Check for updates

Received: 6 September 2021 | Revised: 22 December 2021 | Accepted: 23 December 2021

DOI: 10.1002/jbm.a.37353

REVIEW ARTICLE

Society For Biomaterials | WILEY

Selection of natural biomaterials for micro-tissue and organ-on-chip models

Berivan Cecen[1] | Ayca Bal-Ozturk[2,3] | Gokcen Yasayan[4] | Emine Alarcin[4] | Polen Kocak[5] | Rumeysa Tutar[6] | Leyla Didem Kozaci[7] | Su Ryon Shin[8] | Amir K. Miri[9,10]

[1]Department of Mechanical Engineering, Rowan University, Glassboro, New Jersey, USA

[2]Department of Analytical Chemistry, Faculty of Pharmacy, Istinye University, Istanbul, Turkey

[3]Department of Stem Cell and Tissue Engineering, Institute of Health Sciences, Istinye University, Istanbul, Turkey

[4]Department of Pharmaceutical Technology, Faculty of Pharmacy, Marmara University, Istanbul, Turkey

[5]Department of Genetics and Bioengineering, Faculty of Engineering and Architecture, Yeditepe University, Istanbul, Turkey

[6]Department of Chemistry, Faculty of Engineering, Istanbul University-Cerrahpasa, Istanbul, Turkey

[7]Faculty of Medicine, Department of Medical Biochemistry, Ankara Yildirim Beyazit University, Ankara, Turkey

[8]Division of Engineering in Medicine, Department of Medicine, Harvard Medical School, Brigham and Women's Hospital, Cambridge, Massachusetts, USA

[9]Department of Mechanical Engineering, Rowan University, Glassboro, New Jersey, USA

[10]Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, New Jersey, USA

Correspondence
Berivan Cecen, Department of Mechanical Engineering, Rowan University, 08028, New Jersey, USA.
Email: cecen@rowan.edu

Funding information
None.

Abstract

The desired organ in micro-tissue models of organ-on-a-chip (OoC) devices dictates the optimum biomaterials, divided into natural and synthetic biomaterials. They can resemble biological tissues' biological functions and architectures by constructing bioactivity of macromolecules, cells, nanoparticles, and other biological agents. The inclusion of such components in OoCs allows them having biological processes, such as basic biorecognition, enzymatic cleavage, and regulated drug release. In this report, we review natural-based biomaterials that are used in OoCs and their main characteristics. We address the preparation, modification, and characterization methods of natural-based biomaterials and summarize recent reports on their applications in the design and fabrication of micro-tissue models. This article will help bioengineers select the proper biomaterials based on developing new technologies to meet clinical expectations and improve patient outcomes fusing disease modeling.

KEYWORDS
hydrogels, micro-tissue, natural biopolymers, organ-on-a-chip

1 | INTRODUCTION

Engineered micro-tissue models have been used to resemble extracellular matrix (ECM) and natural tissues, with intensive applications ranging from drug injection to sample separation and detection on a single platform.[1] These models can be added to organs-on-chips (OoCs) to precisely monitor cell media across microchannels ranging in size from tens to hundreds of microns.[2] The microchannel has a

Berivan Cecen and Ayca Bal-Ozturk contributed equally.

 © 2022 Wiley Periodicals LLC.

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

large surface area and high throughput volume,[3] which can be used in low regent consumption, controllable volumes, rates of mixing, rapid reactions, and precise control of physical and chemical features. Microfluidics integrates sample preparation, reactions, isolation, identification, and basic operating units such as cell culture, sorting, and lysis.[4] Polydimethylsiloxane (PDMS)-based microfluidics are the common choices in the field. The mass transfer and functionalization are restricted to the surfaces of micro-channels. Another key objective is to recapitulate the structure of the target tissue.[5] The cellular complexity needed for regrowing the ECM to find their way back to their targets inbuilt adult tissue. The recent discoveries are deciphering how this cellular complexity is modulated in the distinct environments of a regenerating tissue with possible reaction to response processes. There is a need for biomaterials and micro-fabrication techniques for creating micro-tissue models.[6]

TABLE 1 A summary of natural biomaterials used in micro-tissue models

Natural biomaterials	Characteristics	Cell source	Target micro-tissue
Fibrin	• RGD bonding spaces • Conveniently produced to shape thin membranes • Noncontracting properties	• Neonatal cardiovascular fibroblasts[61] • Human-induced pluripotent stem cell (hiPSC)[85]	Blood-brain-barrier (BBB)-on-a-chip system,[53,15] Skin micro-tissue[60]system
Hyaluronic acid	• Biocompatibility • Tunable chemical compositions and mechanical properties	• Human-induced pluripotent stem cell (hiPSC)[101] • hiPSCs-HEPs[104]	Liver,[16] heart[17] and skeletal muscle[18]micro-tissue
Gellan gum	• Linear, anionic, and high molecular weight polymer • Stronger and less permeable • Thermo-responsive • Tunable mechanical properties • Reasonable cost of production	• Primary neural cells[107]	The microvascular networks[19] for micro-tissue
Gelatin	• Single-strain protein • Including RGD • Better solubility • Significantly lower cost • Relatively lower antigenicity • Biocompatibility • Biodegradability	• Parenchyma, stroma, and endothelium cell lines[137] • Endothelial cells (ECs)[66] • Smooth muscle cells (SMCs)[66] • Umbilical vein endothelial cells (HUVECs)[69,70] • Breast cancer cells (MCF-7)[70,145] • Human hepatocellular carcinoma (HepG2) cells[69] • Cardiomyocytes[68,146,147]	Microvasculature-on-a-chip system[20] Vessel,[21] heart,[22] liver[23] micro-tissue Tumor spheroids[24]
Silk fibroin	• Excellent biocompatibility • Tunable mechanical strength • Controllable degradation rates • Nonimmunogenic	• Engineering cardiac tissue[71] • Hepatocytes[72,73]	Cardiac micro-tissue[25] 3D cornea-model[146,151] 3D micro-tissue[147] Liver micro-tissue[26,27]
Collagen	• A major structural protein of natural ECM • Triple-helix structure composed of different amino acids • Biocompatibility • Biodegradability with low antigenicity	• Renal proximal tubular epithelial cells[80] • Human glomerular endothelial cells[78] • Peritubular capillary endothelial cells[80] • Primary human brain astrocytes[129] • Primary human brain pericytes[129] • Mesenchymal stem cells (MSCs)[127]	Brain,[28] skin,[29] vessel,[30] kidney,[31] and lung[32] micro-tissue. Glomerulus-on-a-chip (GOC)[33]
Alginate	• Biocompatibility • Mild gelling conditions	• Mesenchymal stem cells (MSCs)[183]	HUVEC-lined microvessel
Chitosan	• Important bioactive properties, hemostatic, bacteriostatic, fungistatic, anti-carcinogen, anti-cholesterol, anti-acid, anti-ulcer Rich nitrogen content • Enable chemical reactions • Positively charged hydrophilic polymer		Chitosan-based MPs for microfluidic[162]
Dextran	• High rheological properties • High purity • High physicochemical properties	• Endothelial cells[175]	Liquid Chromatography integrated micro-tissue system[168] HUVEC-lined microvesse[169]

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Micro-tissue models that mimic the target tissue[7] can be integrated into biological structures or other micro-tissues. The approaches that have emerged for this purpose are based on the use of surface-immobilized biopolymers.[8] Using biomaterial formulations consistently on a micro-tissue would be a game-changer for generating a biomimetic microenvironment. Using biomaterials compositions, it is possible to develop heterogeneous tissue scaffolds including multiple cell types and substrates using multiple exchangeable classifications with different biomaterials.[9]

Different groups of natural biomaterials in tissue engineering are based on the composition of ECM and extraction sources.[10] The modification and characterization processes of natural-based biopolymers are being investigated for integrations into OoCs.[11] Different biomaterial classes have to be selected for the ECM in micro-tissue devices, mimicking the microenvironment and the microfluidic housing. The ECM provides cell adhesion ligands, cell signaling pathways, and biochemical cues that affect their phenotypes.[12] Biomaterials available for the cellular microenvironment in vascularized micro-tissue devices include polymers of naturally derived hydrogels, such as agarose and collagen, chitosan, alginate, and gelatin.[13] Other natural biopolymers are used and modified natural hydrogels such as gelatin methacryloyl (GelMA).[14]

Here we discuss micro-tissues based on natural biopolymers and different application areas in the current studies (Table 1). The first section describes the classification of other biomaterials used in micro-tissue, and the second section explains the different micro-tissue categories to which they belong. The main focuses are biocompatibility, bioinertness, bioactive/surface reactive, biodegradability, stabilizability, good physical and mechanical features, manufacturability, low weight, reasonable cost. In the end, we discuss the significant advantages of biomaterials in micro-tissues.

2 | DESIRED MICRO-TISSUE MODELS

Biomimetic micro-tissue models are typically constructed to replicate the ECM or different tissues' basement membranes.[34] The most significant feature of this design is developing an area that mimics in vivo conditions. The tissue's mechanical properties, shear force, structure and porosity, fluid movement, and specific cell lines communicating with the micro-tissue depend on the desired tissue.[35] The ECM is a complex structure composed of biomaterials and adhesion proteins.[36] The natural biomaterials include collagen, gelatin, hyaluronic acid, fibrin, Matrigel, or other natural polymers such as chitosan, alginate, and silk fibroin.[37] Dynamic biochemical interactions between cells and the ECM have been developed at the molecular level, preserving tissue integrity.[38] Recent studies have highlighted micro-tissue to generate matrices that mimic the ECM's cell and guiding roles, allowing cells to expand, migrate, and differentiate. The micro-tissue architecture considers the ECM's specific features to build biomimetic micro-tissue.[39] Selected fundamental characteristics of natural biomaterials are summarized below.

2.1 | Biochemical characteristics

Cellular adhesion, proliferation, differentiation, and migration could be supported by accumulating growth factors, hormones, and proteins.[40] Cells have adhesion molecules on their surface, and their receptors interact with ECM proteins, such as laminin, fibronectin, and vitronectin.[41] Tripeptide arginine–glycine–aspartic acid (RGD) and peptide sequences such as GFOGER, IKLLI, LRE, IKVAV, YIGSR, DGEA, and PDSGR could be incorporated with the micro-tissue.[42] The RGD-functionalization in tissue constructs is to enhance cell recognition. Accordingly, RGD-conjuucted cell-adhesive species (CAM) are used for mimicking the cell-interaction and regulating the cell-adhesion. Generally, the standard NHS/EDC chemistry is used for the functionalization of biomaterials.[43] The design of ECM- mimicking constructs is still an important challenge in tissue engineering and the biomaterial selection requires to be functionalized for tissue remodeling.

The micro-tissue selectivity and sensitivity depend on the use of stimuli-sensitive polymers that respond to *p*H, temperature, light, electrical impulses, or chemical substances. Stimuli-responsive polymers could retain or release fluids depending on a stimulus and act as a feedback system. A change in the hydrogel network volume is generated by controlling time-dependent stimulus forces. Chemical parameters could be exemplified by the solvent choice, their characteristic properties from the hydrogel network.[44] Stimuli-responsive polysaccharide hydrogels could be used in fabrication to create a biochemical communication system.[45] Natural polymers suffer some drawbacks due to having poorly defined structures and low reproducibility, depending on the compositional variations in their natural origins. Widely used synthetic biopolymers are poly(ethylene glycol) (PEG), poly(vinyl alcohol), polyacrylamide, and methacrylate derivatives.[37,46] Overall, the composition determines the mechanical properties, wettability, electric charge, and plasticity of the micro-tissue, influencing cell behavior.[47]

2.2 | Topographic properties

The topography of cell-laden biomaterials influences cellular behavior changes such as migration, proliferation, differentiation, gene expression, and surface texture.[48] Topography could enhance cell binding to the substrate by creating surface cues that enable cells to attach, improving cell adhesion and proliferation.[49] Similar to topography, surface roughness affects cell adhesion, where cells are affected differently depending on the cell type. In vivo roughness of natural tissues varies depending on the complexity and heterogeneity of the target tissue.[47] Many researchers study surface roughness to increase or decrease cell adherence.[50] The complex nature is not replicated on micro-tissue in which studies are carried out in 2D,[51] limiting cell behavior evaluation (Figure 1A). Recent research in the area has focused on developing 3D cell assays, spheroid assays, and organoid assays to overcome the limitations and simulate the physiological environment of the organs. Tibbitt et al. have discussed 2D and 3D

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

cultures and the use of hydrogels for cell culturing (Figure 1B).[46] They emphasize that cells behave more genuinely in 3D cultures than 2D ones, and they suggest that hydrogels could be used to create 3D cell cultures. The critical attribute of 3D culture is its similarity to cells growing in vivo in cellular topology in molecular path with the desired cell/organoid architecture.

