaurivage et al. [95] developed a gut-on-a-chip system to investigate inflammatory bowel disease (IBD). They seeded 20,000 human colon adenocarcinoma cells (Caco-2) in a 3-lane 400 μm OrganoPlate, with ECM serving as the HM in the bottom channel. To induce an IBD-like condition, they used a cytokine cocktail comprising IL-1β, TNF-α, and IFN-γ to maximize cytokine production in Caco-2 cells. To assess the device's suitability for drug

discovery, the researchers treated the Caco-2 cells with the anti-inflammatory compound TPCA-1 for 2 hours. The results demonstrated that exposure to TPCA-1 significantly reduced cytokine secretion from the Caco-2 cells.

4.3. Toxicity screening

Large pharmaceutical companies could save billions of dollars by utilizing advanced drug screening technologies, improving efficiency and reducing the costs of the drug discovery process [148, 149]. HMs used in OoC devices, serve as an independent platform for drug cytotoxicity screening, effectively mimicking human body cells. Vormann et al. [150] developed a 3D-microfluidic platform for Nephrotoxicity and drug interaction studies. Renal proximal tubule epithelial cells (RPTEC) and human umbilical vein endothelial cells (HUVEC) were cocultured in the OrganoPlate 3-lane to mimic the tubular structure. These two layers were separated by using ECM gel composed of 4 mg/mL collagen I. Cells were exposed to different concentrations of cisplatin, tobramycin, and cyclosporin A (CysA) to induce Nephrotoxicity. After 48 hours, cell viability was measured by the WST-8 assay. In another study, Lee et al. [151] designed a skin-liver model to assess the toxicological effect of drugs. The epidermal layer and the liver part were separated by a collagen hydrogel barrier. Acetaminophen and camphor were applied to the outside of the skin layer and finally diffused to the liver channel. Hepatotoxicity was tested by using a staining assay after 24 hours. Results indicated higher levels of glutathione (GSH) and reactive oxygen species (ROS), which validate the model ability to evaluate the hepatotoxicity of chemical drugs.

4.4. Separation

Microfluidics devices present an excellent alternative for creating separation systems for micro-sized particles due to their inherent advantages: continuous operation, compact size, minimal sample and reagent consumption, and reduced analysis time [152]. Furthermore, the incorporation of hydrogel into the chips has increased their potential for the fabrication of very efficient separation devices. Such studies are essential for enhancement in the representative simulation of the liver, kidney, or gut, as those organs are also separating and filtrating particles. As an example, PEG-DA-based porous HMs were *in situ* photopolymerized inside PDMS microfluidic devices [153]. This platform was able to perform a cascade of analytical steps (elution, preconcentration, and electrophoresis separation) for the detection of β-amyloid (Aβ) peptides, which are markers used for diagnosing Alzheimer's disease. The HM serves to preconcentrate the eluted sample on-chip improving the sensitivity and reducing the time of the assay. The device allowed to analysis of four truncated peptides Aβ (1–37, 1–39, 1–40, and 1–42) with very high sensitivity, being able to detect as low as 25 ng of synthetic Aβ peptides. Decock et al. [154] tuned the membrane nano-porosity, using low molecular weight PEG-DA for the matrix of the membrane and PEG as porogen. PDMS stamps were used to form the shape of the desired membrane. Obtained HM was able to retain nanoparticles bigger than 20 nm and also was highly permeable to solvent flows. It was then used to prepare a chip to investigate ultra- and micro-filtration at the microfluidic scale.

4.5. Biosensors

Proper functionality of cells and the surrounding environment within OoC devices as preclinical platforms need to be assessed. Although imaging techniques are commonly used to

monitor OoC devices, they are incapable of providing real-time information. Integration of biosensors into OoC devices is a non-invasive approach to continuously evaluate the microtissues, ECM and membrane performance. HM could act as a barrier to prevent cells from crossing over into sensors while allowing diffusion of growth factors, cytokines and other molecules into sensing area [155]. Son et al. [156] designed a permeable PEG hydrogel membrane to separate cell culture area from the sensing chambers. Hepatocyte growth factor (HGF) and the transforming growth factor (TGF)-β1 secreted by primary hepatocytes cells diffused through the HM into sensing channels and were detected using fluorescent microbead-based sensors for 7 days. On days 1, 4, and 7 media inside the sensing chamber was replaced with sensing microbeads including non-fluorescent capture microbeads and fluorescent detection beads which modified with anti-growth factor antibodies. Fluorescent dextran, with approximately 20% of TRITC-dextran used to examine the diffusion of analytes through the hydrogel barrier. The fluorescence signal of growth factor secretion was detected for 90 min, then replaced with fresh media.

5. Concluding remarks

OoC platforms are complex devices, thus the selection of materials and manufacturing techniques for each part is crucial. Membrane could provide a controlled microenvironment with specific biochemical and mechanical cues to separate different cell types or tissue to mimic barrier properties of human body. Focusing on the membranes, the primary concern is associated with the use of PDMS polymer, which is the most common material in designing OoC devices, due to their ability to absorb hydrophobic drugs and small molecules from the cell culture. To overcome this limitation, alternative hydrophilic and flexible materials, such as hydrogels, can be employed. Nowadays, naturally-derived materials which mimic the ECM properties like gelatin, collagen, or chitosan are being chosen more often, but they lack proper mechanical properties. Hybrid hydrogels are being manufactured from a combination of synthetic and natural polymers (e.g., PLA-chitosan-gelatin) Which offer higher biocompatibility, cell viability, tunable mechanical properties and lower interference with the system operation. The development of new and adoption of existing manufacturing processes for HM creation allows for personalization and design fitting at an unprecedented level. The pore size, surface roughness, shape, anchoring points, or stimuli type can be adjusted during the production process. HMs in combination with microfluidic platforms have demonstrated their interesting capabilities in the modeling of a broad range of human disorders and diseases, mimicking the architecture and physiological function of different organs, accelerating drug discovery and development, modeling various types of drug delivery and drug cytotoxicity systems.

There are still many challenges related to HMs in OoC models that require further attention from selecting materials, choosing the correct fabrication method to effectively sealing HMs on

OoC, and elucidating their potential applications. Preparation of commonly agreed testing protocols is essential for comparing the experimental data. It will be only possible after conducting a series of validation studies for a specific OoC model, which could generate reproducible and statistically well-powered human-relevant results. It is also worth noting that the establishment of such protocols is well beyond the academic researchers' effort, as the standardization will be decided in the commercial field with the involvement of regulatory bodies, like the FDA. Those stakeholders have to identify and validate the critical OoC design criteria, performance parameters, and microbiological properties that may achieved for introducing such devices in large-scale studies. Future advancements of these innovative devices should consider the utilization of nontoxic, cost-effective materials with tunable mechanical properties that could easily fabricate inside OoC devices. Another predicted advancement is the development of higher-throughput OoC, which is required for the implementation of such devices in the industry. Overall, the OoC reached the tipping point, where the long-term success will be decided. Success in this field requires cooperation between all stakeholders: researchers, pharmaceutical companies, and regulatory boards to make breakthroughs in current ways of thinking.

