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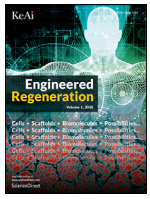

Biomedical applications of gelatin methacryloyl hydrogels

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ABSTRACT

Gelatin methacryloyl (GelMA) has attracted the widespread interest of researchers because of its excellent biocompatibility, biodegradability, and moldability. Various structures have been constructed from GelMA hydrogel, including 3D scaffold, injectable gel, bio-printed scaffold, and electrospun fibrous membrane via precise fabrication methods such as light-induced crosslinking, extrusion 3D printing, electrospinning, or microfluidics. Due to its unique characteristics and simple preparation, GelMA hydrogel demonstrates superior performance and promising potential in a broad range of biomedical applications involving wound healing, drug delivery, biosensing, and tissue regeneration. This review integrates sufficient research works on GelMA hydrogels in the regeneration of tissues such as skin, tendon, bone, cartilage, blood vessel, and cardiovascular system, in addition to applications in drug delivery, organ-on-a-chip, and biosensing, providing a critical review of present work and offering future implications.

1. Introduction

Hydrogels are hydrophilic polymers with three-dimensional (3D) architecture that could absorb and swell in an aqueous solution without dissolution [1,2]. They possess porous structures similar to the extracellular matrix (ECM), which allow for efficient exchange of nutrients and wastes, and have a positive effect on the adhesion, proliferation, migration, and differentiation of various cells such as keratinocytes [3], fibroblasts [4], and mesenchymal stem cells [5]. In addition to the outstanding application of hydrogels for 3D culturing of cells, their tunable properties, both physically and biochemically, designate hydrogels a promising candidate for artificial tissue scaffolds ranging from soft tissues like blood vessels to hard tissues such as bone and cartilage. By blending polymers into physically mixed hybrid materials or chemically combined co-polymers, these materials could possess the advantages of good biocompatibility and mechanical performance. Notably, chemically combined co-polymers have advantages in their mechanical properties over the physically mixed ones and can achieve more complex functions such as the phased release of loaded cargoes, adjustable degradation properties, and cell loading capacity. These properties could be tuned by adjusting the ratio between synthetic and natural components: synthetic polymers have better mechanical properties than natural polymers, whereas natural polymers are preferable to cells [6]. This is because most synthetic polymers have concise repeating units, which contributes to a higher degree of polymerization. Conversely, natural polymers have longer and more complex polymer chains with various functional groups for promoting adhesion of cells and are degradable by enzymes. The designable, water absorbable, biocompatible, and injectable characteristics of hydrogels endow such materials with great potential for tissue engineering, of which the controllable gelation of hydrogel precursors has been regarded as one of the essential characteristics. Photo-induced solidification is superior compared with other methods achieved by chemical reagents like glutaraldehyde because the residual components of the chemicals could affect the performances of cells, in most cases negatively [3].

GelMA, also called photo-crosslinkable gelatin, has been frequently used for biomedical applications because of its excellent biocompatibility, biodegradability, and moldability. GelMA was developed in 2000 by Van den Bulcke et al. [7] and has been optimized over two decades for more robust properties and applications [8]. It is often used to overcome the limitations of gelatin hydrogels: 1. basic gelatin is soluble at body temperature, limiting the direct application of it as a cell carrier; 2. while the solidification of gelatin could be achieved by glutaraldehyde, it is cytotoxic, time-consuming, and highly uncontrollable. Moreover, GelMA has been constructed as various forms of scaffolds based on its characteristics: 1. 3D scaffold. 2. injectable gel. 3. bio-printed scaffold (extrusion-based and photomask-based). 4. electrospun fibrous membrane (EFM) (**Fig. 1**). The 3D scaffold of GelMA can be constructed precisely by photo-crosslinking, during which the photo-crosslinkable functional groups on GelMA are crosslinked with other polymers [9], small organic molecules [10], and inorganic particles [11] to form a co-crosslinked network with reinforced mechanical properties and extra characteristics (e.g., better formability, biocompatibility) for tissue