2.3 | Mechanical properties

Considering the target tissue, the mechanical properties of substrates could be used to regulate cell behavior, and cells respond to changes both in microscale and macroscale.[4] The substrate stiffness or the intrinsic elasticity of the matrix is emerging as a critical physical factor to influence tissue. The relationship between substrate stiffness/elasticity and cellular response is studied by various groups using various cell types on different substrates. Cell responses were evaluated in adhesion, migration, spreading, and contractility via 2D and 3D cultures. It was found that phenotypic and genotypic changes were observed in cells, which could lead to changes in cellular growth, death, differentiation, and morphological changes[52–56] For instance, in a study, it is reported that on stiffer substrates, actin cytoskeletons of the dermal fibroblasts are better organized, cell proliferation is faster, and cell migration is slower compared to softer substrates.[57,58] Therefore, a strong understanding of the relationship between the substrate's stiffness and the stiffness of the target tissue would be very useful in designing micro-chip with optimal mechanical properties.[59] Porosity controlled by the molecular pores could separate compartments in the micro-tissue.[35] The porosity controls the permeability of the model,[60] and it may allow for better cell encapsulation and growth. The pores can enable transport of fluids, nutrients, metabolic molecules, and oxygen. In a study, Esch et al. mimic intestinal villi and tight junctions of the intestinal epithelium by fabricating porous substrates.[61] Casillo et al. have studied the effects of membrane pore spacing on cell behavior. They found that cells had fewer focal adhesions and shorter fibronectin fibrils on porous membranes and soft substrates, promoting cell–cell interactions than nonporous controls.[62] Zhao et al. mentioned the importance of the pores' aspect ratio study to enhance molecule transport efficiency, decrease sensor response time, and eliminate infiltration challenges.[63] Porosity of the

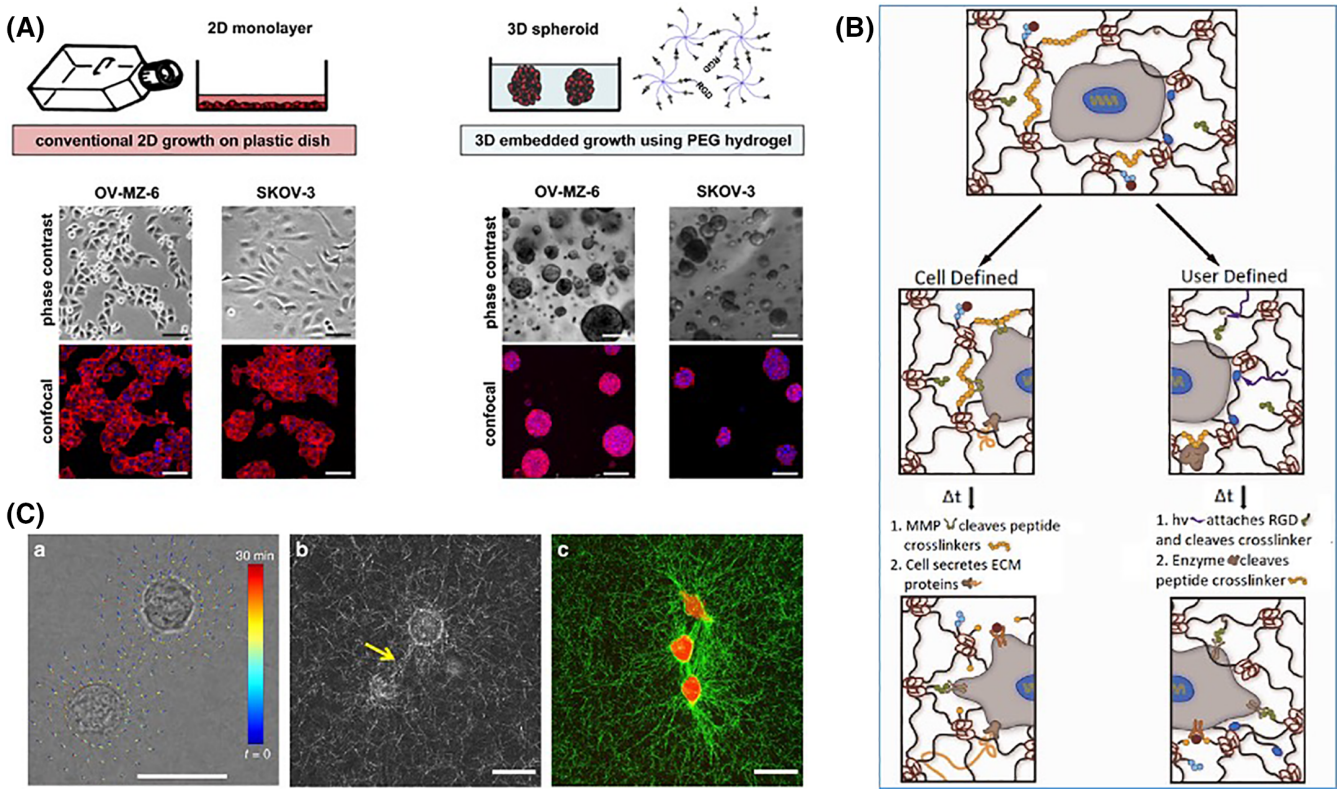

FIGURE 1 (A) Comparison of the 2D and 3D assays in cell morphology and proliferation, where the 2D study is carried in the traditional plastic culture and synthetic PEG hydrogel. Reproduced with permission.[52] Copyright 2010, Elsevier. (B) Comparison of control of the biochemical and mechanical features by cell-defined and user-defined designs. Cell cleaving MMP degradable crosslinks are represented in yellow circles and allow growth factors (red) and RGD (green circles). These changes lead to the deposition of ECM proteins (orange fiber). In user-defined designs, novel structures like photo-degradable crosslinks (blue ellipses) and RGD attachment enable control of the gel's properties and direct cells. Enzyme (brown) placements enable the user-defined release of sequestered growth factors. Reproduced from with permission.[46] Copyright 2009, Wiley-VCH. (C) Formation of collagen bundles; (A) spatial–temporal profile of the cell-induced matrix deformation; (B) a collagen bundle between two cells referred to as an arrow; (C) collagen bundles formed between multiple cells. Reproduced with permission.[38] Copyright 2017, Springer Nature

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

material impacts the mechanical properties of the substrate as the volume of pores increases, the mechanical properties of the material weakened.[57] Plasticity is another parameter, especially in micro-tissue, where cells can be perturbed. A study by Kim et al. demonstrated that cells could remodel connective tissues and the ECM via modeling collagen bundles by densifying and aligning the fibers.[38] This programmable collagen property may enable future possibilities to design more complicated and realistic micro-tissue (Figure 1C).

2.4 | The tissue functions in vitro properties

There are important issues for the tissue specific properties that are needed for proper mimicking of the tissue functions in vitro. Tissue-mimetic in vitro 3D environments have an importance that can lead to meaningful results which can be applied in humans. Different tissue models in these platforms with natural biopolymers can be mimicking tissue-specific architecture and pathophysiology for in vitro research.[64] For tissue functions, cells on these platforms want to mimic their natural in vivo microenvironments. Therefore, they are affected by mechanical forces, fluid flows and physiological stresses. Cell–cell interaction and communication are important for simplifying tissue combination and reassembly during development, injury and disease.[65]

3 | PROTEIN-BASED POLYMERS

Natural hydrogels are one of the main factors for tissue regeneration; owing to their pivotal character in biocompatibility and mechanical stability with higher biocompatibility, excellent biological potential, low immunogenicity, and low cytotoxicity from their degradation elements, they have turned into favorable as micro-tissue.[41] In this section, we illustrate the benefits of natural polymers over certain other micro-scale functionalization products and show a compilation of current publications on biomaterials and their applications used during the design of micro-tissues. We also discuss the desired features of protein-based micro-tissue applications and currently available constructs for skin repair and regeneration and overview widely used or favorable natural biopolymers in cardiac, cornea, and blood brain barrier (BBB).

3.1 | Fibrin

Fibrin hydrogels complemented with laminin-III are efficient in the development and growth of murine and human epithelial organoids. Such tunable composite matrices can significantly enhance the flexibility and reproducibility of special organoids.[66] Fibrin hydrogel-based micro-tissue can provide adequate oxygen and nutrient supply, regulating the long-term survival and preservation of vascularized tissues. The integration of hydrogels and fibrin into the OoCs helps development of vascularized 3D micro-tissue.[67] In one work, neonatal cardiovascular fibroblasts were incorporated into 3D fibrin-based hydrogels, and afterward, mechanical incitement (cyclic extending) was applied to reproduce a fibrosis-like environment.[68] This model overcomes some conventional monolayer cell culture issues by introducing exogenous active morphogens, thus allowing analysis of alternative fibrosis pathways and new therapeutic developments.[61] Fibrin hydrogels can be used to encapsulate human induced pluripotent stem cell derivative endothelial cells, cerebrum pericytes, and astrocytes to make self-amassed vascular matrixes in micro-tissue.[69] The BBB micro-tissue provides a novel method to research the patient-specific neurovascular pathology roles in neurodegenerative ailments and assume neurotherapeutic viability in preclinical applications.[70] Neurons surrounded 3D collagen matrices, and astrocytes were situated near endothelial cells within cylindrical structures.[61] Human skin was introduced by Sriram et al. by joining a fibrin-based dermal lattice with a unique stream framework to reconstruct full-thickness skin.[71] They were equivalents in a biomimetic microenvironment to study micro-tissue skin barrier functions. Skin counterparts displayed better epidermal separation and better barrier work relative to traditional static cultures. Fibrin-based dermal matrices with noncontracting properties help direct downstream assays in micro-tissue permeation, expanding skin model usage in tissue engineering.[72] This demonstrates the advantage of using fibrin hydrogel as a therapeutic adjunct in cell therapy for regeneration. The target tissue survival and differentiation can also be controlled in vivo based on the type of micro-tissue employed.[73]

3.2 | Silk fibroin

Silk fibroin (SF), one of the most encouraging elements obtained from the cocoon of the silkworm Bombyx mori is another naturally available biomaterial and nonimmunogenic,[74] SF-based material that has excellent biocompatibility, tunable mechanical strength, and controllable degradation rates. Importantly, various intrinsic factors such as health of the silkworms, the spinning process and genetic modification could modulate the mechanical properties of silk fibers. Additionally, the mechanical features of silk fibroin hydrogels are highly dependent to heat or cold application, mechanical agitation or sonication, pH change, and/or crosslinking by ions (Ca^{2+} ions).[75,76] The degradation rate of SF-based biomaterials can be configured to meet the requirements of natural extracellular matrices of target tissues,[77] interact with cells, and ensure physiologically associated micro-environments to guide cellular behaviors.[66] The FDA approves SF for biomedical applications. For this reason, SF is a safe and popular choice of biomaterial for the development of artificial organs in micro-tissue.[25,78,79]

Zhao et al. prepared a biofunctionalized SF-based hydrogel to construct multiple fluidic layers using gelatin-molding and layer-by-layer stacking techniques (Figure 2). The SF-based hydrogel microfluidic exhibited tunable mechanical properties from 1 kPa to 1 MPa and controllable degradability, high optical transparency, stability under different environmental conditions showed unique characteristics for target.[78]

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

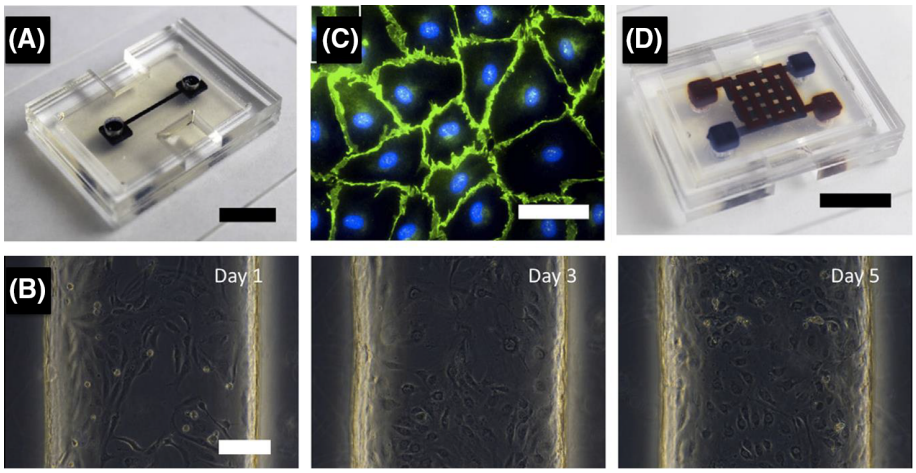

FIGURE 2 (A) Microfluidic platform implemented with silk-based hydrogel for HUVEC culture. (B, C) Proliferation and E-cadherin/DAPI staining results of HUVECs in the chip system. (D) The two-layer microfluidic platform implemented with silk-based hydrogel for 3D fibroblast culture Reproduced with permission.[78] Copyright 2016, Elsevier

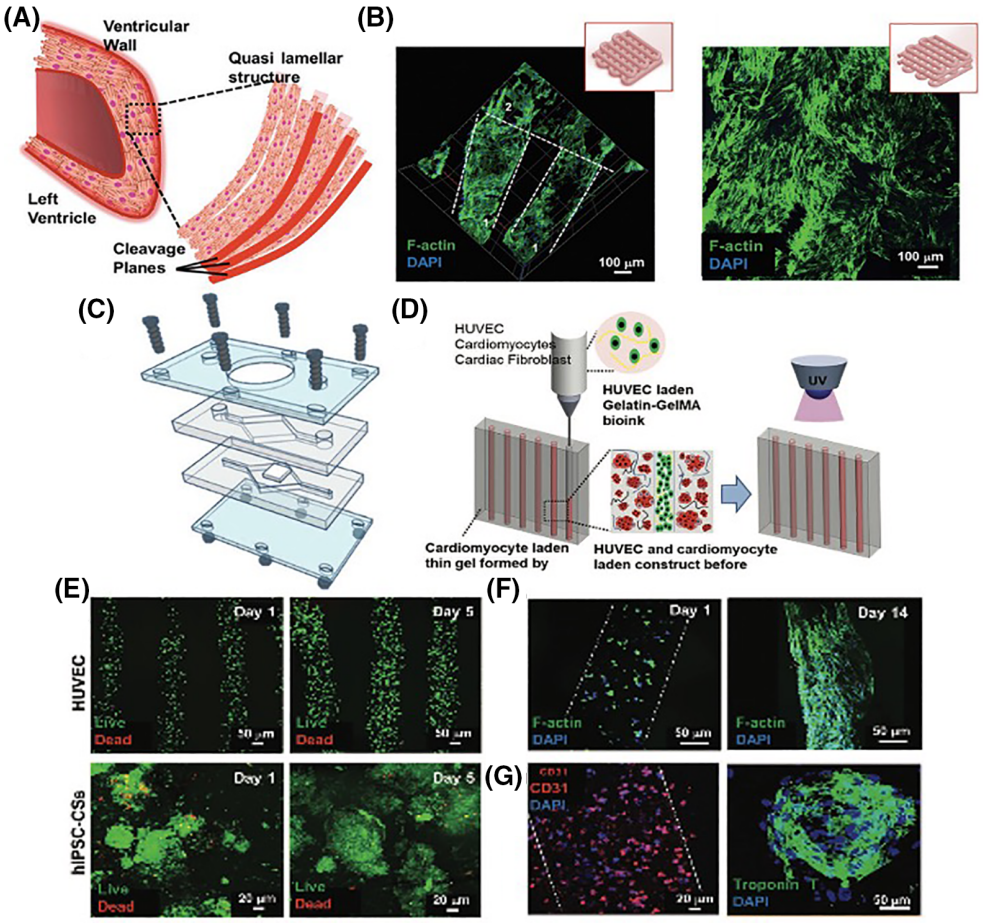

FIGURE 3 (A) Schematic representation of native heart tissue. (B) F-Actin/DAPI images of 3D-printed silk-based construct. (C) Schematic of the microfluidic bioreactor construction. (D) 3D-bioprinting of silk-based vascularized cardiac tissue including microchannels. (E) Cell viability. (F) F-Actin staining. (G) CD31 immunostaining (results in the microfluidic platform. Reproduced with permission.[25] Copyright 2020, Wiley-VCH