6. Outlook and future prospect

Researchers are striving to create interconnected OoC systems that simulate the interactions between different organs within the human body. During the past decades, PDMS has been used to design OoC devices because of its proper optical transparency which allows researchers to image cells and tissues within microfluidic devices. On the other hand, it is very cheap to fabricate a flexible OoC device with tunable mechanical properties. However, PDMS exhibits several drawbacks including absorption of small hydrophobic molecules, such as therapeutic agents. HMs are alternative materials and will play a crucial role in enabling the integration of multiple organ models on a single chip. This advancement could revolutionize drug testing by providing insights into how different organs metabolize and respond to medications. Moreover, the integration of microfluidic systems with HMs will enable precise control over the flow rate of nutrients, gases, and metabolites within the OoC device. This will mimic the circulatory systems of real organs, allowing for a more accurate representation of organ function and response to stimuli. In addition, the automation of OoC devices equipped with HMs will enable rapid and parallelized drug testing. This will significantly accelerate the drug discovery process by providing a platform to test compounds on human organ models before advancing to clinical trials. Ultimately, in the future OoC platform could predict potential efficiency and safety of a drug candidate for every individualized person. OoC has large potential to develop personalized medicine by providing exclusive physiologically relevant context for every individual person.

From another point of view, hydrogel-based OoC devices have the potential to recreate disease states more accurately than traditional cell cultures or animal models (even safer, greener, and more accurate than tissue-modeled studies). In the future, these systems could be used to model

each individual patient-specific diseases by using patient-derived cells, such as induced pluripotent stem cells (iPSCs), facilitating the development of personalized treatment strategies, and reducing the reliance on expensive animal testing and clinical trials. Combination of OoC devices with new technologies such as gene editing could provide a powerful tool for disease modeling and toxicology studies.

There are lots of barriers and challenges to widespread use of HMs in OoC platform for personalized medicine because of complexity of human body and replicating physiological context of each individual. As a result, we are still far from achieving clinical translation of the OoC platform. One challenge is maintaining the viability of cells and tissues within OoC devices over extended periods. HMs should be biocompatible to support cells' adhesion, growth and proliferation. Moreover, they should possess enhanced mechanical properties to withstand physiological stresses. Future research will likely focus on improving the longevity and stability of hydrogel-based systems, ensuring that they accurately represent organ function over time; these can be achieved by the wealth of data generated by OoC devices. Another challenge is to have a reproducible product with specific structure and composition for standardization and scalability. Developing manufacturing tools like new generation of 3D printer using smart materials could produce more accurate and durable HMs in OoC devices. Future advancements will involve developing sophisticated analytical tools coupled with computational models and artificial intelligence to interpret and integrate this data effectively, further enhancing our understanding of organ function and responses. Finally, HMs should meet the regulatory standard for future application in personalized medicine. In this regard European Organ-on-Chip Society (EUROoCS)

plays a key role to connect academic innovators to regulations and industries to fulfil the gap from bench to bedside and develop a new generation of materials for OoC platforms [157].

7. Acknowledgement

Financial support of this study from Gdańsk University of Technology by the DEC-20/1/2022/IDUB/III.4c/Tc grant under the Technetium Talent Management - 'Excellence Initiative - Research University' program is gratefully acknowledged.

References

[1] M.R. Fernandes, A.R. Pedroso, Animal experimentation: A look into ethics, welfare and alternative methods, Rev Assoc Med Bras (1992) 63(11) (2017) 923-928.

[2] C.M. Leung, P. de Haan, K. Ronaldson-Bouchard, G.-A. Kim, J. Ko, H.S. Rho, Z. Chen, P. Habibovic, N.L. Jeon, S. Takayama, M.L. Shuler, G. Vunjak-Novakovic, O. Frey, E. Verpoorte, Y.-C. Toh, A guide to the organ-on-a-chip, Nature Reviews Methods Primers 2(1) (2022).

[3] M.J. Waring, J. Arrowsmith, A.R. Leach, P.D. Leeson, S. Mandrell, R.M. Owen, G. Pairaudeau, W.D. Pennie, S.D. Pickett, J. Wang, O. Wallace, A. Weir, An analysis of the attrition of drug candidates from four major pharmaceutical companies, Nat Rev Drug Discov 14(7) (2015) 475-86.

[4] P. Zarrintaj, M.R. Saeb, F.J. Stadler, M.K. Yazdi, M.N. Nezhad, S. Mohebbi, F. Seidi, M.R. Ganjali, M. Mozafari, Human Organs-on-Chips: A Review of the State-of-the-Art, Current Prospects, and Future Challenges, Adv Biol (Weinh) 6(1) (2022) e2000526.

[5] M. Kapalczynska, T. Kolenda, W. Przybyla, M. Zajaczkowska, A. Teresiak, V. Filas, M. Ibbs, R. Blizniak, L. Luczewski, K. Lamperska, 2D and 3D cell cultures - a comparison of different types of cancer cell cultures, Arch Med Sci 14(4) (2018) 910-919.

[6] D. Antoni, H. Burckel, E. Josset, G. Noel, Three-dimensional cell culture: a breakthrough in vivo, International journal of molecular sciences 16(3) (2015) 5517-5527.

[7] J. Kim, B.K. Koo, J.A. Knoblich, Human organoids: model systems for human biology and medicine, Nat Rev Mol Cell Biol 21(10) (2020) 571-584.

[8] N.B. Robinson, K. Krieger, F.M. Khan, W. Huffman, M. Chang, A. Naik, R. Yongle, I. Hameed, K. Krieger, L.N. Girardi, M. Gaudino, The current state of animal models in research: A review, Int J Surg 72 (2019) 9-13.

[9] A.E. Danku, E.H. Dulf, C. Braicu, A. Jurj, I. Berindan-Neagoe, Organ-On-A-Chip: A Survey of Technical Results and Problems, Front Bioeng Biotechnol 10 (2022) 840674.

[10] T. Pasman, D. Grijpma, D. Stamatialis, A. Poot, Flat and microstructured polymeric membranes in organs-on-chips, J R Soc Interface 15(144) (2018) 20180351.

[11] A.P.M. Guttenplan, Z. Tahmasebi Birgani, S. Giselbrecht, R.K. Truckenmuller, P. Habibovic, Chips for Biomaterials and Biomaterials for Chips: Recent Advances at the Interface between Microfabrication and Biomaterials Research, Adv Healthc Mater 10(14) (2021) e2100371.

[12] E.W. Esch, A. Bahinski, D. Huh, Organs-on-chips at the frontiers of drug discovery, Nature reviews Drug discovery 14(4) (2015) 248-260.

[13] J. Fentem, I. Malcomber, G. Maxwell, C. Westmoreland, Upholding the EU's commitment to ‘animal testing as a last Resort'Under REACH requires a paradigm shift in how we assess chemical safety to close the gap between regulatory testing and modern safety science, Alternatives to Laboratory Animals 49(4) (2021) 122-132.