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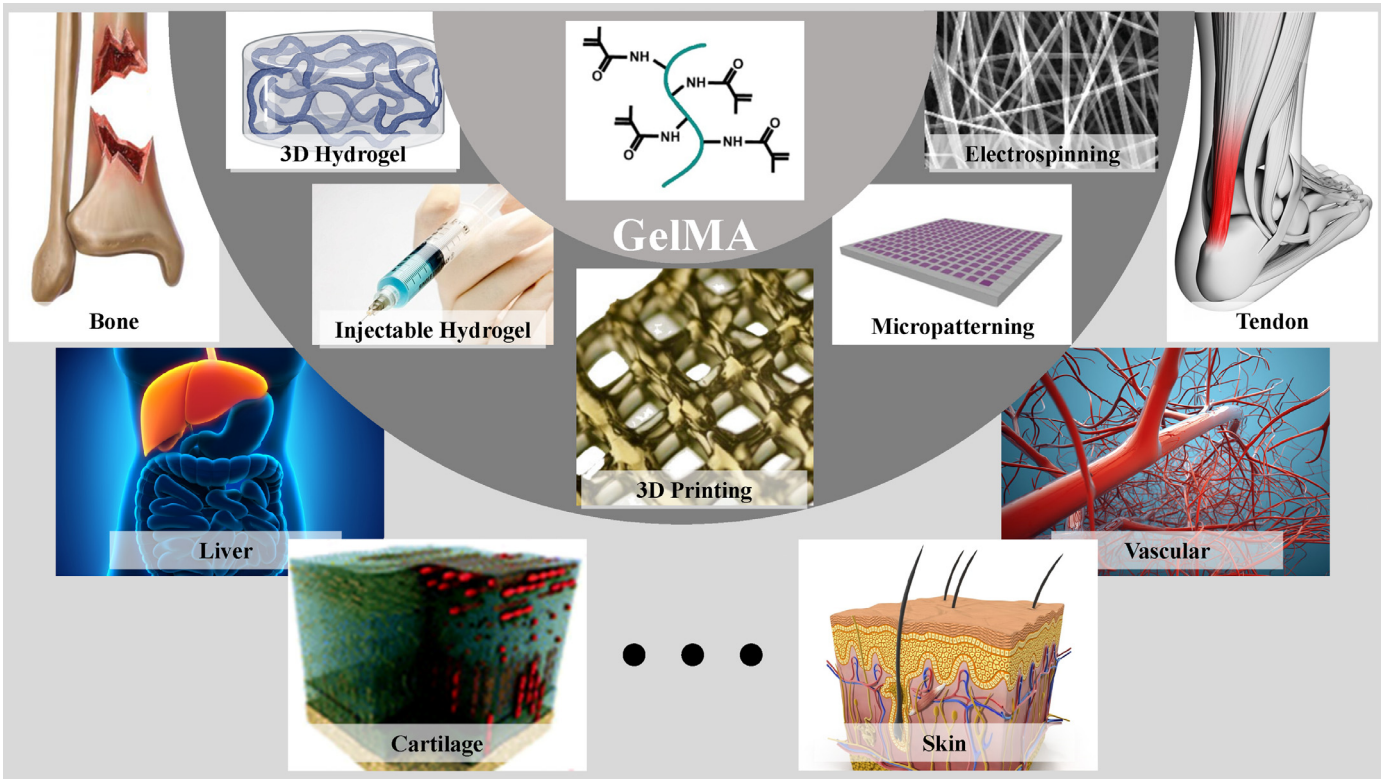

Fig. 1. Biomedical applications of GelMA hydrogel. GelMA designed as injectable hydrogels, 3D printed scaffold, electrospun fibrous membrane, and micropatterns for various tissues regeneration, such as bone, cartilage, tendon, vasculature, skin, and liver.

engineering. This can then be used for wound dressing [9], cartilage regeneration [12], and bone regeneration [11].

The low viscosity of GelMA solution and the rapid photo-crosslinkable features grant GelMA injectability of various unique properties such as minimal invasiveness and superior filling properties in irregular sites like bone defects [13] and ventricular wall wounds [14]. The gels can be injected to fill the defected area, then crosslinked by light to form a robust and complete scaffold. The shear-thinning ability of GelMA ensures smooth injection through the syringe. However, pre-crosslinked pure GelMA hydrogel can hardly serve as an injectable material due to the lack of self-healing ability to heal the covalent bond broken by large shear stress. Self-healing ability is also desired for some specific applications, such as structural color hydrogels, which need to bear cycling stress. Other polymers such as bovine serum albumin (BSA) hydrogel [15] and host-guest supramolecular system [16] are blended to endow GelMA hydrogel with self-healing properties.