Engineering of cardiac micro-tissue has become the most significant problem due to complexities related to replicating its natural form and bench-to-bedside translation.[25] Cardiac micro-tissue is an important post to pharmaceutical companies for analyzing various new drugs related to cardiac toxicity.[80] In an exciting study, Mehrotra et al. developed a no mulberry SF-based biomaterial as engineered cardiac tissue. A dual crosslinking method was used for the preparation of a stable anisotropic scaffold. The developed SF-based scaffold offered a huge capability toward constructing cardiac tissue while keeping its functionality (Figure 3). The drug-DOX was screened in the micro-tissue for cardiac-related toxicity.[25]

To achieve a successful in vitro cornea model, it is essential to replicate the cornea microenvironment due to the corneal construct's complexness and the mechanical environment formed by the intraocular pressure of the cornea's body (Figure 4A,B). Mechanical-shaped strain typically has an impact on in vitro cell features. In a pioneering

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

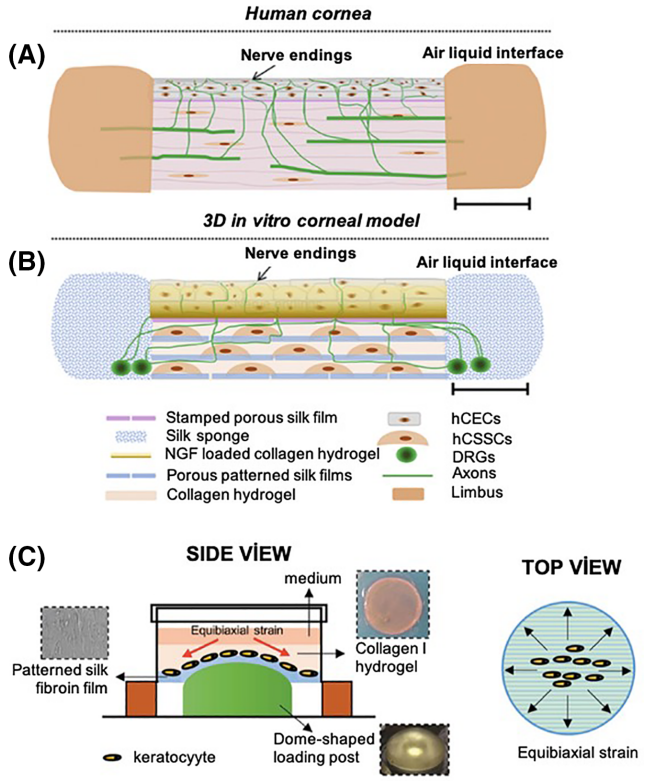

FIGURE 4 Schematic of the natural human cornea (A) and a 3D in vitro cornea-tissue model (B). Reproduced with permission.[83] Copyright 2017, Elsevier. Biomimetic 3D in vitro cornea-model with SF-based material, collagen I hydrogel, and 3% dome-shaped strain (C). Reproduced with permission.[81] Copyright 2017, Wiley-VCH

work, Zhao et al. built a biomimetic 3D in vitro cornea model that superiorly supports the keratocyte phenotype and ECM production according to the conventional 2D in vitro cornea model. A new static equiaxial dome-shaped strain was developed to mimic the cornea shape and strain. The structure of the natural cornea was replicated using patterned collagen-modified SF-based material (Figure 4C). The impact of the mechanical-shaped strain on the keratocyte phenotype and ECM production was studied, and keratocyte marker expression was found to be 3% higher in the dome-shaped mechanical strain cornea-model than the flat-shaped strain.[81] In conclusion, SF micro-tissue can represent a precious implement to understand better cell migration functions, consisting of a proof of concept, where different ECM like biomaterials and the influence of chemoattractants.[82]

4 | POLYPEPTIDE-BASED POLYMERS

Polypeptides form with a rod-coil structure. The ß-strand configuration presents the benefits of an additional means to direct nanoscale assembly formation[84] through intermolecular hydrogen bonding of body and make them highly necessary for biomedical applications.[85] Polypeptide-based polymers can be used in the inquiry of self-assembling nanostructures, mainly in aqueous solutions.[86] In this context, polypeptide-based copolymers display substantial promise as building blocks that permit improved control over intra- and intermolecular relations, in concert with stable yet adjustable secondary and tertiary constructions. We propose using the protein-based natural polymer, which can stand against a synthetic polymer.

Polypeptide-based materials offer significant benefits over synthetic polymers in terms of applicability. For instance, short peptide motifs like RGD, KNEED, and IKVAV, ubiquitous compounds for cell receptors and mediate numerous cell behaviors including attachment and spread, may be attached to or inserted inside repetitious polypeptides more easily than synthetic materials. Second, self-assembly and directed assembly of peptides have lately piqued the curiosity of researchers as possible methods of producing multifunctional biomaterials. Self-assembling biomaterials derived from peptides include leucine zipper-based biomaterials, peptide amphiphiles, beta-sheet forming ionic oligopeptides, and beta-hairpin peptides. Third, because the body quickly destroys many peptide-based biomaterials, they appeal to drug delivery vehicles and scaffolds for tissue engineering.[87]

4.1 | Collagen

Collagen (COL) types I–IV are the main structural proteins of the natural ECM, they are widely used in the design of micro-tissue.[88] Type-I COL is the most abundant form of collagen and is mostly found in skin, bone, tendon, and ligaments, whereas others can be distinctive for tissues such as type-II COL and cartilage.[89] Notably, the mechanical properties of COLs can be easily tuned by crosslinking or blending them with other polymers[27] having cell adhesive domains,[66] and it was reported that they have significantly enhanced the adhesion, proliferation, and differentiation of several cells such as osteoblasts, chondroblasts, and mesenchymal stem cells.

Importantly, crosslinking of collagen is a possible strategy using chemical crosslinking agent such as glutaraldehyde and diphenylphosphoryl azide to enhance stability of collagen constructs.[90,91] The use of specific geometries of collagen constructs to govern cell behaviors has been widely studied. For instance, breast cancer cells in a continuous collagen network were demonstrated to migrate faster than arraying only droplets in the chambers. It can be attributed to length difference of ECM network where cells encapsulated in thicker collagen constructs could be migrate faster than those in thin collagen constructs.[92] Also, functionalized collagen by amino acid side chain modification reactions of methylation and succinylation was used for layer by layer deposition of collagen on top of cells cultured in microfluidic devices and resulted in stabilization of cell morphology and function.[93] Biomimetic collagen vessels with a stable biochemical gradients was fabricated For microenvironmental regulation of angiogenesis to show mechanical and/or autocrine mechanisms that may suppress pro-angiogenic paracrine signaling under certain conditions.[94] Importantly, 3D collagen fiber orientation was studied to 3D reconstruction of neuronal tissue by manipulating the cultivable gel region using photothermal etching method.[95]

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Recently, various research groups have focused on engineering glomerulus-on-a-chip (GOC) using collagen.[33] Petrosyan et al. described a GOC model using COL-IV and laminin as matrix materials, the glomerular basement membrane's main components. Human podocytes and human glomerular endothelial cells were seeded onto microfluidic to better mimic the glomerular filtration barrier by selective permeation and responding to nephrotoxic agents.[31] They reported that their system serves as a useful model for studying the human renal filtration barrier, different glomerular diseases, and drug response.[31] Musah et al. presented a GOC system and a protocol to evaluate mechanical forces' function in glomerular development. They achieved the differentiation of the human induced pluripotent stem cells into podocytes with >90% efficiency.[4] Then, they used COL-IV as a matrix material in a two-channel microfluidic device and applied podocytes into one channel and endothelial cells into the second channel within 35 days succeeded in keeping the cells alive undifferentiated. This method can help mimic the human glomerular structure and the mechanical and related disorders, nephrotoxicity, and drug screening.[96]

Yin et al. has developed a three-layer microfluidic consisting of a drug concentration gradient and a temperature-controlled flow system to culture cells. The collagen-coated polycarbonate membranes were added to the micro-tissue to provide cellular adhesion. The renal proximal tubular epithelial cells and peritubular capillary endothelial cells were used to evaluate drug-induced nephrotoxicity. Notably, cells cultured in the microfluidic system revealed better physiological relevance than cells cultured in static conditions for assessing drug nephrotoxicity.[33] Maoz et al. described a microfluidic neurovascular unit model using three linked micro-tissue incorporated with type-IV COL and a fibronectin-coated membrane to mimic BBB influx efflux of the brain's parenchymal compartment. This linked OoCs represents a useful tool for both the modeling of metabolically critical physiological functions and drug screening across the BBB.[28] Park et al. designed a microfluidic OoC-BBB using polyethylene terephthalate membrane coated type-IV COL and fibronectin. To improve the barrier's function, pluripotent stem cell-derived human brain microvascular endothelium, primary human brain pericytes, and astrocytes were cultured for at least 1 week.[97] Song et al. measured the usage of COLs from various sources as scaffold elements for micro-tissue skin. The results gave valuable information on rat tail COLs in both well-plate and environments. Both showed robust staining of COLs; COLs stained slightly more substantially in the well-plate culture environment. Different COLs as scaffold elements caused other scaffold elements responses in cultured cells. COLs from rat tails most successfully supported the differentiation of the dermis and epidermis in micro-tissue skin.[29] Menon et al. developed a new micro-tissue atherosclerosis with COLs-patterned and endothelialized microchannels in different geometries. The vascular micro-tissue was prepared using soft-lithography and photolithography methodologies. COLs-patterned constricted vascular micro-channels were designed to replicate stenosis in atherosclerosis. Neutrophil transendothelial movement and barrier permeability were evaluated.[30]

The small intestine is a specific organ that plays a main role in nutrient absorption and digestion, facilitating essential metabolism and drug uptake functions.[98] Zamprogno et al. designed an unequaled, biological, thin, and stretchable COLs- and elastin-based membrane for lung micro-tissue applications. The membrane was prepared by using the drop-casting method. A gold mesh with a pore size of 260 μm was preferred as the scaffold. The developed membrane recapitulated the natural ECM of the lung parenchyma.[32]

COL can open the route to the novel establishment of micro-tissue that allows for the reproduction of the entire organ biological barrier due to its strength, and absorption-free features make it a potent instrument in drug analysis, modeling the diseases and applications of precision medicine.[32]

4.2 | Gelatin

Gelatin is a widely used single-strain protein derived from the partial hydrolysis of collagen.[99] It maintains the bioactive motifs of collagen, including RGD, which regulates cell attachment, proliferation, and differentiation. It is susceptible to matrix metalloproteinases (MMPs), important in cell and matrix remodeling.[100,101]

GelMA is widely used for micro-tissue due to its unique properties.[102] GelMA has been synthesized by chemically modifying gelatin with methacrylic anhydride and crosslinking the combination under UV light in a photoinitiator's presence to create a covalently crosslinked hydrogel.[103] The methacrylation degree and photopolymerization time of a GelMA hydrogel can be easily modified to provide the desired mechanical, degradation, and biological features to mimic the ECM with outstanding biocompatibility. Notably, GelMA maintains the bioactive motifs of gelatin (such as RGD motifs and MMP sensitive motifs), and it comprises less than 5% of the amino acid residues in the molar ratio.[14] Abudupataer et al. designed a microfluidic consisting of two parts, including a three-layer micro-tissue of poly (methyl methacrylate) and a 3D bioprinted tissue with spatial heterogeneity by incorporating GelMA with endothelial cells (ECs) and smooth muscle cells (SMCs). When ECs and SMCs were co-cultured in the micro-tissue, αSMA and SM22 protein expressions and the SMC's contractile phenotype were upregulated compared to cells grown in monoculture.[21]

Liver steatosis on a micro-tissue designed using PDMS micro-tissue incorporated GelMA constructs, which consisted of spheroids of the co-culture of human hepatocellular carcinoma (HepG2) cells and The umbilical vein endothelial cells (HUVECs), is under study by Lasli et al.[104] According to their analysis, in the presence of 20% of HUVECs in HepG2 spheroids, the disease could be modeled better. The designed micro-tissue was connected to an array of interconnected hexagonal micro-wells to monitor functionality via detecting the generation of reactive oxygen species and elevated albumin secretion.[104] Zhang et al. developed endothelialized myocardial tissues using cardiomyocytes seeded in alginate and GelMA microfibrous hydrogel scaffolds by 3D bioprinting. Notably, dose-

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

dependent responses were observed for both cardiomyocytes and ECs through this method.[22]

Some research groups have benefited from the structural color change of hydrogels to monitor cellular change in heart micro-tissue. For instance, Fu et al. designed a conceptually color-shifting material with autonomic regulation capability by incorporating cardiomyocyte-laden GelMA hydrogels and nano-silicate.[105] Along with the beating of cardiomyocytes, cell elongation and contraction resulted in changes in structural colors. Interestingly, they combined biohybrid living structural color hydrogels and microfluidics to obtain a heart micro-tissue for drug screening and biological studies. They reported that some cell behaviors could be detected easily through color changes.