[14] D. Grimm, EPA plan to end animal testing splits scientists, American Association for the Advancement of Science, 2019.

[15] D. Huh, H.J. Kim, J.P. Fraser, D.E. Shea, M. Khan, A. Bahinski, G.A. Hamilton, D.E. Ingber, Microfabrication of human organs-on-chips, Nat Protoc 8(11) (2013) 2135-57.

[16] C. Ding, X. Chen, Q. Kang, X. Yan, Biomedical Application of Functional Materials in Organ-on-a-Chip, Front Bioeng Biotechnol 8 (2020) 823.

[17] T.C. Cameron, A. Randhawa, S.M. Grist, T. Bennet, J. Hua, L.G. Alde, T.M. Caffrey, C.L. Wellington, K.C. Cheung, PDMS Organ-On-Chip Design and Fabrication: Strategies for Improving Fluidic Integration and Chip Robustness of Rapidly Prototyped Microfluidic In Vitro Models, Micromachines (Basel) 13(10) (2022).

[18] J. Grant, A. Ozkan, C. Oh, G. Mahajan, R. Prantil-Baun, D.E. Ingber, Simulating drug concentrations in PDMS microfluidic organ chips, Lab Chip 21(18) (2021) 3509-3519.

[19] S.B. Campbell, Q. Wu, J. Yazbeck, C. Liu, S. Okhovatian, M. Radisic, Beyond Polydimethylsiloxane: Alternative Materials for Fabrication of Organ-on-a-Chip Devices and Microphysiological Systems, ACS Biomater Sci Eng 7(7) (2021) 2880-2899.

[20] U.M.N. Cao, Y. Zhang, J. Chen, D. Sayson, S. Pillai, S.D. Tran, Microfluidic Organ-on-A-chip: A Guide to Biomaterial Choice and Fabrication, Int J Mol Sci 24(4) (2023) 3232.

[21] K. Corral-Najera, G. Chauhan, S.O. Serna-Saldivar, S.O. Martinez-Chapa, M.M. Aeinehvand, Polymeric and biological membranes for organ-on-a-chip devices, Microsyst Nanoeng 9 (2023) 107.

[22] S. Correa, A.K. Grosskopf, H. Lopez Hernandez, D. Chan, A.C. Yu, L.M. Stapleton, E.A. Appel, Translational Applications of Hydrogels, Chem Rev 121(18) (2021) 11385-11457.

[23] M.K. Yazdi, V. Vatanpour, A. Taghizadeh, M. Taghizadeh, M.R. Ganjali, M.T. Munir, S. Habibzadeh, M.R. Saeb, M. Ghaedi, Hydrogel membranes: A review, Mater Sci Eng C Mater Biol Appl 114 (2020) 111023.

[24] M. Khodadadi Yazdi, P. Zarrintaj, A. Khodadadi, A. Arefi, F. Seidi, H. Shokrani, M.R. Saeb, M. Mozafari, Polysaccharide-based electroconductive hydrogels: Structure, properties and biomedical applications, Carbohydr Polym 278 (2022) 118998.

[25] M. Khodadadi Yazdi, A. Taghizadeh, M. Taghizadeh, F.J. Stadler, M. Farokhi, F. Mottaghitalab, P. Zarrintaj, J.D. Ramsey, F. Seidi, M.R. Saeb, M. Mozafari, Agarose-based biomaterials for advanced drug delivery, J Control Release 326 (2020) 523-543.

[26] H. Yuk, B. Lu, X. Zhao, Hydrogel bioelectronics, Chem Soc Rev 48(6) (2019) 1642-1667.

[27] P. Zarrintaj, M. Khodadadi Yazdi, M. Youssefi Azarfam, M. Zare, J.D. Ramsey, F. Seidi, M. Reza Saeb, S. Ramakrishna, M. Mozafari, Injectable Cell-Laden Hydrogels for Tissue Engineering: Recent Advances and Future Opportunities, Tissue Eng Part A 27(11-12) (2021) 821-843.

[28] M.K. Yazdi, P. Zarrintaj, A. Khodadadi, A. Arefi, F. Seidi, H. Shokrani, M.R. Saeb, M. Mozafari, Polysaccharide-based electroconductive hydrogels: Structure, properties and biomedical applications, Carbohydrate Polymers 278 (2022) 118998.

[29] M.A. Nilforoushzadeh, M. Khodadadi Yazdi, S. Baradaran Ghavami, S. Farokhimanesh, L. Mohammadi Amirabad, P. Zarrintaj, M.R. Saeb, M.R. Hamblin, M. Zare, M. Mozafari, Mesenchymal Stem Cell Spheroids Embedded in an Injectable Thermosensitive Hydrogel: An In Situ Drug Formation Platform for Accelerated Wound Healing, ACS Biomater Sci Eng 6(9) (2020) 5096-5109.

[30] S. Manouchehri, B. Bagheri, S.H. Rad, M.N. Nezhad, Y.C. Kim, O.O. Park, M. Farokhi, M. Jouyandeh, M.R. Ganjali, M.K. Yazdi, P. Zarrintaj, M.R. Saeb, Electroactive bio-epoxy incorporated chitosan-oligoaniline as an advanced hydrogel coating for neural interfaces, Progress in Organic Coatings 131 (2019) 389-396.

[31] Z. Li, Y. Zhou, T. Li, J. Zhang, H. Tian, Stimuli-responsive hydrogels: fabrication and biomedical applications, View 3(2) (2022) 20200112.

[32] P. Zarrintaj, F. Seidi, M. Youssefi Azarfam, M. Khodadadi Yazdi, A. Erfani, M. Barani, N.P.S. Chauhan, N. Rabiee, T. Kuang, J. Kucinska-Lipka, M.R. Saeb, M. Mozafari, Biopolymer-based composites for tissue engineering applications: A basis for future opportunities, Composites Part B: Engineering 258 (2023).

[33] A. Taghizadeh, M. Taghizadeh, M.K. Yazdi, P. Zarrintaj, J.D. Ramsey, F. Seidi, F.J. Stadler, H. Lee, M.R. Saeb, M. Mozafari, Mussel-inspired biomaterials: From chemistry to clinic, Bioeng Transl Med 7(3) (2022) e10385.

[34] M. Taghizadeh, A. Taghizadeh, M.K. Yazdi, P. Zarrintaj, F.J. Stadler, J.D. Ramsey, S. Habibzadeh, S. Hosseini Rad, G. Naderi, M.R. Saeb, M. Mozafari, U.S. Schubert, Chitosan-based inks for 3D printing and bioprinting, Green Chemistry 24(1) (2022) 62-101.

[35] D. Sivaraj, K. Chen, A. Chattopadhyay, D. Henn, W. Wu, C. Noishiki, N.J. Magbual, S. Mittal, A.M. Mermin-Bunnell, C.A. Bonham, A.A. Trotsyuk, J.A. Barrera, J. Padmanabhan, M. Januszyk, G.C. Gurtner, Hydrogel Scaffolds to Deliver Cell Therapies for Wound Healing, Front Bioeng Biotechnol 9 (2021) 660145.