In addition, the double solidification method extends the realm of GelMA application, making it a promising candidate as the bioink for extrusion bioprinting. The low temperature can help maintain the shape of the printed scaffold, and the rapid photo-crosslinking of GelMA hydrogel avoids the thermal expansion associated with heat-induced solidification and diffusion during other nonlight-based chemical solidification [12,17–19]. Lower precursor viscosity can reduce the extrusion pressure and possibly decrease the nozzle diameter, contributing to a higher printing resolution and precision. GelMA with higher crosslinking density is superior to lower ones on their printability and moldability, which are significant properties for 3D-printing bioinks [20]. Meanwhile, by using advanced dynamic patterning systems instead of photomasks or spacers [21], such as digital micro-mirror devices (DMD), bioprinting can also be achieved via microfluidic devices [22]. These bio-printed scaffolds are applied for drug delivery systems [19], tissue engineering scaffolds [12,17], and *in vitro* construction of various organs and tissues [22]. GelMA can be electrospun by placing a bio-printing system in an electric field to form a jet flow of polymers due to its high molecular weight. The nano-scale fiber endows the scaffolds a high surface-to-volume ratio to promote cell-material interactions and facilitate the exchange of nutrients and wastes [23]. Due to their ECM-mimetic architecture, the electrospun fibrous membranes have been applied to the engineering of various tissues, such as bone [24,25], cartilage [26], myocardium [27], skin [28], and nerve (**Fig. 1**) [29].

This mini-review article aims to provide a helicopter view of the status quo of the biomedical applications of GelMA hydrogels, with particular emphasis on the applications in tissue engineering, including wound healing, load-bearing tissue engineering, and other tissue engineering applications.

2. Synthesis of GelMA hydrogels

GelMA is developed from gelatin, the product of hydrolysis and collagen's denaturation at high temperatures. In brief, GelMA is synthesized by the substitution of lysine and hydroxyl lysine with methacrylic anhydride in an alkalic buffer solution such as phosphate-buffered saline (pH = 7.4) [8, 30] and carbonate-bicarbonate buffer [31]. The reaction is achieved by adding methacrylic anhydride (MA) dropwise into a gelatin/buffer solution under vigorous stirring. Residual MA, as well as accompanied methacrylic acids, is removed by dialysis for over 5 days. Foam-like GelMA is obtained after freeze-drying.

GelMA retains the biochemical functions of gelatin, including superior biocompatibility and enzymatic degradability since the functional amine groups of the arginine-glycine-aspartic acid (RGD) peptide and matrix metalloproteinase (MMP) degradable peptide are uninfluenced during methacrylate coupling. GelMA possesses both reversible and non-reversible solidification processes attributed to the gelatin backbone and the introduced photo-crosslinkable functional groups. Reversible solidification, inherited from gelatin, occurs due to the temperature-dependent solid-liquid transition. In contrast, non-reversible photo-

crosslinking occurs at the presence of a photo-initiator (e.g., Irgacure 2959 or Lithium phenyl-2,4,6-trimethylbenzoylphosphinate) and the irritation of visible or ultraviolet (UV) light matching the photo-initiator. The crucial parameter for controlling mechanical property, water retention, and degradability of GelMA is the amount of carbon double bonds substituted with MA in a single GelMA molecule, also known as the degree of substitution (DS). In PBS solution ($7 < pH < 8$), the DS range from 5.7% to 76.0% with increasing amounts of MA up to 1.0 mL/g (MA/GelMA) [32]. The use of carbonate-bicarbonate buffer at higher pH ($8 < pH < 11$) raises the DS to over 95% despite using only one-tenth of the amount of MA in PBS [31,33]. The effects of DS on the properties of GelMA have been thoroughly mapped: GelMA with higher DS possess higher Young's modulus, longer degradation period, and the lower swelling ratio [4, 34]. The concise one-step fabrication and controllable structures of GelMA provide wide and designable applications in biomedical fields.