In contrast, weak cellular forces may be overlooked due to weak morphological variances in the elastomer films or hydrogels.[105] Li et al. designed a heart micro-tissue to reduce graphene oxide (rGO) hybrid anisotropic structural color film based on poly (ethylene glycol) diacrylate (PEGDA) and GelMA study cardiac sensing. GelMA and rGO having high adhesion rates helped with growing and orientating cardiomyocytes.[106]

The main advantages of gelatin over collagen are its better solubility, significantly lower cost, and relatively lower antigenicity due to exhibition of fewer aromatic groups.[103] Gelatin can only form a gel with low mechanical strength.[107] It can be easily manipulated by physically blending with other polymers, chemical crosslinkers, or physical treatment to enhance its physicochemical properties.[66]

5 | POLYSACCHARIDE-BASED POLYMERS

Glycosidic bonds connect long monosaccharide chains to form polymeric carbohydrate molecules known as polysaccharides.[108] These natural-based structural elements are primarily used in biomedical applications.[109] Here, we propose to discuss the three types of polysaccharides and their chemical modifications, preclinical studies, preparatory strategies, and clinical translations in OoCs discussed.[110] Studies to date have been devoted to developing a variety of nanotherapeutics linked through a microfluidic circulatory system. Some of these applications are known as liposomes, micelles, polymeric conjugates, and polymerases.[111]

Microfluidic instruments may be designed and adapted for specific purposes. They can indeed be combined with postsynthesis approaches and measurement methods on a single technology framework to monitor the in-situ formulation of polysaccharide-based polymers using residence time-based resolution.[112] Polysaccharides are sugar molecules that are covalently bound by a glycosidic bond and contain more than two sugar molecules. Monosaccharides and disaccharides, in addition to polysaccharides, are used in the classification of carbohydrates. Polysaccharides have a wide range of functional usefulness, versatility, and structural diversity due to their varying molecular weights and variations in reagent groups such as carbonyl, carboxyl, amine, hydroxyl in the polysaccharide backbone.[113] Polysaccharides of natural origin are usually derived from plants (cellulose), animals (chitosan, the exoskeleton of insects, chitin), algae (alginate), and microorganisms (dextran). Polysaccharides are composed of a high amount of hydroxyl groups when compared with other synthetic hydrophobic polymers.[114]

Additionally, polysaccharides may have other hydrophilic groups.[115] For example, large numbers of carboxyl groups and large chitosan numbers of amino groups are found in alginate. These features additionally provide aqueous solubility and cause increased biological adhesion and biological recognition properties called noncovalent bonding between target tissues and polysaccharides.[116] To exemplify, only positively charged polysaccharides, such as chitosan, can attach to negatively charged mucosal layers with an electrostatic reaction.[114] Another commonly used polysaccharide, hyaluronic acid (HA), can perceive and bind to CD44 antigens on the cell surface. Polysaccharides are readily detected and metabolized by the body due to their biochemical properties.[117]

Because polysaccharides include a variety of functional groups, they may be modified with different chemical groups, which can aid in the loading of desired medicinal compounds.[118] The therapeutic component might be delivered by simple diffusion or via degradable crosslinking. It should be highlighted that biocompatibility and biodegradability are critical factors to consider when selecting a material for biomedical applications.[119] Because polysaccharides have these qualities by nature, they are frequently used as a polymer matrix to develop novel products. Polysaccharide-based nanomaterials, unlike other nanoparticles, can breakdown into harmless byproducts under biological circumstances, followed by renal clearance.[120]

5.1 | Chitosan

Chitosan consists of D-glucosamine units (1–4) due to chitin's deacetylation in an alkaline medium.[121,122] Chitosan dissolves in aqueous acidic environments because of the protonation of $-NH_2$ groups in the C-2 position, turning into polyelectrolyte in acidic environments. Chitosan has various bioactive features, including fungistatic, bacteriostatic, hemostatic activity, anti-acid anti-cholesterol, anti-carcinogen, anti-ulcer, wound and bone healing efficiency, and immune system stimulation.[123]

Chitosan has a diverse set of properties that allows integrating biological components with electronic devices for OoCs purposes. In designing OoCs, there is a great deal of interest in conducting high throughput studies with limited sample volumes.[124] OoCs devices, for example, are used to quickly examine biological substances (e.g., blood or saliva) for metabolites (e.g., glucose) or protein biomarkers. Chitosan has various features that suggest it can interface biological constituents with electronic tools for OoCs applications.[125] Chitosan's pH-responsive film-forming features enable it to be electrodeposited as a stable thin film in reply to regional cathodic signals in these ways. When the chitosan-coated electrode is submerged in an aqueous solution including NaCl, the electrodeposited chitosan film can be electrochemically activated for protein conjugation by applying an anodic prospective chitosan-coated electrode.[124] Electrochemical protein conjugation and electrodeposition work together to permit

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

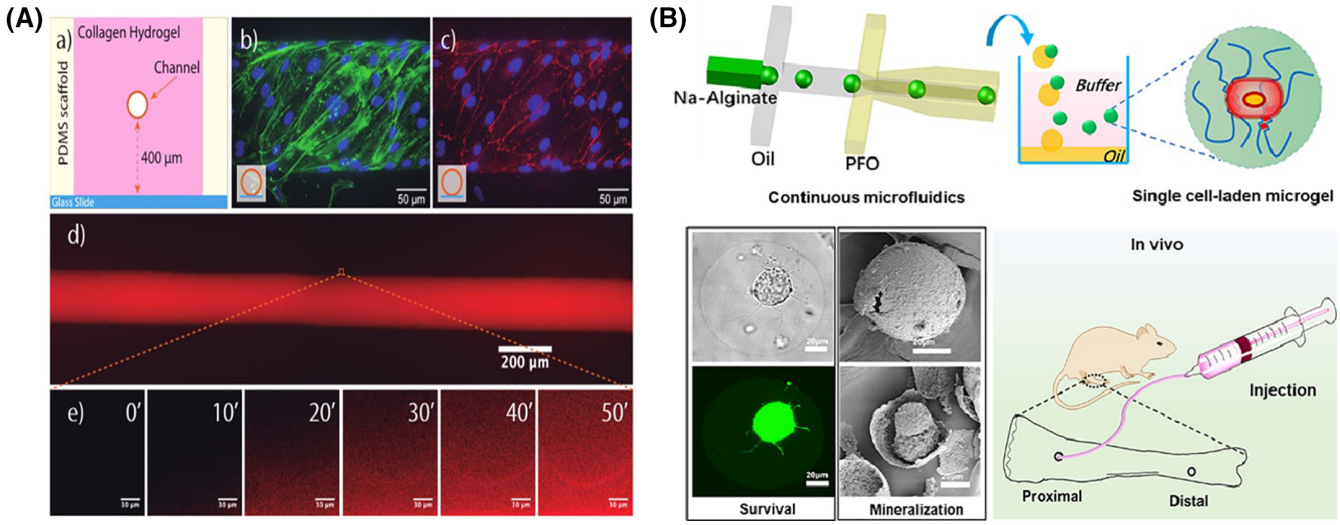

FIGURE 5 (A) HUVEC-lined microvessel (A) micro-tissue schema. (B) HUVECs staining with phalloidin green (Actin) and DAPI (nucleus). (C) V-cadherin in (red). (D) Dextran inside the micro-vessel lumen. (E) Dextran diffusion into the hydrogel. Reproduced with permission.[135] Copyright 2020, Taylor & Francis. (B) Micro-tissue continuous encapsulation of single MSCs in alginate MPs. Reproduced with permission.[137] Copyright 2020, MDPI

proteins to be effectively electrode-addressed to electrode surfaces without reactive reagent.[126]

Chitosan's hydrophilic nature makes it ideal for encapsulating hydrophilic drugs, but the most well-known anticancer drugs are hydrophobic.[127] Finding the best polymer to create a vesicle is very necessary. Many scientists have tried to address the various cancer treatment challenges, the battle to make cancer treatable, not the death penalty.[128] Today, existing chitosan synthesis methods cannot shape well-defined and monodispersed NPs, although some studies suggest that such particles are produced microscale. Hydrophobic alteration of chitosan can be used to overcome its hydrophilicity with N-palmitoyl groups.[129] This approach would allow drug packaging independent of ionic gelation/ chemical-crosslinking and address the issues associated with crosslinking substitutes used for particle formation to retain hydrophobic products.[110]

5.2 | Dextran

Dextran has taken its place in the field of food and pharmacy since 1940. Due to their different structures, some dextrans are soluble in water while some are not. Dextran, derived from sucrose by the catalyzing activity of dextransucrase outside the cell, protects bacteria in acid and alkaline conditions in absence times.[130,131] Dextrans' properties are mostly dependent on their branching degree and their molecular weight as other types of polysaccharide-based micro/ nanoparticles. Yu et al.[132] developed a dextran-modified PDMS microfluidic computer with a unique structure that eliminates crossover interference. With an outstanding sensitivity of 100 pg mL and a dynamic range of five orders of magnitude, the system was used to identify numerous important biomarkers such as IL-5, HBsAg, and IgG rabbit biomarkers through a flow-through technique, dramatically improving the potential of the reported hydrophobic and plasma-treated PDMS flow-through processes.[133]

Chan et al. created a pressure-driven liquid chromatography microfluidic device combined with mesoporous silica as a stationary HPLC phase on a PDMS micro-tissue. This LC micro-tissue demonstrated the chromatographic separation of the fluorescein/rhodamine B dye mixture and the biomolecule mix of 10 kDa dextran and 66 kDa BSA. As a result, the standard HPLC system software can potentially be adapted to the LC micro-tissue. This microfluidic device's architecture can be changed to fit different biomolecular separations, such as capillary electrochromatography.[134]

Another significant work regarding dextran has been done by Lozano et al. who have characterized dextran's transportation through the micro-vessel's wall. Their findings showed that lining the channel walls with endothelial cells meaningly decreases micro-vessel permeability and that this cellular coating functions as a buffer. This significant feature of endothelial cells is important in the regulation of vascular permeability. They focused on the permeability of microvessels to molecules of different sizes in the presence and absence of endothelial cells and static and flowed environments. They calculated the transport of fluorescently-labeled dextran of varying molecular weights (3–70 kDa) from the micro-vessel lumen to the COL-based hydrogel in which the channel is shaped to determine permeability[135] (Figure 5A).

Consequently, the dextran-modified PDMS microfluidic technology demonstrates a promising ability to produce low-cost, fast-responding OoCs for screening different types of infectious diseases, as well as a potential for creating a compact microfluidic device.[132,136]

5.3 | Alginate

Alginates are water-soluble polysaccharides. They are composed of the alginic acid salt with repeating units of β-1,4-linked d-mannuronic

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

acid (M) and l-guluronic acid (G) extracted (isolated) from the Phaeophyceae family.[138,139] Colloidal alginic acid and its salts are widely used in medicine and dentistry, pharmaceutical technology, biotechnology, the cosmetics and food industries, textiles, and the paper industry. In pharmaceutical technology, this natural and biologically compatible polymer is used for the preparation of controlled release.[140]

Alginate is a biocompatible polymer, which has mild ionic gelatin conditions.[141] Research conducted in recent years has revealed that microfluidics is a powerful tool for manipulating and encapsulating cells in microgels.[142] There are some technical barriers, such as the limited capacity to apply Ca^{2+} induced gelation in microfluidics. Creating hydrogel scaffolds that can mimic the ECM with its biochemical and physical properties is promising in micro-tissue.[143] Thus, alginate has been a suitable candidate for encapsulating cells in alginate hydrogels due to its mild gelling conditions and biocompatible properties for micro-tissues. Researchers showed the feasibility of encapsulating human-derived cell lines using a novel approach of micro-tissue in stable, highly monodispersed alginate microspheres.[144]

Alginate gelling in the micro-tissue is a big obstacle as gelling kinetics or hysicochemical conditions are not biocompatible.[145] Recently, Hati et al. introduced a new approach that provides an unparalleled degree of control over gelling kinetics and *p*H applied to several cells' encapsulation in bead and fiber geometries. This scalable approach proved to be easy to modify to obtain the necessary solution conditions for microfluidic applications. It resulted in a highly stable operation of the device and the relatively high viability of many different encapsulated cell types in OoC.[142]

A micro-tissue for continuously encapsulating mesenchymal stem cells (MSCs) in single-cell alginate microparticles (MPs) has been developed. This has provided for the scalable development of cell-charged microgels while keeping encapsulated cells viable and functional. Osteogenesis of encapsulated MSCs in alginate MPs was greatly intensified, as was the hydrogel matrix's mineralization (Figure 5B). A novel method to produce shape-controlled calcium alginate gel MPs in micro-tissue was discovered in another paper. Both the processing of shape-controlled MPs and hydrogel MPs' synthesizing could be carried out simultaneously in a microfluidic system. The novel microfluidic device, consisting of two separate flow-focusing channels and a synthesizing tube, was efficiently used as a continuous microfluidic reactor to produce gel MPs of varying sizes and forms. The sodium alginate MPs' form and the scale can be changed by altering the various streams' flow rates. Further chemical reaction stages could be started by combining sodium alginate MPs and calcium chloride solution in the synthesizing channel. The synthesis of calcium alginate gel MPs could hold the forms of sodium alginate MPs indefinitely.[137]

5.4 | Hyaluronic acid

HA, a natural glycosaminoglycan in all soft tissues, is biocompatible and essential for controlling cell activities, such as migration, proliferation, differentiation, and angiogenesis.[146] HA hydrogels acting as 3D have been inserted into OoCs to design target tissues with multi-cellular networks and organ-specific roles through the spatial modulation of micro-environment cues,[147] such as liver,[16] heart,[18] and skeletal muscle.[148] While light exposure contributes to material streaming during deposition, it contributes to material fracturing before extrusion.[149] For instance, β-recombinant spider silk proteins hydrogen bonds or guest-host interactions of β-cyclodextrin or adamantane in modified HA polymers break under shear stress allowing for extrusion bioprinting followed by rapid deposition stabilization.[150] Kolesky et al. have demonstrated that thick human vascularized tissues (>1 cm) could be delivered by a multi-material 3D-bioprinting strategy based on a crosslinked gelatin-fibrin matrix[151] (Figure 6-I). The composite hydrogel was interlinked either by thrombin and transglutaminase (a dual-enzymatic) process or by gelation, which was thermally reversible relevant to the actual printing and the following casting phases micro-tissue. Various cell types have been replanted inside the grid to frame that can be perfused ceaselessly to the micro-tissue for significant stretches[152] (> a month and a half), thus assuring osteogenic pathway separation in situ.[153]

Ouyang et al. used HA macromers as 3D printable hydrogels in extrusion-based bioprinters and investigated that event types of crosslinking types in print filament output and stability.[146] They found a dual crosslinking, which enabled the prompt stabilization of the filaments via supramolecular bonds immediately postextrusion. This may contribute to short-term stability before covalent crosslinking, resulting in stabilization. They stated the dual-crosslinking technique that does not need the use of other supporting biomaterials, such as gelatin or alginate, enabling the HA-based method to be optimized for a particular application without the need to incorporate secondary contents (Figure 6-II).

5.5 | Gellan gum

Gellan gum (GG) is a water-soluble microbial polysaccharide, a linear, anionic, and high molecular weight polymer produced by Pseudomonas elodea.[154] The GG is a reference substrate that can develop gelation properties with divalent cations such as calcium ions. The GG can make stable hydrogel structures through ionotropic processes, i.e., physical crosslinking induced by cations' presence. These structures are robust and less penetrable than alginate-based gels. Hydrogels have been used to make PDMS water-absorbing. Natural and synthetic hydrogen products, such as gelatin, GelMA, alginate, and cross-linked PEG, were used.[66] For constructing functional 3D vascular micro-tissue, the microvascular networks based on GG-hydrogels are beneficial. Koivisto et al. indicated that GG is capable of forming hydrogels with tunable mechanical properties.[19] The GelMA and the methacrylate gellan gum (MAGG) were crosslinked into hydrogels and enveloped cells. Robinson et al.[155] worked on MAGG[156] and chitosan as biomaterial ink.[157] They claimed that MAGG is a well-established anionic polymer biotechnology that can be modified or tuned based on the methacrylate ratio.