[36] L. Xing, Y.T. Fan, L.J. Shen, C.X. Yang, X.Y. Liu, Y.N. Ma, L.Y. Qi, K.H. Cho, C.S. Cho, H.L. Jiang, pH-sensitive and specific ligand-conjugated chitosan nanogels for efficient drug delivery, Int J Biol Macromol 141 (2019) 85-97.

[37] F. Scheffold, Pathways and challenges towards a complete characterization of microgels, Nat Commun 11(1) (2020) 4315.

[38] M. Koosha, M. Raoufi, H. Moravvej, One-pot reactive electrospinning of chitosan/PVA hydrogel nanofibers reinforced by halloysite nanotubes with enhanced fibroblast cell attachment for skin tissue regeneration, Colloids Surf B Biointerfaces 179 (2019) 270-279.

[39] H.H. Le, M.T.I. Mredha, J.Y. Na, J.-K. Seon, I. Jeon, Thin-film hydrogels with superior stiffness, strength, and stretchability, Extreme Mechanics Letters 37 (2020) 100720.

[40] S. Trombino, R. Sole, F. Curcio, R. Cassano, Polymeric Based Hydrogel Membranes for Biomedical Applications, Membranes (Basel) 13(6) (2023).

[41] R.M. Abdel-Rahman, A.M. Abdel-Mohsen, J. Frankova, F. Piana, L. Kalina, V. Gajdosova, L. Kapralkova, M.A. Thottappali, J. Jancar, Self-Assembled Hydrogel Membranes with Structurally Tunable Mechanical and Biological Properties, Biomacromolecules 25(6) (2024) 3449-3463.

[42] N. Annabi, J.W. Nichol, X. Zhong, C. Ji, S. Koshy, A. Khademhosseini, F. Dehghani, Controlling the porosity and microarchitecture of hydrogels for tissue engineering, Tissue Eng Part B Rev 16(4) (2010) 371-83.

[43] D. Huh, B.D. Matthews, A. Mammoto, M. Montoya-Zavala, H.Y. Hsin, D.E. Ingber, Reconstituting organ-level lung functions on a chip, Science 328(5986) (2010) 1662-8.

[44] H. Liu, Y. Wang, K. Cui, Y. Guo, X. Zhang, J. Qin, Advances in Hydrogels in Organoids and Organs-on-a-Chip, Adv Mater 31(50) (2019) e1902042.

[45] C.B. Goy, R.E. Chaile, R.E. Madrid, Microfluidics and hydrogel: A powerful combination, Reactive and Functional Polymers 145 (2019).

[46] Z. Zhao, X. Chen, A.M. Dowbaj, A. Sljukic, K. Bratlie, L. Lin, E.L.S. Fong, G.M. Balachander, Z. Chen, A. Soragni, Organoids, Nature Reviews Methods Primers 2(1) (2022) 94.

[47] M. Hofer, M.P. Lutolf, Engineering organoids, Nat Rev Mater 6(5) (2021) 402-420.

[48] C. Shao, Y. Yu, X. Lei, J. Cao, Y. Zhao, F. Ye, Organ-on-a-chip for dynamic tumor drug resistance investigation, Chemical Engineering Journal 460 (2023).

[49] P. Zamprogno, S. Wuthrich, S. Achenbach, G. Thoma, J.D. Stucki, N. Hobi, N. Schneider-Daum, C.M. Lehr, H. Huwer, T. Geiser, R.A. Schmid, O.T. Guenat, Second-generation lung-on-a-chip with an array of stretchable alveoli made with a biological membrane, Commun Biol 4(1) (2021) 168.

[50] N.S. Bhise, V. Manoharan, S. Massa, A. Tamayol, M. Ghaderi, M. Miscuglio, Q. Lang, Y. Shrike Zhang, S.R. Shin, G. Calzone, N. Annabi, T.D. Shupe, C.E. Bishop, A. Atala, M.R. Dokmeci, A. Khademhosseini, A liver-on-a-chip platform with bioprinted hepatic spheroids, Biofabrication 8(1) (2016) 014101.

[51] H. Liu, O.A. Bolonduro, N. Hu, J. Ju, A.A. Rao, B.M. Duffy, Z. Huang, L.D. Black, B.P. Timko, Heart-on-a-Chip Model with Integrated Extra- and Intracellular Bioelectronics for Monitoring Cardiac Electrophysiology under Acute Hypoxia, Nano Lett 20(4) (2020) 2585-2593.

[52] M.J. Wilmer, C.P. Ng, H.L. Lanz, P. Vulto, L. Suter-Dick, R. Masereeuw, Kidney-on-a-Chip Technology for Drug-Induced Nephrotoxicity Screening, Trends Biotechnol 34(2) (2016) 156-170.

[53] S. Clerc, M. Villien, Organ-on-chips market and technology landscape 2019, 2019.

[54] D. Vera, M. Garcia-Diaz, N. Torras, M. Alvarez, R. Villa, E. Martinez, Engineering Tissue Barrier Models on Hydrogel Microfluidic Platforms, ACS Appl Mater Interfaces 13(12) (2021) 13920-13933.

[55] H.H. Chung, M. Mireles, B.J. Kwarta, T.R. Gaborski, Use of porous membranes in tissue barrier and co-culture models, Lab Chip 18(12) (2018) 1671-1689.

[56] B. Ye, R. Xiang, F. Luo, Hydrogel-Based drug delivery systems for diabetes bone defects, Chemical Engineering Journal 497 (2024).

[57] X. Liu, T. Fang, T. Shi, Y. Wang, G. Liu, Hydrogels provide microenvironments to mesenchymal stem cells for craniofacial bone regeneration: Review, J Biomater Appl 38(1) (2023) 3-24.

[58] Y.N. Ye, M. Frauenlob, L. Wang, M. Tsuda, T.L. Sun, K. Cui, R. Takahashi, H.J. Zhang, T. Nakajima, T. Nonoyama, Tough and self-recoverable thin hydrogel membranes for biological applications, Advanced functional materials 28(31) (2018) 1801489.

[59] K.Y. Lee, D.J. Mooney, Hydrogels for tissue engineering, Chemical reviews 101(7) (2001) 1869-1880.

[60] C. Wang, N. Tanataweethum, S. Karnik, A. Bhushan, Novel Microfluidic Colon with an Extracellular Matrix Membrane, ACS Biomater Sci Eng 4(4) (2018) 1377-1385.

[61] Y. Xiao, B. Zhang, H. Liu, J.W. Miklas, M. Gagliardi, A. Pahnke, N. Thavandiran, Y. Sun, C. Simmons, G. Keller, M. Radisic, Microfabricated perfusable cardiac biowire: a platform that mimics native cardiac bundle, Lab Chip 14(5) (2014) 869-82.

[62] M. Wang, B. Duan, Materials and Their Biomedical Applications, Encyclopedia of Biomedical Engineering2019, pp. 135-152.

[63] M. Dattilo, F. Patitucci, S. Prete, O.I. Parisi, F. Puoci, Polysaccharide-Based Hydrogels and Their Application as Drug Delivery Systems in Cancer Treatment: A Review, J Funct Biomater 14(2) (2023).

[64] P. Safarzadeh Kozani, P. Safarzadeh Kozani, M. Hamidi, O. Valentine Okoro, M. Eskandani, M. Jaymand, Polysaccharide-based hydrogels: properties, advantages, challenges, and optimization methods for applications in regenerative medicine, International Journal of Polymeric Materials and Polymeric Biomaterials 71(17) (2021) 1319-1333.

[65] P. Zamprogno, G. Thoma, V. Cencen, D. Ferrari, B. Putz, J. Michler, G.E. Fantner, O.T. Guenat, Mechanical Properties of Soft Biological Membranes for Organ-on-a-Chip Assessed by Bulge Test and AFM, ACS Biomater Sci Eng 7(7) (2021) 2990-2997.

[66] M.J. Mondrinos, Y.S. Yi, N.K. Wu, X. Ding, D. Huh, Native extracellular matrix-derived semipermeable, optically transparent, and inexpensive membrane inserts for microfluidic cell culture, Lab Chip 17(18) (2017) 3146-3158.

[67] A.P. Kuo, N. Bhattacharjee, Y.S. Lee, K. Castro, Y.T. Kim, A. Folch, High-Precision Stereolithography of Biomicrofluidic Devices, Adv Mater Technol 4(6) (2019) 1800395.

[68] J.H. Wen, L.G. Vincent, A. Fuhrmann, Y.S. Choi, K.C. Hribar, H. Taylor-Weiner, S. Chen, A.J. Engler, Interplay of matrix stiffness and protein tethering in stem cell differentiation, Nat Mater 13(10) (2014) 979-87.

[69] J. Zhu, R.E. Marchant, Design properties of hydrogel tissue-engineering scaffolds, Expert Rev Med Devices 8(5) (2011) 607-26.

[70] Q. Chai, Y. Jiao, X. Yu, Hydrogels for Biomedical Applications: Their Characteristics and the Mechanisms behind Them, Gels 3(1) (2017).

[71] G. Ying, N. Jiang, C. Yu, Y.S. Zhang, Three-dimensional bioprinting of gelatin methacryloyl (GelMA), Bio-Design and Manufacturing 1 (2018) 215-224.

[72] J. He, Y. Sun, Q. Gao, C. He, K. Yao, T. Wang, M. Xie, K. Yu, J. Nie, Y. Chen, Y. He, Gelatin Methacryloyl Hydrogel, from Standardization, Performance, to Biomedical Application, Adv Healthc Mater (2023) e2300395.

[73] B.K. Nahak, A. Mishra, S. Preetam, A. Tiwari, Advances in Organ-on-a-Chip Materials and Devices, ACS Appl Bio Mater 5(8) (2022) 3576-3607.

[74] S. Pradhan, A.M. Smith, C.J. Garson, I. Hassani, W.J. Seeto, K. Pant, R.D. Arnold, B. Prabhakarpandian, E.A. Lipke, A Microvascularized Tumor-mimetic Platform for Assessing Anti-cancer Drug Efficacy, Sci Rep 8(1) (2018) 3171.

[75] A. Bhusal, E. Dogan, H.A. Nguyen, O. Labutina, D. Nieto, A. Khademhosseini, A.K. Miri, Multi-material digital light processing bioprinting of hydrogel-based microfluidic chips, Biofabrication 14(1) (2021) 014103.

[76] Y. Berkovitch, D. Seliktar, Semi-synthetic hydrogel composition and stiffness regulate neuronal morphogenesis, Int J Pharm 523(2) (2017) 545-555.

[77] N. Rabiee, M.R. Dokmeci, A. Zarrabi, P. Makvandi, M.R. Saeb, H. Karimi-Maleh, S. Jafarzadeh, C. Karaman, Y. Yamauchi, M.E. Warkiani, S.A. Bencherif, G. Mehta, M. Eguchi, A.

Kaushik, M.-A. Shahbazi, A.C. Paiva-Santos, J. Ryl, E.C. Lima, M.R. Hamblin, R.S. Varma, Y. Huh, A.T.E. Vilian, P.K. Gupta, S.K. Lakhera, K.K. Kesari, Y.-T. Liu, M. Tahriri, G.S. Rama Raju, M. Adeli, A. Mohammadi, J. Wang, M.Z. Ansari, T. Aminabhavi, H. Savoji, G. Sethi, T. Bączek, A. Kot-Wasik, M.E. Penoff, A.M. Nafchi, J. Kucinska-Lipka, M. Zargar, M. Asadnia, A.R. Aref, M. Safarkhani, M. Ashrafizadeh, R. Umapathi, A. Ghasemi, M. Radisic, Green Biomaterials

: fundamental principles, Green Biomaterials 1(1) (2023) 1-4.

[78] S. Liu, J.M. Yu, Y.C. Gan, X.Z. Qiu, Z.C. Gao, H. Wang, S.X. Chen, Y. Xiong, G.H. Liu, S.E. Lin, A. McCarthy, J.V. John, D.X. Wei, H.H. Hou, Biomimetic natural biomaterials for tissue engineering and regenerative medicine: new biosynthesis methods, recent advances, and emerging applications, Mil Med Res 10(1) (2023) 16.

[79] M.K. Yazdi, P. Zarrintaj, M. Ghavami, R. Alizadeh, M.R. Saeb, Protein and peptide-based delivery systems, Nanoengineered Biomaterials for Advanced Drug Delivery, Elsevier2020, pp. 145-161.

[80] M.K. Yazdi, S.M. Sajadi, F. Seidi, N. Rabiee, Y. Fatahi, M. Rabiee, C.M. Dominic, P. Zarrintaj, K. Formela, M.R. Saeb, Clickable polysaccharides for biomedical applications: a comprehensive review, Progress in Polymer Science (2022) 101590.

[81] Y.B. Arik, A. de Sa Vivas, D. Laarveld, N. van Laar, J. Gemser, T. Visscher, A. van den Berg, R. Passier, A.D. van der Meer, Collagen I Based Enzymatically Degradable Membranes for Organ-on-a-Chip Barrier Models, ACS Biomater Sci Eng 7(7) (2021) 2998-3005.

[82] F.P. Nicoletta, G. DE FILPO, P. Formoso, Hydrogel Membranes, Encyclopedia of Membranes2015.

[83] K. Ye, X. Wang, L. Cao, S. Li, Z. Li, L. Yu, J. Ding, Matrix Stiffness and Nanoscale Spatial Organization of Cell-Adhesive Ligands Direct Stem Cell Fate, Nano Lett 15(7) (2015) 4720-9.

[84] J. Zhu, J. Hu, R.E. Marchant, Biomimetic hydrogels as scaffolds for tissue-engineering applications, Biomimetic Biomaterials2013, pp. 238-275.

[85] C. Shen, H. Yang, W. She, Q. Meng, A microfluidic lung-on-a-chip based on biomimetic hydrogel membrane, Biotechnol Bioeng 120(7) (2023) 2027-2038.