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

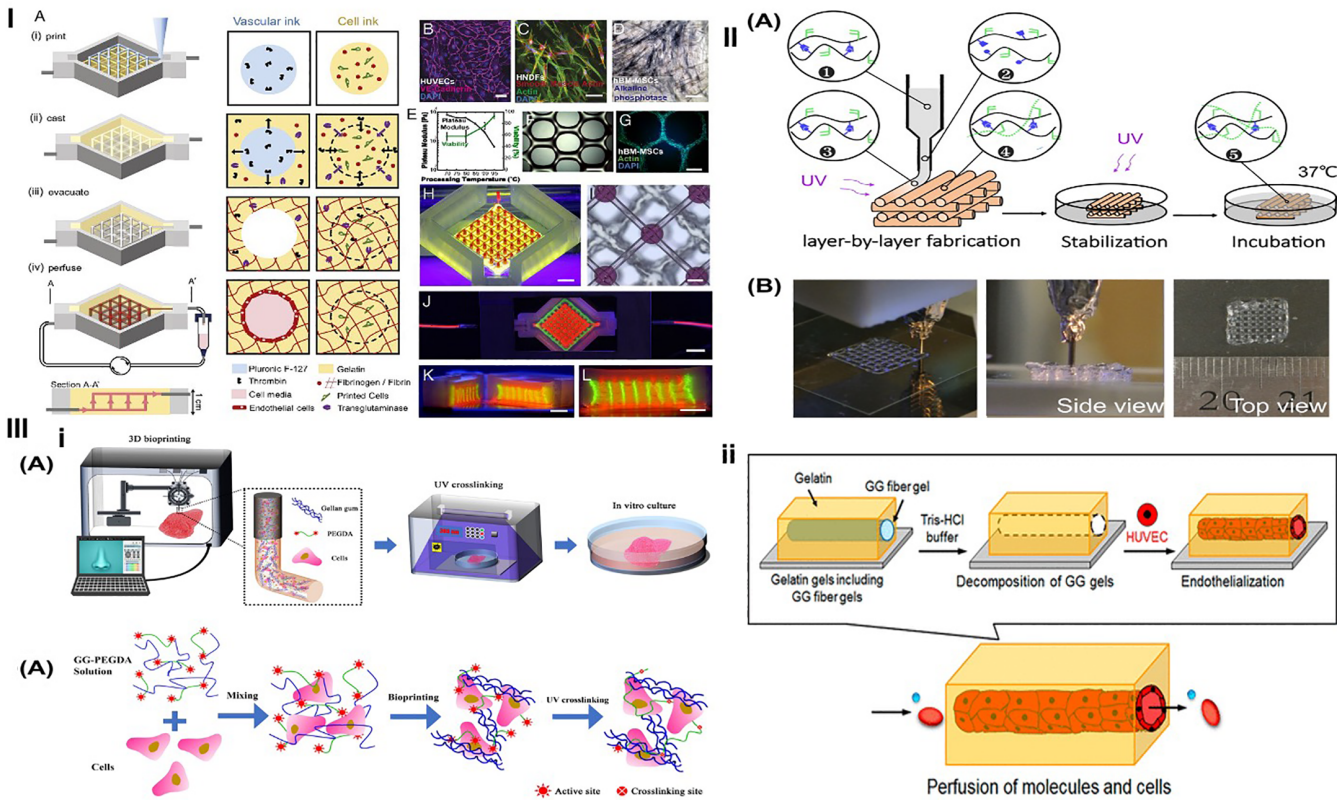

FIGURE 6 (I) (A) Diagram of the micro-tissue manufacturing process. (i) Vascular bioink, which includes thrombin and pluronic, and cell-laden bioinks including gelatin, fibrinogen, and cells, are bioprinted within a 3D-perfusion micro-tissue. (ii) ECM biomaterial containing fibrinogen, gelatin, cells, thrombin, and TG. TG disperses from the molten casting matrix and slowly cross-links the fibrin and gelatin. (iii) The vascular bioink dissolves and is displaced, leaving behind an extensive vascular network (iv) Endothelialized and perfused by an external pump. (B) HUVECs on top of the matrix in 2D, (C) HNDFs inside the matrix in 3D, (D) hMSCs on top of the matrix in 2D. (Scale bar: 50 μm.) (E and F) Images of bioprinted hMSC-laden bioink equipped using gelatin (E) as printed (F) 3D-printed filament where Actin (green) and nuclei (blue) are stained. (G) Cell viability after printing. (H) Photographs of diffused sacrificial (red) and cell inks (green) as bioprinted on micro-tissue. (Scale bar: 2 Mm.) (I) Top-down bright-field image of sacrificial and cell bioinks. (Scale bar: 50 μm.). (J–L) A 3D-bioprinted tissue scaffold housed within a perfusion chamber (J) and corresponding cross-sections (K and L). (Scale bars: 5 Mm.). Reproduced with permission.[151] Copyright 2016, PNAS. (II) (A) Diagram of 3D printing, stabilization, and incubation processes for HA hydrogels. (B) Illustrative images of the printing process and multilayer structure. Reproduced with permission.[146] Copyright 2016, American Chemical Society. III) (i) (a) Scheme of the 3D-bioprinting process. (b) Assembly changing process of the cell-laden GG/PEGDA DN hydrogels. Reproduced with permission.[161] Copyright 2018, Elsevier. III) (ii) Representation of perfusable endothelialized tube constructs made by dissolving a GG template fiber gel implemented in gelatin. Reproduced with permission.[162] Copyright 2016, American Chemical Society

As a bioink, GG has numerous advantages compared with hydrogels, including a shear-thinning feature, the high gelling potential at physiological temperatures, and a reasonable production cost. Mouser et al. have engineered a bioink with GG and GelMA for cartilage bioprinting.[158] Lozano et al. used RGD peptide to modify GG with primary neural cells to print a 3D-brain-like construct.[159] These studies support GG-based biomaterial' applications to print layered, elaborate, and 3D viable cell constructs. However, GG's inherent fragility limits its printability and structural integrity when manipulated and implanted.[160] Scientists have explored methods to overcome GG fragilities, such as GG functionalization, double network strategies, and methodologies for processing. GG/PEGDA blends noncovalent and covalent links and reaches a highly robust, stretchable network construct. The production of GG-based bioinks with high fidelity for 3D printing and good cell integration is still a critical task[161] (Figure 6-III-i).

Perfuse micro-vascular networks on a GG-hydrogel micro-tissue can supply and control the microenvironment sufficient oxygen and nutrients for long-term tissue survival and maintenance. As mentioned above, incorporating GG hydrogels into the micro-tissue provides a new strategy in vitro, either in the simple form of a micro-tissue vessel or a complex 3D vessel tissue embedded design for constructing the functional tissues[162] (Figure 6-III-ii).

6 | INTEGRATION OF MICRO-TISSUES TO OOCS

Recent advancements in tissue engineering have been primarily attributed to developing innovative biomaterials-based techniques that better imitate native tissue and organ architecture. These biomaterials

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

can use cells' intrinsic capacities to perceive their immediate environment via cell–cell and cell–ECM interactions and self-assemble into complex mechanisms to reveal emerging behaviors. Many biofabrication approaches attempt to represent better the complex heterogeneous features of endogenous cells, tissues, and organs for tissue engineering and regenerative medicine applications, in response to the requirements for enhanced biomaterials-based cell culture approaches. Several biofabrication processes are available for creating 3D scaffolds from both synthetic and naturally occurring biomaterials, such as freeze-drying, gas foaming, solvent casting, drop-based bioprinting, extrusion bioprinting, and multiphoton. These biofabrication technologies employ biomaterials to create scaffolds with well-defined 3D topologies and geometries to include biomolecules into the 3D matrix with specified orientation and concentration. A scaffold with high porosity, variable pore diameters, and mechanical strength is preferred for tissue engineering applications. Large pores allow molecules, waste products, and gases to diffuse inside a 3D structure quickly. Freeze-drying, also known as lyophilization, is the process of cooling a polymer (synthetic or natural) solution below its freezing point, causing the solvent molecules to solidify. Shapiro and Cohen used lyophilization to create 3D alginate porous sponges for researching biological interactions. They discovered that alginate sponges with holes ranging from 70 to 300 m were suitable for fibroblast culture.[163] Gas foaming is a biofabrication process in which a polymeric scaffold is immersed at high pressures with a foaming ingredient such as carbon dioxide, nitrogen, or water. Kim et al. used gas-foamed polyurethane as a template to create a porous biphasic calcium phosphate (BCP) scaffold. The BCP scaffold was biocompatible and capable of bone development and regeneration in vivo and in vitro studies.[164] Drop-based bioprinting has risen in importance due to the speed it can create scaffolds and biomaterials with complex 3D structures. Villar et al. recently showed the capacity to print complicated 3D geometries by producing lipid bilayer–coated microspheres groupings using picoliter aqueous droplets in lipid-containing oil. These lipid bilayers were subsequently modified to include membrane proteins and create linked networks.[165] All of the biofabrication approaches listed above strive to produce scaffolds that closely resemble the physiological microenvironments that cells encounter.[160] The next generation of scaffolds must monitor the cells in these 3D niches in real-time. Furthermore, in the future, biofabrication techniques may be used to create scaffolds that both differentiate stem cells and present microenvironmental signals that allow these cells to mature into adult tissue.[166,167]

The GG-hydrogels can be implemented with microfluidic to supply cell culture scaffolding and mimic biological vascularization interfaces that develop physiologically relevant micro-tissue. Visser et al. integrated GG/GelMA-based hydrogels as a part of a multi-material 3D printing approach to create complicated target tissue.[168] Levato et al. also printed mixtures of GelMA and GG, seeding cells into the scaffold using poly(lactic acid) microcarriers.[169]

Vieria et al. was demonstrated the relative fabrication of biofabrication science by shaping cast disks, foils, fibers, spheres lyophilized GG scaffolds.[170] The substance in several new biofabrication techniques provides a straightforward path for GG microtissue. Ferris et al. reported a new GG bioink by preselling GG under high shear to produce a suspension of GG microgels.[171] These GG microgel suspensions were shown to have been highly suitable for the injection, supplemented with biocompatible surfactants, to enable single-cell patterns and reportedly stabilized live cell culture. This technique was used by Lozano et al. to manufacture a multi-coating cortical tissue imitating GG modified RGD-peptides[172] into OoC with GG-hydrogels as micro-tissue. Extending MAGG in UV-bioprinting provides a novel type of GG biomanufacturing with considerable potential in a micro-tissue. However, GG has not obtained that much attention in the biofabrication literature compared with other hydrogel-forming biomaterials. GG cell scaffolds have been fabricated mainly by casting approaches.[36]

Miri et al. fabricated GelMA (bioactive hydrogel) and PEGDA (framing structure) based constructs using stereolithography-based bioprinting while incorporating microfluidics for fabrication. The neovascularization capacity of this system was evaluated in a rat subcutaneous implantation model. Even though GelMA hydrogels induced new blood vessels, the target tissue was higher for %5 and % 10 GelMA compared to %15 GelMA due to the prevention of cell invasion in denser hydrogel networks.[173]

MPs may be used for the targeted drug delivery to enhance oral and intravenous drug delivery effectiveness.[174] For in vivo drug delivery, the therapeutic agent needs to be encapsulated in biodegradable polymers such as polyesters to overcome the degradative effects of the digestive system.[175] Several factors, including the form of polymer, the shape and size of the microparticles, and the chemical structure, may significantly impact drug delivery efficiency in this situation.[175] Standard chitosan MPs, such as those made with tripolyphosphate, have particle sizes ranging from 500 to 710 μm. Chitosan micro/nanoparticles can transmit medicines to various body areas, such as the colon, buccal gland, and gastrointestinal tract.[176] Another microfluidic micro-tissue synthesizes chitosan composite MPs forming a poly(methyl methacrylate) plate with screw holes, three inlets, one outlet one cross-connection tube was manufactured by Yang et al.[177] Central and side inlets were built for scattered and continuous stages, respectively. The cross-connection channel focused on flow and the shearing force and made it possible to change the emulsion size by adjusting the distributed phase or continuous phase flow rate (Figure 7A). Controlling the solidification cycle produced chitosan MPs in various forms, including microspheres, porous MPs, and core-shell MPs, allowing controlled drug distribution with structurally dependent release features. Stimuli-sensitive chitosan MPs, which alter their physical or chemical behaviors in response to external stimuli such as magnetic field and pH, may be used to trigger drug delivery.[178] Since their acid-induced volume swelling behavior, these chitosan microcapsules have a pH-sensitive release profile, as well as a temperature-responsive volume transfer and solid magnetic properties due to the presence of MPs. These chitosan parliamentarians could allow for

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

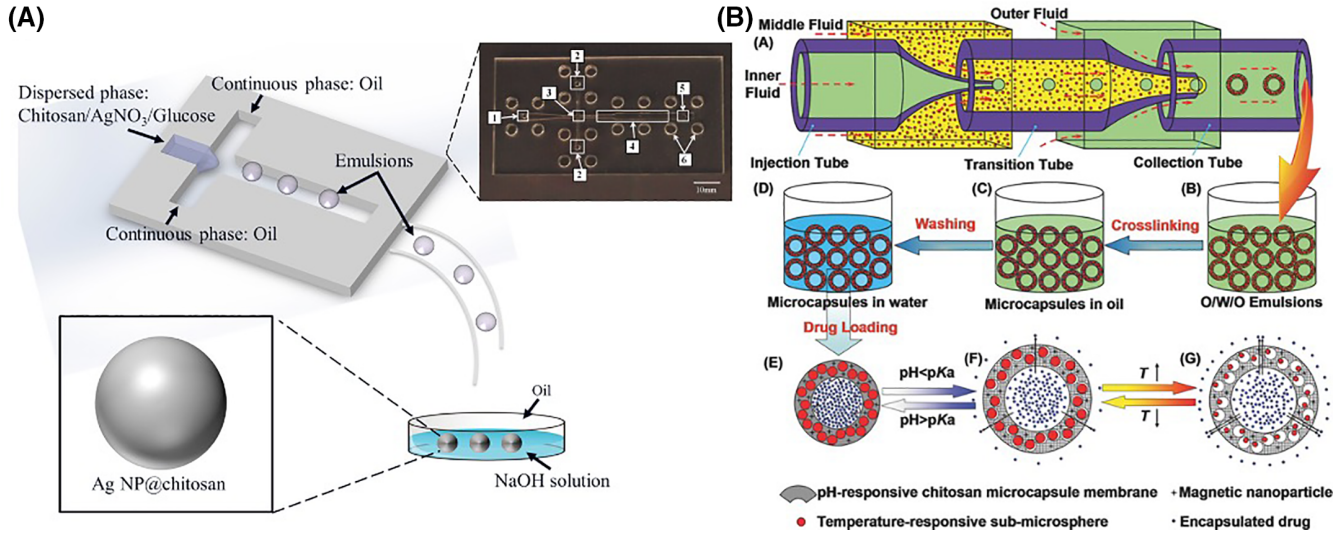

FIGURE 7 Chitosan-based MPs for micro-tissue. (A) Schematic overview of the chitosan MPs. Reproduced with permission.[177] Copyright 2016, Elsevier. (B) Schematic overview of (a–d) the manufacturing procedure and (e–g) the controlled-release mechanism of multi-stimulus sensitive chitosan micro-capsules. Reproduced with permission.[179] Copyright 2020, Springer

targeted distribution and manage the release to micro-tissue[179] (Figure 7B).