[86] W. She, C. Shen, Y. Ying, Q. Meng, Fabrication of sac-like hydrogel membranes for replicating curved tissue barriers on chips, Lab Chip 24(1) (2023) 85-96.

[87] B.J. Engel, P.E. Constantinou, L.K. Sablatura, N.J. Doty, D.D. Carson, M.C. Farach-Carson, D.A. Harrington, T.I. Zarembinski, Multilayered, Hyaluronic Acid-Based Hydrogel Formulations Suitable for Automated 3D High Throughput Drug Screening of Cancer-Stromal Cell Cocultures, Adv Healthc Mater 4(11) (2015) 1664-74.

[88] K. Yue, G. Trujillo-de Santiago, M.M. Alvarez, A. Tamayol, N. Annabi, A. Khademhosseini, Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels, Biomaterials 73 (2015) 254-71.

[89] S. Massa, M.A. Sakr, J. Seo, P. Bandaru, A. Arneri, S. Bersini, E. Zare-Eelanjegh, E. Jalilian, B.H. Cha, S. Antona, A. Enrico, Y. Gao, S. Hassan, J.P. Acevedo, M.R. Dokmeci, Y.S. Zhang, A.

Khademhosseini, S.R. Shin, Bioprinted 3D vascularized tissue model for drug toxicity analysis, Biomicrofluidics 11(4) (2017) 044109.

[90] M. Guvendiren, J.A. Burdick, Stiffening hydrogels to probe short- and long-term cellular responses to dynamic mechanics, Nat Commun 3 (2012) 792.

[91] E.L. Fong, M. Martinez, J. Yang, A.G. Mikos, N.M. Navone, D.A. Harrington, M.C. Farach-Carson, Hydrogel-based 3D model of patient-derived prostate xenograft tumors suitable for drug screening, Mol Pharm 11(7) (2014) 2040-50.

[92] L. Almany, D. Seliktar, Biosynthetic hydrogel scaffolds made from fibrinogen and polyethylene glycol for 3D cell cultures, Biomaterials 26(15) (2005) 2467-77.

[93] J. Nie, Q. Gao, Y. Wang, J. Zeng, H. Zhao, Y. Sun, J. Shen, H. Ramezani, Z. Fu, Z. Liu, M. Xiang, J. Fu, P. Zhao, W. Chen, Y. He, Vessel-on-a-chip with Hydrogel-based Microfluidics, Small 14(45) (2018) e1802368.

[94] M. Humayun, C.W. Chow, E.W.K. Young, Microfluidic lung airway-on-a-chip with arrayable suspended gels for studying epithelial and smooth muscle cell interactions, Lab Chip 18(9) (2018) 1298-1309.

[95] C. Beaurivage, E. Naumovska, Y.X. Chang, E.D. Elstak, A. Nicolas, H. Wouters, G. van Moolenbroek, H.L. Lanz, S.J. Trietsch, J. Joore, P. Vulto, R.A.J. Janssen, K.S. Erdmann, J. Stallen, D. Kurek, Development of a Gut-On-A-Chip Model for High Throughput Disease Modeling and Drug Discovery, Int J Mol Sci 20(22) (2019) 5661.

[96] L. Liu, Y. Koo, T. Russell, E. Gay, Y. Li, Y. Yun, Three-dimensional brain-on-chip model using human iPSC-derived GABAergic neurons and astrocytes: Butyrylcholinesterase post-treatment for acute malathion exposure, PLoS One 15(3) (2020) e0230335.

[97] B. Grigoryan, S.J. Paulsen, D.C. Corbett, D.W. Sazer, C.L. Fortin, A.J. Zaita, P.T. Greenfield, N.J. Calafat, J.P. Gounley, A.H. Ta, Multivascular networks and functional intravascular topologies within biocompatible hydrogels, Science 364(6439) (2019) 458-464.

[98] S. Preetam, B.K. Nahak, S. Patra, D.C. Toncu, S. Park, M. Syväjärvi, G. Orive, A. Tiwari, Emergence of microfluidics for next generation biomedical devices, Biosensors and Bioelectronics: X 10 (2022) 100106.

[99] Z. Yang, X. Yan, B. Xu, Z. Wang, Y. Wang, Precisely writing/printing hydrogel patterns on polymer surfaces, Chemical Engineering Journal 485 (2024).

[100] M.A. Chliara, S. Elezoglou, I. Zergioti, Bioprinting on Organ-on-Chip: Development and Applications, Biosensors (Basel) 12(12) (2022) 1135.

[101] V. Carvalho, I. Gonçalves, T. Lage, R.O. Rodrigues, G. Minas, S.F. Teixeira, A.S. Moita, T. Hori, H. Kaji, R.A. Lima, 3D printing techniques and their applications to organ-on-a-chip platforms: A systematic review, Sensors 21(9) (2021) 3304.

[102] M. Dong, D. Jiao, Q. Zheng, Z.L. Wu, Recent progress in fabrications and applications of functional hydrogel films, Journal of Polymer Science 61(11) (2022) 1026-1039.

[103] M. Taghizadeh, A. Taghizadeh, M.K. Yazdi, P. Zarrintaj, F.J. Stadler, J.D. Ramsey, S. Habibzadeh, S.H. Rad, G. Naderi, M.R. Saeb, Chitosan-based inks for 3D printing and bioprinting, Green Chemistry 24(1) (2022) 62-101.

[104] H. Lee, D.W. Cho, One-step fabrication of an organ-on-a-chip with spatial heterogeneity using a 3D bioprinting technology, Lab Chip 16(14) (2016) 2618-25.

[105] N. Ashammakhi, S. Ahadian, C. Xu, H. Montazerian, H. Ko, R. Nasiri, N. Barros, A. Khademhosseini, Bioinks and bioprinting technologies to make heterogeneous and biomimetic tissue constructs, Mater Today Bio 1 (2019) 100008.

[106] T.G. Papaioannou, D. Manolesou, E. Dimakakos, G. Tsoucalas, M. Vavuranakis, D. Tousoulis, 3D Bioprinting Methods and Techniques: Applications on Artificial Blood Vessel Fabrication, Acta Cardiol Sin 35(3) (2019) 284-289.

[107] Z.P. Kacarevic, P.M. Rider, S. Alkildani, S. Retnasingh, R. Smeets, O. Jung, Z. Ivanisevic, M. Barbeck, An Introduction to 3D Bioprinting: Possibilities, Challenges and Future Aspects, Materials (Basel) 11(11) (2018).

[108] J. Yu, S.A. Park, W.D. Kim, T. Ha, Y.Z. Xin, J. Lee, D. Lee, Current Advances in 3D Bioprinting Technology and Its Applications for Tissue Engineering, Polymers (Basel) 12(12) (2020).

[109] J.Y. Park, J. Jang, H.-W. Kang, 3D Bioprinting and its application to organ-on-a-chip, Microelectronic Engineering 200 (2018) 1-11.

[110] H. Li, C. Tan, L. Li, Review of 3D printable hydrogels and constructs, Materials & Design 159 (2018) 20-38.

[111] J. Zhang, F. Chen, Z. He, Y. Ma, K. Uchiyama, J.M. Lin, A novel approach for precisely controlled multiple cell patterning in microfluidic chips by inkjet printing and the detection of drug metabolism and diffusion, Analyst 141(10) (2016) 2940-7.

[112] C. Liu, N. Xu, Q. Zong, J. Yu, P. Zhang, Hydrogel prepared by 3D printing technology and its applications in the medical field, Colloid and Interface Science Communications 44 (2021).

[113] H. Lee, J. Kim, Y. Choi, D.W. Cho, Application of Gelatin Bioinks and Cell-Printing Technology to Enhance Cell Delivery Capability for 3D Liver Fibrosis-on-a-Chip Development, ACS Biomater Sci Eng 6(4) (2020) 2469-2477.

[114] J. Saroia, W. Yanen, Q. Wei, K. Zhang, T. Lu, B. Zhang, A review on biocompatibility nature of hydrogels with 3D printing techniques, tissue engineering application and its future prospective, Bio-Design and Manufacturing 1(4) (2018) 265-279.

[115] S. Zips, L. Hiendlmeier, L.J.K. Weiß, H. Url, T.F. Teshima, R. Schmid, M. Eblenkamp, P. Mela, B. Wolfrum, Biocompatible, Flexible, and Oxygen-Permeable Silicone-Hydrogel Material for Stereolithographic Printing of Microfluidic Lab-On-A-Chip and Cell-Culture Devices, ACS Applied Polymer Materials 3(1) (2020) 243-258.

[116] D. Kefallinou, M. Grigoriou, D.T. Boumpas, E. Gogolides, A. Tserepi, Fabrication of a 3D microfluidic cell culture device for bone marrow-on-a-chip, Micro and Nano Engineering 9 (2020) 100075.

[117] M.A. Rose, J.J. Bowen, S.A. Morin, Emergent Soft Lithographic Tools for the Fabrication of Functional Polymeric Microstructures, Chemphyschem 20(7) (2019) 909-925.

[118] G. Camci-Unal, P. Zorlutuna, A. Khademhosseini, Fabrication of Microscale Hydrogels for Tissue Engineering Applications, Biofabrication2013, pp. 59-80.

[119] D. Qin, Y. Xia, G.M. Whitesides, Soft lithography for micro- and nanoscale patterning, Nat Protoc 5(3) (2010) 491-502.

[120] J. Kajtez, S. Buchmann, S. Vasudevan, M. Birtele, S. Rocchetti, C.J. Pless, A. Heiskanen, R.A. Barker, A. Martinez-Serrano, M. Parmar, J.U. Lind, J. Emneus, 3D-Printed Soft Lithography for Complex Compartmentalized Microfluidic Neural Devices, Adv Sci (Weinh) 7(16) (2020) 2001150.

[121] J. Nie, Q. Gao, C. Xie, S. Lv, J. Qiu, Y. Liu, M. Guo, R. Guo, J. Fu, Y. He, Construction of multi-scale vascular chips and modelling of the interaction between tumours and blood vessels, Materials Horizons 7(1) (2020) 82-92.

[122] A. Aazmi, H. Zhou, Y. Li, M. Yu, X. Xu, Y. Wu, L. Ma, B. Zhang, H. Yang, Engineered Vasculature for Organ-on-a-Chip Systems, Engineering 9 (2022) 131-147.

[123] J. Jang, H.G. Yi, D.W. Cho, 3D Printed Tissue Models: Present and Future, ACS Biomater Sci Eng 2(10) (2016) 1722-1731.

[124] K. Thakare, L. Jerpseth, Z. Pei, A. Elwany, F. Quek, H. Qin, Bioprinting of Organ-on-Chip Systems: A Literature Review from a Manufacturing Perspective, Journal of Manufacturing and Materials Processing 5(3) (2021).

[125] S. Ahadian, R. Civitarese, D. Bannerman, M.H. Mohammadi, R. Lu, E. Wang, L. Davenport-Huyer, B. Lai, B. Zhang, Y. Zhao, S. Mandla, A. Korolj, M. Radisic, Organ-On-A-Chip Platforms: A Convergence of Advanced Materials, Cells, and Microscale Technologies, Adv Healthc Mater 7(2) (2018).

[126] A. Zhang, F. Wang, L. Chen, X. Wei, M. Xue, F. Yang, S. Jiang, 3D printing hydrogels for actuators: A review, Chinese Chemical Letters 32(10) (2021) 2923-2932.

[127] A. Tajeddin, N. Mustafaoglu, Design and Fabrication of Organ-on-Chips: Promises and Challenges, Micromachines (Basel) 12(12) (2021) 1443.

[128] Z. Zhang, B. Wang, D. Hui, J. Qiu, S. Wang, 3D bioprinting of soft materials-based regenerative vascular structures and tissues, Composites Part B: Engineering 123 (2017) 279-291.

[129] A.K. Nashihah, F.I. Muhammad Firdaus, M.B. Fauzi, N.N. Mobarak, Y. Lokanathan, Role of Biomaterials in the Development of Epithelial Support in 3D In Vitro Airway Epithelium Development: A Systematic Review, Int J Mol Sci 24(19) (2023).

[130] R.D. Sochol, N.R. Gupta, J.V. Bonventre, A Role for 3D Printing in Kidney-on-a-Chip Platforms, Curr Transplant Rep 3(1) (2016) 82-92.

[131] N.K. Singh, W. Han, S.A. Nam, J.W. Kim, J.Y. Kim, Y.K. Kim, D.W. Cho, Three-dimensional cell-printing of advanced renal tubular tissue analogue, Biomaterials 232 (2020) 119734.

[132] J. Ma, Y. Wang, J. Liu, Bioprinting of 3D tissues/organs combined with microfluidics, RSC Adv 8(39) (2018) 21712-21727.

[133] K.A. Homan, D.B. Kolesky, M.A. Skylar-Scott, J. Herrmann, H. Obuobi, A. Moisan, J.A. Lewis, Bioprinting of 3D Convoluted Renal Proximal Tubules on Perfusable Chips, Sci Rep 6 (2016) 34845.

[134] B. Pan, L. Shao, J. Jiang, S. Zou, H. Kong, R. Hou, Y. Yao, J. Du, Y. Jin, 3D printing sacrificial templates for manufacturing hydrogel constructs with channel networks, Materials & Design 222 (2022).

[135] A.G. Niculescu, C. Chircov, A.C. Birca, A.M. Grumezescu, Fabrication and Applications of Microfluidic Devices: A Review, Int J Mol Sci 22(4) (2021) 2011.

[136] S.W. Choe, B. Kim, M. Kim, Progress of Microfluidic Continuous Separation Techniques for Micro-/Nanoscale Bioparticles, Biosensors (Basel) 11(11) (2021) 464.

[137] N. Clapp, A. Amour, W.C. Rowan, P.L. Candarlioglu, Organ-on-chip applications in drug discovery: an end user perspective, Biochem Soc Trans 49(4) (2021) 1881-1890.