Duchamp et al. engineered perforated and endothelialized thin PDMS tubes with small pores on the walls within a blend hydrogel of GelMA and collagen type I to model blood vessels. They placed a pair of perforated PDMS tubes parallel with the matrix. HUVECs were gradually sprouted out from PDMS tubes' pores to generate interconnected microvasculature between two tubes. To determine this system's suitability in the tumor angiogenesis model, breast tumor spheroids were co-cultured in endothelialized tubes. The migration of breast cancer cells (MCF-7) indicated tumor angiogenesis and invasion.[24] Then, develop an antitumor drug screening model using a bioprinted hollow blood and lymphatic vessel pair placed in a microfluidic bioreactor to obtain a dynamic microenvironment to culture MCF-7 breast cancer cells in a 3D GelMA matrix containing PEGDA and 8-arm polyethylene glycol-octaacrylate.[180] The diffusion rates of an anticancer drug in the blood vessel and lymph circulation were considerably higher than the single blood vessel system's diffusion rates.[181]

The use of bioinks from a broad variety of bioprinting materials in tissue engineering, such as norborne-modified HA, GelMA, and PEGDA is a technique that allows building a perfusable vascular network.[182] In the same manner, optical light processing can produce structures on the cellular scale in PEGDA and GelMA with a fast manufacturing speed. Digital light manipulation may be used for high-resolution patterning vasculatures utilizing GelMA HA-containing scaffolds.[183] Adamantane (Ad, Guest) and β-cyclodextrin (CD, Host) batches can be linked separately to HA to form two hydrogel precursors and supramolecular composite after mixing.[146] Materials crosslinked by solid, noncovalent bonds increase the solution's viscosity, thus exhibiting shear-thinning during flow to mimic the microscale devices that combine microfabrication and microfluidics technologies.

7 | CURRENT CHALLENGES AND LIMITATIONS

Natural-based biomaterials have excellent properties such as biodegradability, biocompatibility, and natural abundance. Low cost and environmental sustainability also make them beneficial and desirable for extensive applications in many fields. Particularly the section on drug-controlled release and 3D-bioprinting was addressed in this work.[184] Here, we aim to highlight the dominance of stimulus-responsive micro-tissue in various applications due to their controllability, high performance, and convenience. Indeed, in drug delivery, more sophisticated monitoring and modulation of more accurate and efficient releases can be achieved by natural biomaterials and toxicity and side effects, biological incompatibility, and costly materials, etc., can be prevented efficiently, to some degree.[109] While micro-tissue has tremendous potential for this use. We cannot neglect the fact that many shortcomings need to be fixed or improved. The properties of natural-based biomaterials, such as mechanical strength and wearability, require further study.[109] There is still a long way to go regarding the practical implementation and large-scale commercial production of micro-tissue. The existing OoCs still has limited application because of infrastructure problems.[185] Although it is possible to develop micro-tissue in a laboratory environment with biomaterials that provide a compatible interface between microdevices and biology. The major problem is based on the low yield of sampling and perfusion. In addition to these challenges, cell injection has a common throughput structure.[186]

These platforms and natural biomaterials offer opportunities to develop new clinical applications. But the application of natural biomaterials and organ-on-a-chip systems are currently facing critical challenges to provide the solutions for their applications in the industry or clinics.[5] One of these challenges is that they are in their early

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

stages for industry and clinics. Many risk factors come to the fore at this stage. The necessity of long scientific research, especially financial risks, affects the process for research institutions. Thus, the transition period to clinical practice is prolonged.[10]

Further enhancement of the functionality of biomaterials will be possible by the immobilization of the cells on the micro-tissue surfaces. Micro-physiology is the most significant limitation, while the design must be simple and suitable for real-time monitoring and analysis. It is very important to design the micro-tissues to imitate the human organs' anatomical and physiological features in this context.[187] Finally, and importantly, another challenge is the integrity of the target tissue or organ-specific cells with this design and the opportunity to work in vitro. For high-efficiency applications in OoCs, it is necessary to follow target tissue's biological and physiological status, work with many samples, and monitor the output.

CONFLICT OF INTEREST

The authors declare that no conflict of interests was associated with the present study.

DATA AVAILABILITY STATEMENT

There is no data available

REFERENCES

1. Maimouni I, Cejas CM, Cossy J, Tabeling P, Russo M. Microfluidics mediated production of foams for biomedical applications. *Micromachines*. 2020;11(1):83.
2. Daw R, Finkelstein J. Insight: lab on a chip. *Nature*. 2006;442(7101):367-418.
3. Whitesides GM. The origins and the future of microfluidics. *Nature*. 2006;442(7101):368-373.
4. Wu Q, Liu J, Wang X, et al. Organ-on-a-chip: recent breakthroughs and future prospects. *Biomed Eng Online*. 2020;19(1):9.
5. Chen F-M, Liu X. Advancing biomaterials of human origin for tissue engineering. *Prog Polym Sci*. 2016;53:86-168.
6. Cattin A-L, Lloyd AC. The multicellular complexity of peripheral nerve regeneration. *Curr Opin Neurobiol*. 2016;39:38-46.
7. Ronaldson-Bouchard K, Vunjak-Novakovic G. Organs-on-a-chip: a fast track for engineered human tissues in drug development. *Cell Stem Cell*. 2018;22(3):310-324.
8. Mishra MK, Dubey V, Mishra PM, Khan I. MEMS Technology: A Review. *Journal of Engineering Research and Reports*, 2019;4(1):1-24. http://dx.doi.org/10.9734/jerr/2019/v4i116891
9. Nikolova MP, Chavali MS. Recent advances in biomaterials for 3D scaffolds: a review. *Bioactive Mater*. 2019;4:271-292.
10. Brovold M, Almeida JI, Pla-Palacín I, et al. Naturally-derived biomaterials for tissue engineering applications. *Novel Biomater Regenerative Med*. 2018;1077, 421-449.
11. Huh D, Kim HJ, Fraser JP, et al. Microfabrication of human organs-on-chips. *Nat Protoc*. 2013;8(11):2135-2157.
12. Boudreau N, Bissell MJ. Extracellular matrix signaling: integration of form and function in normal and malignant cells. *Curr Opin Cell Biol*. 1998;10(5):640-646.
13. Zhu J, Marchant RE. Design properties of hydrogel tissue-engineering scaffolds. *Expert Rev Med Devices*. 2011;8(5):607-626.
14. Yue K, Trujillo-de Santiago G, Alvarez MM, Tamayol A, Annabi N, Khademhosseini A. Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. *Biomaterials*. 2015;73:254-271.
15. Tibbe MP, Leferink AM, van den Berg A, Eijkel JCT, Segerink LI. Microfluidic gel patterning method by use of a temporary membrane for organ-on-Chip applications. *Adv Mater Technol*. 2018;3(3):1700200.
16. Lu S, Cuzzucoli F, Jiang J, et al. Development of a biomimetic liver tumor-on-a-chip model based on decellularized liver matrix for toxicity testing. *Lab Chip*. 2018;18(22):3379-3392.
17. Kong M, Lee J, Yazdi IK, et al. Cardiac fibrotic remodeling on a chip with dynamic mechanical stimulation. *Adv Healthc Mater*. 2019;8(3):1801146.
18. Occhetta P, Isu G, Lemme M, et al. A three-dimensional in vitro dynamic micro-tissue model of cardiac scar formation. *Integr Biol*. 2018;10(3):174-183.
19. Koivisto JT, Joki T, Parraga JE, et al. Bioamine-crosslinked gellan gum hydrogel for neural tissue engineering. *Biomed Mater*. 2017;12(2):25014.
20. Qiu Y, Ahn B, Sakurai Y, et al. Microvasculature-on-a-chip for the long-term study of endothelial barrier dysfunction and microvascular obstruction in disease. *Nat Biomed Eng*. 2018;2(6):453-463.
21. Abudupataer M, Chen N, Yan S, et al. Bioprinting a 3D vascular construct for engineering a vessel-on-a-chip. *Biomed Microdevices*. 2020;22(1):1-10.
22. Zhang YS, Arneri A, Bersini S, et al. Bioprinting 3D microfibrous scaffolds for engineering endothelialized myocardium and heart-on-a-chip. *Biomaterials*. 2016;110:45-59.
23. Mao Q, Wang Y, Li Y, et al. Fabrication of liver microtissue with liver decellularized extracellular matrix (dECM) bioink by digital light processing (DLP) bioprinting. *Mater Sci Eng C*. 2020;109:110625.
24. Duchamp M, Bakht SM, Ju J, Yazdi IK, Zhang W, Zhang YS. Perforated and Endothelialized elastomeric tubes for vascular modeling. *Adv Mater Technol*. 2019;4(9):1800741.
25. Mehrotra S, de Melo BA, Hirano M, et al. Nonmulberry silk based ink for fabricating mechanically robust cardiac patches and Endothelialized myocardium-on-a-Chip application. *Adv Funct Mater*. 2020;30(12):1907436.
26. Li X, He J, Liu Y, et al. Biomaterial scaffolds with biomimetic fluidic channels for hepatocyte culture. *J Bionic Eng*. 2013;10(1):57-64.
27. Ahadian S, Civitarese R, Bannerman D, et al. Organ-on-a-Chip platforms: A convergence of advanced materials, cells, and microscale technologies. *Adv Healthc Mater*. 2018;7(2):1700506.
28. Maoz BM, Herland A, FitzGerald EA, et al. A linked organ-on-chip model of the human neurovascular unit reveals the metabolic coupling of endothelial and neuronal cells. *Nat Biotechnol*. 2018;36(9):865-874.
29. Song HJ, Lim HY, Chun W, Choi KC, Sung JH, Sung GY. Fabrication of a pumpless, microfluidic skin chip from different collagen sources. *J Indus Eng Chem*. 2017;56:375-381.
30. Menon NV, Tay HM, Wee SN, Li KHH, Hou HW. Micro-engineered perfusable 3D vasculatures for cardiovascular diseases. *Lab Chip*. 2017;17(17):2960-2968.
31. Petrosyan A, Cravedi P, Villani V, et al. A glomerulus-on-a-chip to recapitulate the human glomerular filtration barrier. *Nat Commun*. 2019;10(1):1-17.
32. Zamprogno PGV, Wüthrich S, Achenbach S, et al. Second-generation lung-on-a-chip array with a stretchable biological membrane. *BioRxiv*. 2019.1–10.
33. Yin L, Du G, Zhang B, et al. Efficient drug screening and nephrotoxicity assessment on co-culture microfluidic kidney Chip. *Sci Rep*. 2020;10(1):1-11.
34. Edmondson R, Broglie JJ, Adcock AF, Yang L. Three-dimensional cell culture systems and their applications in drug discovery and cell-based biosensors. *Assay Drug Dev Technol*. 2014;12(4):207-218.
35. Pasman T, Grijpma D, Stamatialis D, Poot A. Flat and microstructured polymeric membranes in organs-on-chips. *J R Soc Interface*. 2018;15(144):20180351.

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

36. Stevens L, Gilmore KJ, Wallace GG. Tissue engineering with gellan gum. *Biomater Sci*. 2016;4(9):1276-1290.
37. Xie R, Zheng W, Guan L, Ai Y, Liang Q. Engineering of hydrogel materials with perfusable microchannels for building vascularized tissues. *Small*. 2020;16(15):1902838.
38. Kim J, Feng J, Jones CAR, et al. Stress-induced plasticity of dynamic collagen networks. *Nat Commun*. 2017;8(1):842.
39. Frantz C, Stewart KM, Weaver VM. The extracellular matrix at a glance. *J Cell Sci*. 2010;123(24):4195-4200.
40. Harjunpää H, Llort Asens M, Guenther C, Fagerholm SC. Cell adhesion molecules and their roles and regulation in the immune and tumor microenvironment. *Front Immunol*. 2019;10:1078.
41. Camacho P, Busari H, Seims KB, Tolbert JW, Chow LW. Materials as bioinks and bioink design. *3D Bioprint Med Springer*. 2019;67-100.
42. Pidhatika B, Zhao N, Zinggeler M, Rühe J. Surface-attached dual-functional hydrogel for controlled cell adhesion based on poly (N, N-dimethylacrylamide). *J Polym Res*. 2019;26(3):1-12.
43. Bicho D, Ajami S, Liu C, Reis RL, Oliveira JM. Peptide-biofunctionalization of biomaterials for osteochondral tissue regeneration in early stage osteoarthritis: challenges and opportunities. *J Mater Chem B*. 2019;7(7):1027-1044.
44. Yaşayan G, Magnusson JP, Sicilia G, et al. Multi-modal switching in responsive DNA block co-polymer conjugates. *Phys Chem Chem Phys*. 2013;15(38):16263-16274.
45. Cheng Y, Luo X, Payne GF, Rubloff GW. Biofabrication: programmable assembly of polysaccharide hydrogels in microfluidics as biocompatible scaffolds. *J Mater Chem*. 2012;22(16):7659-7666.
46. Tibbitt MW, Anseth KS. Hydrogels as extracellular matrix mimics for 3D cell culture. *Biotechnol Bioeng*. 2009;103(4):655-663.
47. Lotfi M, Nejib M, Naceur M. Cell adhesion to biomaterials: concept of biocompatibility. *Adv Biomater Sci Biomed Appl*. 2013;8:208-240.
48. Dalby MJ, Gadegaard N, Oreffo RO. Harnessing nanotopography and integrin–matrix interactions to influence stem cell fate. *Nat Mater*. 2014;13(6):558-569.
49. Yao X, Peng R, Ding J. Cell–material interactions revealed via material techniques of surface patterning. *Adv Mater*. 2013;25(37):5257-5286.
50. Ferrari M, Cirisano F. Mammalian cell behavior on hydrophobic substrates: influence of surface properties. *Coll Interfaces*. 2019;3(2):48.
51. Ranga A, Gjorevski N, Lutolf MP. Drug discovery through stem cell-based organoid models. *Adv Drug Deliv Rev*. 2014;69:19-28.
52. Loessner D, Stok KS, Lutolf MP, Hutmacher DW, Clements JA, Rizzi SC. Bioengineered 3D platform to explore cell–ECM interactions and drug resistance of epithelial ovarian cancer cells. *Biomaterials*. 2010;31(32):8494-8506.
53. Vogel V, Sheetz M. Local force and geometry sensing regulate cell functions. *Nat Rev Mol Cell Biol*. 2006;7(4):265-275.
54. Hasan A, Saliba J, Pezeshgi Modarres H, et al. Micro and nanotechnologies in heart valve tissue engineering. *Biomaterials*. 2016;103:278-292.
55. Chaudhuri O, Gu L, Klumpers D, et al. Hydrogels with tunable stress relaxation regulate stem cell fate and activity. *Nat Mater*. 2016;15(3):326-334.
56. Wong JY, Leach JB, Brown XQ. Balance of chemistry, topography, and mechanics at the cell–biomaterial interface: issues and challenges for assessing the role of substrate mechanics on cell response. *Surf Sci*. 2004;570(1):119-133.
57. Vedadghavami A, Minooei F, Mohammadi MH, et al. Manufacturing of hydrogel biomaterials with controlled mechanical properties for tissue engineering applications. *Acta Biomater*. 2017;62:42-63.
58. Ghosh K, Pan Z, Guan E, et al. Cell adaptation to a physiologically relevant ECM mimic with different viscoelastic properties. *Biomaterials*. 2007;28(4):671-679.
59. Kim HN, Choi N. Consideration of the mechanical properties of hydrogels for brain tissue engineering and brain-on-a-chip. *Biochip J*. 2019;13(1):8-19.
60. Joseph J, Siva Kumar Gunda N, Mitra SK. On-chip porous media: porosity and permeability measurements. *Chem Eng Sci*. 2013;99:274-283.
61. Esch MB, Sung JH, Yang J, et al. On chip porous polymer membranes for integration of gastrointestinal tract epithelium with microfluidic 'body-on-a-chip'devices. *Biomed Microdev*. 2012;14(5):895-906.
62. Casillo SM, Peredo AP, Perry SJ, Chung HH, Gaborski TR. Membrane pore spacing can modulate endothelial cell-substrate and cell-cell interactions. *ACS Biomater Sci Eng*. 2017;3(3):243-248.
63. Zhao Y, Gaur G, Retterer ST, Laibinis PE, Weiss SM. Flow-through porous silicon membranes for real-time label-free biosensing. *Anal Chem*. 2016;88(22):10940-10948.
64. Weinhart M, Hocke A, Hippenstiel S, Kurreck J, Hedtrich S. 3D organ models-revolution in pharmacological research? *Pharmacol Res*. 2019;139:446-451.
65. Wang J, Song Y. Microfluidic synthesis of nanohybrids. *Small*. 2017;13(18):1604084.
66. Liu H, Wang Y, Cui K, Guo Y, Zhang X, Qin J. Advances in hydrogels in organoids and organs-on-a-Chip. *Adv Mater*. 2019;31(50):1902042.
67. Hasan A, Paul A, Vrana NE, et al. Microfluidic techniques for development of 3D vascularized tissue. *Biomaterials*. 2014;35(26):7308-7325.
68. Chung E, Rytlewski JA, Merchant AG, Dhada KS, Lewis EW, Suggs LJ. Fibrin-based 3D matrices induce angiogenic behavior of adipose-derived stem cells. *Acta Biomater*. 2015;17:78-88.
69. Barrs RW, Jia J, Silver SE, Yost M, Mei Y. Biomaterials for Bioprinting Microvasculature. *Chem Rev*. 2020;120(19):10887-10949.
70. Logan S, Arzua T, Canfield SG, et al. Studying human neurological disorders using induced pluripotent stem cells: from 2D monolayer to 3D organoid and blood brain barrier models. *Compr Physiol*. 2011;9(2):565-611.
71. Sriram G, Alberti M, Dancik Y, et al. Full-thickness human skin-on-chip with enhanced epidermal morphogenesis and barrier function. *Mater Today*. 2018;21(4):326-340.
72. Chaudhari AA, Vig K, Baganizi DR, et al. Future prospects for scaffolding methods and biomaterials in skin tissue engineering: a review. *Int J Mol Sci*. 2016;17(12):1974.
73. Li Y, Meng H, Liu Y, Lee BP. Fibrin gel as an injectable biodegradable scaffold and cell carrier for tissue engineering. *Scientific World Journal*. 2015;2015:1-10.
74. Bhattacharya S, Calar K, de la Puente P. Mimicking tumor hypoxia and tumor-immune interactions employing three-dimensional in vitro models. *J Exp Clin Cancer Res*. 2020;39:1-16.
75. Kim U-J, Park J, Li C, Jin H-J, Valluzzi R, Kaplan DL. Structure and properties of silk hydrogels. *Biomacromolecules*. 2004;5(3):786-792.
76. Koh L-D, Cheng Y, Teng C-P, et al. Structures, mechanical properties and applications of silk fibroin materials. *Prog Polym Sci*. 2015;46:86-110.
77. Bandyopadhyay A, Chowdhury SK, Dey S, Moses JC, Mandal BB. Silk: a promising biomaterial opening new vistas towards affordable healthcare solutions. *Journal of the Indian Institute of Science*. 2019;99:1-43.
78. Zhao S, Chen Y, Partlow BP, et al. Bio-functionalized silk hydrogel microfluidic systems. *Biomaterials*. 2016;93:60-70.
79. Konwarh R, Gupta P, Mandal BB. Silk-microfluidics for advanced biotechnological applications: a progressive review. *Biotechnol Adv*. 2016;34(5):845-858.
80. Mathur A, Ma Z, Loskill P, Jeeawoody S, Healy KE. In vitro cardiac tissue models: current status and future prospects. *Adv Drug Deliv Rev*. 2016;96:203-213.
81. Zhang W, Chen J, Backman LJ, Malm AD, Danielson P. Surface topography and mechanical strain promote keratocyte phenotype and extracellular matrix formation in a biomimetic 3D corneal model. *Adv Healthc Mater*. 2017;6(5):1601238.

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

82. Carvalho MR, Maia FR, Vieira S, Reis RL, Oliveira JM. Tuning enzymatically crosslinked silk fibroin hydrogel properties for the development of a colorectal cancer extravasation 3D model on a chip. *Global Challenges*. 2018;2(5–6):1700100.
83. Wang S, Ghezzi CE, Gomes R, Pollard RE, Funderburgh JL, Kaplan DL. In vitro 3D corneal tissue model with epithelium, stroma, and innervation. *Biomaterials*. 2017;112:1-9.
84. Zhao L, Zhang X, Liu X, Li J, Luan Y. pH-responsive poly (ethylene glycol)-poly (ϵ-caprolactone)-poly (glutamic acid) polymersome as an efficient doxorubicin carrier for cancer therapy. *Polym Int*. 2017;66(11):1579-1586.
85. Zhao L, Li N, Wang K, Shi C, Zhang L, Luan Y. A review of polypeptide-based polymersomes. *Biomaterials*. 2014;35(4):1284-1301.
86. Yadav S, Sharma AK, Kumar P. Nanoscale self-assembly for therapeutic delivery. *Front Bioeng Biotechnol*. 2020;8:127.
87. Connor RE, Tirrell DA. Non-canonical amino acids in protein polymer design. *J Macromol Sci Part C: Polym Rev*. 2007;47(1):9-28.
88. Jalili-Firoozinezhad S, Gazzaniga FS, Calamari EL, et al. A complex human gut microbiome cultured in an anaerobic intestine-on-a-chip. *Nat Biomed Eng*. 2019;3(7):520-531.
89. Marques CF, Diogo GS, Pina S, Oliveira JM, Silva TH, Reis RL. Collagen-based bioinks for hard tissue engineering applications: a comprehensive review. *J Mater Sci Mater Med*. 2019;30(3):32.
90. Perez-Puyana V, Romero A, Guerrero A. Influence of collagen concentration and glutaraldehyde on collagen-based scaffold properties. *J Biomed Mater Res A*. 2016;104(6):1462-1468.
91. Marinucci L, Lilli C, Guerra M, et al. Biocompatibility of collagen membranes crosslinked with glutaraldehyde or diphenylphosphoryl azide: an in vitro study. *J Biomed Mater Res Part A Off J Soc Biomater Japan Soc Biomater Aus Soc Biomater Korean Soc Biomater*. 2003;67(2):504-509.
92. Che X, Nuhn J, Schneider I, Que L. High throughput studies of cell migration in 3D microtissues fabricated by a droplet microfluidic chip. *Micromachines*. 2016;7(5):84.
93. McCarty William J., Prodanov Ljupcho, Bale Shyam Sundhar, Bhushan Abhinav, Jindal Rohit, Yarmush Martin L., Usta O. Berk (2015). Layer-by-layer Collagen Deposition in Microfluidic Devices for Microtissue Stabilization. *Journal of Visualized Experiments*, (103), 1–9. http://dx.doi.org/10.3791/53078
94. Verbridge SS, Chakrabarti A, DelNero P, et al. Physicochemical regulation of endothelial sprouting in a 3D microfluidic angiogenesis model. *J Biomed Mater Res A*. 2013;101(10):2948-2956.
95. Odawara A, Gotoh M, Suzuki I. A three-dimensional neuronal culture technique that controls the direction of neurite elongation and the position of soma to mimic the layered structure of the brain. *RSC Adv*. 2013;3(45):23620-23630.
96. Musah S, Dimitrakakis N, Camacho DM, Church GM, Ingber DE. Directed differentiation of human induced pluripotent stem cells into mature kidney podocytes and establishment of a glomerulus Chip. *Nat Protoc*. 2018;13(7):1662-1685.
97. Park T-E, Mustafaoglu N, Herland A, et al. Hypoxia-enhanced blood-brain barrier Chip recapitulates human barrier function and shuttling of drugs and antibodies. *Nat Commun*. 2019;10(1):1-12.
98. Schweinlin M, Wilhelm S, Schwedhelm I, et al. Development of an advanced primary human in vitro model of the small intestine. *Tissue Eng Part C Methods*. 2016;22(9):873-883.
99. Hassan S, Heinrich M, Cecen B, Prakash J, Zhang YS. Biomaterials for on-chip organ systems. *Biomaterials for on-Chip Organ Systems. Biomaterials for Organ and Tissue Regeneration*. Elsevier; 2020:669-707.
100. Naahidi S, Jafari M, Logan M, et al. Biocompatibility of hydrogel-based scaffolds for tissue engineering applications. *Biotechnol Adv*. 2017;35(5):530-544.
101. Kim S, Shah SB, Graney PL, Singh A. Multiscale engineering of immune cells and lymphoid organs. *Nat Rev Mater*. 2019;4(6):355-378.
102. Sharifi F, Htwe SS, Righi M, et al. A foreign body response-on-a-Chip platform. *Adv Healthc Mater*. 2019;8(4):1801425.
103. Xiao S, Zhao T, Wang J, et al. Gelatin methacrylate (GelMA)-based hydrogels for cell transplantation: an effective strategy for tissue engineering. *Stem Cell Rev Reports*. 2019;15(5):664-679.
104. Lasli S, Kim HJ, Lee K, et al. A human liver-on-a-Chip platform for modeling nonalcoholic fatty liver disease. *Adv Biosys*. 2019;3(8):1900104.
105. Fu F, Shang L, Chen Z, Yu Y, Zhao Y. Bioinspired living structural color hydrogels. *Science Robotics*, 2018;3(16):1-8. http://dx.doi.org/10.1126/scirobotics.aar8580
106. Li L, Chen Z, Shao C, Sun L, Sun L, Zhao Y. Graphene hybrid anisotropic structural color film for Cardiomyocytes' monitoring. *Adv Funct Mater*. 2020;30(3):1906353.
107. Shirahama H, Lee BH, Tan LP, Cho N-J. Precise tuning of facile one-pot gelatin methacryloyl (GelMA) synthesis. *Sci Rep*. 2016;6(1):1-11.
108. Tathe A, Ghodke M, Nikalje AP. A brief review: biomaterials and their application. *Int J Pharm Pharmaceutic Sci*. 2010;2(4):19-23.
109. Song R, Murphy M, Li C, Ting K, Soo C, Zheng Z. Current development of biodegradable polymeric materials for biomedical applications. *Drug des Devel Ther*. 2018;12:3117-3145.
110. Majedi FS, Hasani-Sadrabadi MM, Emami SH, et al. Microfluidic assisted self-assembly of chitosan based nanoparticles as drug delivery agents. *Lab Chip*. 2013;13(2):204-207.
111. Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC. Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. *Adv Drug Deliv Rev*. 2014;66:2-25.
112. Chiesa E, Dorati R, Pisani S, et al. The microfluidic technique and the manufacturing of polysaccharide nanoparticles. *Pharmaceutics*. 2018;10(4):267.
113. Dumitriu S. *Polysaccharides: Structural Diversity and Functional Versatility*. CRC press; 2004.
114. Miao T, Wang J, Zeng Y, Liu G, Chen X. Polysaccharide-based controlled release systems for therapeutics delivery and tissue engineering: from bench to bedside. *Adv Sci*. 2018;5(4):1700513.
115. Guo MQ, Hu X, Wang C, Ai L. Polysaccharides: structure and solubility. *Solubility Polysacchar*. 2017;7-21.
116. Caetano LA, Almeida AJ, Gonçalves L. Effect of experimental parameters on alginate/chitosan microparticles for BCG encapsulation. *Mar Drugs*. 2016;14(5):90.
117. Mohammed ASA, Naveed M, Jost N. Polysaccharides; classification, chemical properties, and future perspective applications in fields of pharmacology and biological medicine (a review of current applications and upcoming potentialities). *J Polym Environ*. 2021;29:1-13.
118. Barclay TG, Day CM, Petrovsky N, Garg S. Review of polysaccharide particle-based functional drug delivery. *Carbohydr Polym*. 2019;221:94-112.
119. Sood A, Gupta A, Agrawal G. Recent advances in polysaccharides based biomaterials for drug delivery and tissue engineering applications. *Carbohydr Polym Technol Appl*. 2021;2:100067.
120. Caló E, Khutoryanskiy VV. Biomedical applications of hydrogels: a review of patents and commercial products. *Eur Polym J*. 2015;65:252-267.
121. Wang W, Meng Q, Li Q, et al. Chitosan derivatives and their application in biomedicine. *Int J Mol Sci*. 2020;21(2):487.
122. Bakshi PS, Selvakumar D, Kadirvelu K, Kumar N. Chitosan as an environment friendly biomaterial–a review on recent modifications and applications. *Int J Biol Macromol*. 2020;150:1072-1083.
123. Majedi FS, Hasani-Sadrabadi MM, VanDersarl JJ, et al. On-chip fabrication of paclitaxel-loaded chitosan nanoparticles for cancer therapeutics. *Adv Funct Mater*. 2014;24(4):432-441.