[138] E. Rosella, N. Jia, D. Mantovani, J. Greener, A microfluidic approach for development of hybrid collagen-chitosan extracellular matrix-like membranes for on-chip cell cultures, Journal of Materials Science & Technology 63 (2021) 54-61.

[139] J. Deng, Z. Chen, X. Zhang, Y. Luo, Z. Wu, Y. Lu, T. Liu, W. Zhao, B. Lin, A liver-chip-based alcoholic liver disease model featuring multi-non-parenchymal cells, Biomed Microdevices 21(3) (2019) 57.

[140] H. Ryan, C.S. Simmons, Potential Applications of Microfluidics to Acute Kidney Injury Associated with Viral Infection, Cell Mol Bioeng 13(4) (2020) 305-311.

[141] G.D. Vatine, R. Barrile, M.J. Workman, S. Sances, B.K. Barriga, M. Rahnama, S. Barthakur, M. Kasendra, C. Lucchesi, J. Kerns, N. Wen, W.R. Spivia, Z. Chen, J. Van Eyk, C.N. Svendsen, Human iPSC-Derived Blood-Brain Barrier Chips Enable Disease Modeling and Personalized Medicine Applications, Cell Stem Cell 24(6) (2019) 995-1005 e6.

[142] D. Huang, T. Liu, J. Liao, S. Maharjan, X. Xie, M. Perez, I. Anaya, S. Wang, A. Tirado Mayer, Z. Kang, W. Kong, V.L. Mainardi, C.E. Garciamendez-Mijares, G. Garcia Martinez, M. Moretti, W. Zhang, Z. Gu, A.M. Ghaemmaghami, Y.S. Zhang, Reversed-engineered human alveolar lung-on-a-chip model, Proc Natl Acad Sci U S A 118(19) (2021).

[143] M. Kasendra, A. Tovaglieri, A. Sontheimer-Phelps, S. Jalili-Firoozinezhad, A. Bein, A. Chalkiadaki, W. Scholl, C. Zhang, H. Rickner, C.A. Richmond, H. Li, D.T. Breault, D.E. Ingber, Development of a primary human Small Intestine-on-a-Chip using biopsy-derived organoids, Sci Rep 8(1) (2018) 2871.

[144] J.H. Sung, Y.I. Wang, N. Narasimhan Sriram, M. Jackson, C. Long, J.J. Hickman, M.L. Shuler, Recent Advances in Body-on-a-Chip Systems, Anal Chem 91(1) (2019) 330-351.

[145] N. Picollet-D'hahan, A. Zuchowska, I. Lemeunier, S. Le Gac, Multiorgan-on-a-Chip: A Systemic Approach To Model and Decipher Inter-Organ Communication, Trends Biotechnol 39(8) (2021) 788-810.

[146] L. Si, H. Bai, M. Rodas, W. Cao, C.Y. Oh, A. Jiang, R. Moller, D. Hoagland, K. Oishi, S. Horiuchi, S. Uhl, D. Blanco-Melo, R.A. Albrecht, W.C. Liu, T. Jordan, B.E. Nilsson-Payant, I. Golynker, J. Frere, J. Logue, R. Haupt, M. McGrath, S. Weston, T. Zhang, R. Plebani, M. Soong, A. Nurani, S.M. Kim, D.Y. Zhu, K.H. Benam, G. Goyal, S.E. Gilpin, R. Prantil-Baun, S.P. Gygi, R.K. Powers, K.E. Carlson, M. Frieman, B.R. tenOever, D.E. Ingber, A human-airway-on-a-chip for the rapid identification of candidate antiviral therapeutics and prophylactics, Nat Biomed Eng 5(8) (2021) 815-829.

[147] G. Goyal, P. Prabhala, G. Mahajan, B. Bausk, T. Gilboa, L. Xie, Y. Zhai, R. Lazarovits, A. Mansour, M.S. Kim, A. Patil, D. Curran, J.M. Long, S. Sharma, A. Junaid, L. Cohen, T.C. Ferrante, O. Levy, R. Prantil-Baun, D.R. Walt, D.E. Ingber, Ectopic Lymphoid Follicle Formation and Human Seasonal Influenza Vaccination Responses Recapitulated in an Organ-on-a-Chip, Adv Sci (Weinh) 9(14) (2022) e2103241.

[148] Y. Liu, L. Sun, H. Zhang, L. Shang, Y. Zhao, Microfluidics for Drug Development: From Synthesis to Evaluation, Chem Rev 121(13) (2021) 7468-7529.

[149] B. Zhang, A. Korolj, B.F.L. Lai, M. Radisic, Advances in organ-on-a-chip engineering, Nature Reviews Materials 3(8) (2018) 257-278.

[150] M.K. Vormann, L. Gijzen, S. Hutter, L. Boot, A. Nicolas, A. van den Heuvel, J. Vriend, C.P. Ng, T.T.G. Nieskens, V. van Duinen, B. de Wagenaar, R. Masereeuw, L. Suter-Dick, S.J. Trietsch, M. Wilmer, J. Joore, P. Vulto, H.L. Lanz, Nephrotoxicity and Kidney Transport Assessment on 3D Perfused Proximal Tubules, AAPS J 20(5) (2018) 90.

[151] J.S. Lee, J. Kim, B. Cui, S.K. Kim, S.A. Cho, S. An, S.W. Cho, Hybrid skin chips for toxicological evaluation of chemical drugs and cosmetic compounds, Lab Chip 22(2) (2022) 343-353.

[152] E.J. Fong, C. Huang, J. Hamilton, W.J. Benett, M. Bora, A. Burklund, T.R. Metz, M. Shusteff, A Microfluidic Platform for Precision Small-volume Sample Processing and Its Use to Size Separate Biological Particles with an Acoustic Microdevice, J Vis Exp (105) (2015) e53051.

[153] R.M. Mohamadi, Z. Svobodova, Z. Bilkova, M. Otto, M. Taverna, S. Descroix, J.L. Viovy, An integrated microfluidic chip for immunocapture, preconcentration and separation of beta-amyloid peptides, Biomicrofluidics 9(5) (2015) 054117.

[154] J. Decock, M. Schlenk, J.B. Salmon, In situ photo-patterning of pressure-resistant hydrogel membranes with controlled permeabilities in PEGDA microfluidic channels, Lab Chip 18(7) (2018) 1075-1083.

[155] E. Ferrari, C. Palma, S. Vesentini, P. Occhetta, M. Rasponi, Integrating Biosensors in Organs-on-Chip Devices: A Perspective on Current Strategies to Monitor Microphysiological Systems, Biosensors (Basel) 10(9) (2020).

[156] K.J. Son, P. Gheibi, G. Stybayeva, A. Rahimian, A. Revzin, Detecting cell-secreted growth factors in microfluidic devices using bead-based biosensors, Microsyst Nanoeng 3 (2017).

[157] Y. Wang, Y. Gao, Y. Pan, D. Zhou, Y. Liu, Y. Yin, J. Yang, Y. Wang, Y. Song, Emerging trends in organ-on-a-chip systems for drug screening, Acta Pharm Sin B 13(6) (2023) 2483-2509.