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

124. Liu Y, Shi X-W, Kim E, et al. Chitosan to electroaddress biological components in lab-on-a-chip devices. *Carbohydr Polym*. 2011;84(2):704-708.
125. Shi XW, Yang X, Gaskell KJ, et al. Reagentless protein assembly triggered by localized electrical signals. *Adv Mater*. 2009;21(9):984-988.
126. Shi X-W, Qiu L, Nie Z, Xiao L, Payne GF, Du Y. Protein addressing on patterned microchip by coupling chitosan electrodeposition and 'electro-click'chemistry. *Biofabrication*. 2013;5(4):41001.
127. Wang JJ, Zeng ZW, Xiao RZ, et al. Recent advances of chitosan nanoparticles as drug carriers. *Int J Nanomedicine*. 2011;6:765.
128. Verhoef MJ, Rose M, White M, Balneaves L. Declining conventional cancer treatment and using complementary and alternative medicine: a problem or a challenge? *Current Oncology*. 2008;15-(Suppl 2):s101.
129. Quiñones JP, Peniche H, Peniche C. Chitosan based self-assembled nanoparticles in drug delivery. *Polymers*. 2018;10(3):235.
130. Yang Z. Antimicrobial compounds and extracellular polysaccharides produced by lactic acid bacteria: their structures and properties. 2000.
131. Patel A, Prajapat J. Food and health applications of exopolysaccharides produced by lactic acid bacteria. *Adv Dairy Res*. 2013;01:1-8.
132. Yu L, Li CM, Liu Y, Gao J, Wang W, Gan Y. Flow-through functionalized PDMS microfluidic channels with dextran derivative for ELISAs. *Lab Chip*. 2009;9(9):1243-1247.
133. Arora A, Simone G, Salieb-Beugelaar GB, Kim JT, Manz A. Latest developments in micro total analysis systems. *Anal Chem*. 2010;82(12):4830-4847.
134. Chan AS, Danquah MK, Agyei D, Hartley PG, Zhu Y. A simple microfluidic chip design for fundamental bioseparation. *J Analytic Method Chem*. 2014;2014:1-6.
135. Ramón-Lozano C, Dessalles C, Babataheri A, Barakat A. Assessment of the permeability of a microvessel-on-chip to small and large molecules. *Comput Methods Biomech Biomed Engin*. 2020;23(sup1):S250-S252.
136. Perestrelo AR, Águas AC, Rainer A, Forte G. Microfluidic organ/body-on-a-chip devices at the convergence of biology and microengineering. *Sensors*. 2015;15(12):31142-31170.
137. Boso D, Maghin E, Carraro E, Giagante M, Pavan P, Piccoli M. Extracellular matrix-derived hydrogels as biomaterial for different skeletal muscle tissue replacements. *Materials*. 2020;13(11):2483.
138. Sanderson G. Polysaccharides in foods. 1981.
139. Lu F, Liu D, Ye X, Wei Y, Liu F. Alginate–calcium coating incorporating nisin and EDTA maintains the quality of fresh northern snakehead (Channa argus) fillets stored at 4 C. *J Sci Food Agric*. 2009;89(5):848-854.
140. Liechty WB, Kryscio DR, Slaughter BV, Peppas NA. Polymers for drug delivery systems. *Ann Rev Chem Biomol Eng*. 2010;1:149-173.
141. Rastin H, Ormsby RT, Atkins GJ, Losic D. 3D bioprinting of methylcellulose/gelatin-Methacryloyl (MC/GelMA) bioink with high shape integrity. *ACS Applied Bio Materials*. 2020;3(3):1815-1826.
142. Håti AG, Bassett DC, Ribe JM, Sikorski P, Weitz DA, Stokke BT. Versatile, cell and chip friendly method to gel alginate in microfluidic devices. *Lab Chip*. 2016;16(19):3718-3727.
143. Geckil H, Xu F, Zhang X, Moon S, Demirci U. Engineering hydrogels as extracellular matrix mimics. *Nanomedicine*. 2010;5(3):469-484.
144. Pajoumshariati SR, Azizi M, Wesner D, Miller PG, Shuler ML, Abbaspourrad A. Microfluidic-based cell-embedded microgels using nonfluorinated oil as a model for the gastrointestinal niche. *ACS Appl Mater Interfaces*. 2018;10(11):9235-9246.
145. Park JY, Jang J, Kang H-W. 3D bioprinting and its application to organ-on-a-chip. *Microelectron Eng*. 2018;200:1-11.
146. Ouyang L, Highley CB, Rodell CB, Sun W, Burdick JA. 3D printing of shear-thinning hyaluronic acid hydrogels with secondary cross-linking. *ACS Biomater Sci Eng*. 2016;2(10):1743-1751.
147. Kim K, Jeon HM, Choi KC, Sung GY. Testing the effectiveness of Curcuma longa leaf extract on a skin equivalent using a Pumpless skin-on-a-Chip model. *Int J Mol Sci*. 2020;21(11):3898.
148. Agrawal G, Aung A, Varghese S. Skeletal muscle-on-a-chip: an in vitro model to evaluate tissue formation and injury. *Lab Chip*. 2017;17(20):3447-3461.
149. Ouyang L, Highley CB, Sun W, Burdick JA. A generalizable strategy for the 3D bioprinting of hydrogels from nonviscous photo-crosslinkable inks. *Adv Mater*. 2017;29(8):1604983.
150. Moroni L, Burdick JA, Highley C, et al. Biofabrication strategies for 3D in vitro models and regenerative medicine. *Nat Rev Mater*. 2018;3(5):21-37.
151. Kolesky DB, Homan KA, Skylar-Scott MA, Lewis JA. Three-dimensional bioprinting of thick vascularized tissues. *Proc Natl Acad Sci U S A*. 2016;113(12):3179-3184.
152. Grottkau BE, Yang X, Zhang L, Ye L, Lin Y. Comparison of effects of mechanical stretching on osteogenic potential of ASCs and BMSCs. *Bone Research*. 2013;1(1):282-290.
153. Park YL, Park K, Cha JM. 3D-bioprinting strategies based on in situ bone-healing mechanism for vascularized bone tissue engineering. *Micromachines*. 2021;12(3):287.
154. Palumbo FS, Federico S, Pitarresi G, Fiorica C, Giammona G. Gellan gum-based delivery systems of therapeutic agents and cells. *Carbohydr Polym*. 2020;229:115430.
155. Robinson TM, Talebian S, Foroughi J, Yue Z, Fay CD, Wallace GG. Fabrication of aligned biomimetic Gellan gum-chitosan microstructures through 3D printed microfluidic channels and multiple in situ cross-linking mechanisms. *ACS Biomater Sci Eng*. 2020;6(6):3638-3648.
156. Xu Z, Li Z, Jiang S, Bratlie KM. Chemically modified Gellan gum hydrogels with tunable properties for use as tissue engineering scaffolds. *ACS Omega*. 2018;3(6):6998-7007.
157. Groll J, Burdick JA, Cho DW, et al. A definition of bioinks and their distinction from biomaterial inks. *Biofabrication*. 2018;11(1):13001.
158. Mouser VH, Melchels FP, Visser J, Dhert WJ, Gawlitta D, Malda J. Yield stress determines bioprintability of hydrogels based on gelatin-methacryloyl and gellan gum for cartilage bioprinting. *Biofabrication*. 2016;8(3):35003.
159. Wang F, Wen Y, Bai T. The composite hydrogels of polyvinyl alcohol–gellan gum-Ca2+ with improved network structure and mechanical property. *Mater Sci Eng C*. 2016;69:268-275.
160. Bajaj P, Schweller RM, Khademhosseini A, West JL, Bashir R. 3D biofabrication strategies for tissue engineering and regenerative medicine. *Annu Rev Biomed Eng*. 2014;16:247-276.
161. Wu D, Yu Y, Tan J, et al. 3D bioprinting of gellan gum and poly (ethylene glycol) diacrylate based hydrogels to produce human-scale constructs with high-fidelity. *Mater Des*. 2018;160:486-495.
162. Matsusaki M, Ikeguchi H, Kubo C, Sato H, Kuramochi Y, Takagi D. Fabrication of Perfusable pseudo blood vessels by controlling sol–gel transition of Gellan gum templates. *ACS Biomater Sci Eng*. 2019;5(11):5637-5643.
163. Shapiro L, Cohen S. Novel alginate sponges for cell culture and transplantation. *Biomaterials*. 1997;18(8):583-590.
164. Kim HJ, Park IK, Kim JH, Cho C-s, Kim MS. Gas foaming fabrication of porous biphasic calcium phosphate for bone regeneration. *Tissue Eng Regenerative Med*. 2012;9:63-68.
165. Villar G, Graham AD, Bayley H. A tissue-like printed material. *Science*. 2013;340(6128):48-52.
166. Li J, Chen M, Fan X, Zhou H. Recent advances in bioprinting techniques: approaches, applications and future prospects. *J Transl Med*. 2016;14(1):271.
167. Datta P, Dey M, Ataie Z, Unutmaz D, Ozbolat IT. 3D bioprinting for reconstituting the cancer microenvironment. *Npj Precision Oncol*. 2020;4(1):18.

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

168. Visser J, Peters B, Burger TJ, et al. Biofabrication of multi-material anatomically shaped tissue constructs. *Biofabrication*. 2013;5(3):35007.
169. Levato R, Visser J, Planell JA, Engel E, Malda J, Mateos-Timoneda MA. Biofabrication of tissue constructs by 3D bioprinting of cell-laden microcarriers. *Biofabrication*. 2014;6(3):35020.
170. Vieira S, da Silva MA, Garet E, et al. Self-mineralizing ca-enriched methacrylated gellan gum beads for bone tissue engineering. *Acta Biomater*. 2019;93:74-85.
171. Ferris C, Gilmore K, Beirne S, McCallum D, Wallace G. Bio-ink for inkjet printing of living cells. 2013.
172. Lozano R, Stevens L, Thompson BC, et al. 3D printing of layered brain-like structures using peptide modified gellan gum substrates. *Biomaterials*. 2015;67:264-273.
173. Miri AK, Nieto D, Iglesias L, et al. Microfluidics-enabled multimaterial maskless stereolithographic bioprinting. *Adv Mater*. 2018;30(27):1800242.
174. Homayun B, Lin X, Choi H-J. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. *Pharmaceutics*. 2019;11(3):129.
175. Kamaly N, Yameen B, Wu J, Farokhzad OC. Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release. *Chem Rev*. 2016;116(4):2602-2663.
176. Nguyen N-T, Shaegh SAM, Kashaninejad N, Phan D-T. Design, fabrication and characterization of drug delivery systems based on lab-on-a-chip technology. *Adv Drug Deliv Rev*. 2013;65(11–12):1403-1419.
177. Yang C-H, Wang L-S, Chen S-Y, et al. Microfluidic assisted synthesis of silver nanoparticle–chitosan composite microparticles for antibacterial applications. *Int J Pharm*. 2016;510(2):493-500.
178. Jo YK, Lee D. Biopolymer microparticles prepared by microfluidics for biomedical applications. *Small*. 2020;16(9):1903736.
179. Fischer KM, Scott TE, Browe DP, et al. Hydrogels for Skeletal Muscle Regeneration. *Regenerative Eng Trans Med*. 2020;7:1-9.
180. Cao X, Ashfaq R, Cheng F, et al. A tumor-on-a-chip system with bioprinted blood and lymphatic vessel pair. *Adv Funct Mater*. 2019;29(31):1807173.
181. Dewhirst MW, Secomb TW. Transport of drugs from blood vessels to tumour tissue. *Nat Rev Cancer*. 2017;17(12):738-750.
182. Gu Z, Fu J, Lin H, He Y. Development of 3D bioprinting: from printing methods to biomedical applications. *Asian J Pharmaceut Sci*. 2019;15:529-557.
183. Zhu W, Qu X, Zhu J, et al. Direct 3D bioprinting of prevascularized tissue constructs with complex microarchitecture. *Biomaterials*. 2017;124:106-115.
184. Gao S, Tang G, Hua D, et al. Stimuli-responsive bio-based polymeric systems and their applications. *J Mater Chem B*. 2019;7(5):709-729.
185. Esch EW, Bahinski A, Huh D. Organs-on-chips at the frontiers of drug discovery. *Nat Rev Drug Discov*. 2015;14(4):248-260.
186. Balijepalli A, Sivaramakrishan V. Organs-on-chips: research and commercial perspectives. *Drug Discov Today*. 2017;22(2):397-403.
187. Wang K, Man K, Liu J, et al. Microphysiological systems: design, fabrication and applications. *ACS Biomater Sci Eng*. 2020;6:3231-3257.

How to cite this article: Cecen B, Bal-Ozturk A, Yasayan G, et al. Selection of natural biomaterials for micro-tissue and organ-on-chip models. *J Biomed Mater Res*. 2022;110(5):1147-1165. doi:10.1002/jbm.a.37353

15524965, 2022, 5, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.37353 by Marmara University, Wiley Online Library on [14/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License