3. Biomedical applications

GelMA plays an important role in the biomedical field due to its great biocompatibility and tunable physicochemical properties. It is widely used in tissue engineering for regeneration. GelMA has been applied in different forms, such as a 3D hydrogel, electrospun fibrous membranes, 3D printed scaffolds, etc. These kinds of scaffolds, when incorporated in other polymers, growth factors, and small molecule drugs, can meet the requirement of engineering repairs for skin [2–4], tendon [35–37], bone [5,38–40], cartilage [36,41–43], vasculature [44–47], etc. Meanwhile, depending on the adjustable biodegradability, swelling, mechanical, and crosslinking property, GelMA can be used for drug delivery [48–51]. Furthermore, the high-performance biofabrication and biocompatibility of GelMA make it a promising raw material for organ-on-chip [52–55]. In addition to these applications, modified GelMA can be used for the fabrication of food analysis tools [56,57]. With more features of GelMA being discovered, more GelMA applications and products will certainly flourish in the future.

3.1. Tissue engineering

3.1.1. Skin regeneration

GelMA hydrogels with similarity to natural dermal ECM and controllable mechanical and degradation properties can serve as a bulk material of wound dressings. Compared with other hydrogels like collagen, GelMA could achieve greater biocompatibility and better mechanical and degradation properties by varying the degree of substitution. In one study, Zhao et al. have shown that GelMA scaffolds can support the formation of the multi-layered epidermis and growth of keratinocytes into functional multi-layered epidermis-type tissue [3]. This group further used GelMA hydrogels to build a 3D, fully cellularized ECM-mimetic scaffold to accelerate wound healing. These scaffolds were made by electrospinning and can form cutaneous tissues within two weeks in a rat full-thickness skin wound healing model (**Fig. 2A**) [2] and accelerate the vascularization for the treatment of distal necrosis of random skin flap [4]. In another study, Zhou et al. devised GelMA-based intelligent, responsive wound dressing vesicle systems that respond to the simple color change in the microenvironment to kill or inhibit bacteria such as *methicillin resistant S. aureus* and *P. aeruginosa* with a visual warning of infection [58]. In a recent contribution, Jahan et al. have shown that Ag-nanoparticle entrapped GelMA scaffolds can accelerate wound healing, especially the deep dermal wounds. These scaffolds promote fibroblast migration and minimize the microbial infections when used as wound dressing [59].

3.1.2. Tendon regeneration

Tendons play the role of connecting the muscle and bone, enabling the former to maneuver the latter quickly and efficiently. Due to the tendons' load-bearing nature, they are prone to rupture and laceration [35]. To imbue GelMA hydrogels with appropriate properties to meet the vigorous mechanical and biological requirements for tendon regeneration, Visser et al. put forward a highly organized and high-porosity GelMA composite microfibre network using 3D printing to improve the mechanical and biological properties. The stiffness and elasticity of this composite scaffold are similar to the native tissue, bestowing the constructs with biological and mechanical compatibility [36]. Yang et al. synthesized a GelMA/poly-ε-caprolactone (PCL) composite scaffold by dual electrospinning. These multilayer-structures mimic the native structure of tendon tissue, and the cells encapsulated within these scaffolds remained responsive to topographical cues and exogenous tenogenic factors (**Fig. 2B**) [37]. For improvement of GelMA based composite scaffolds, Deepthi et al. used aligned poly-L-lactide (PLLA) fiber bundles to mimic the native glycosaminoglycans of sheath ECM for tendon regeneration, then coated it with GelMA and alginate gel to prevent the adhesion of tendon. The alginate-coated outer layer of the scaffolds showed lower protein adsorption, which could prevent the tendon sheath from proliferation. Meanwhile, tenocytes exhibited suitable attachment and spreading on the inside layer of the scaffolds. These results showed that the GelMA based PLLA scaffolds are ideal for tendon regeneration and preventing tendon adhesion [60]. In recent research, Rinoldi et al. used GelMA and alginate as bioinks to fabricate a tendon-mimetic scaffold that emulates the morphology and structure of native tendon tissues. Such scaffold provides mechanical stretching and aligned orientation recapitulating the real tendon. With the addition of bone morphogenetic protein (BMP)−12, the scaffold effectively promotes stem cell differentiation, aligns cell orientation, and enhances collagen expression, demonstrating great potential in tissue engineering for tendon regeneration. [61].

3.1.3. Bone regeneration

For stem cell-assisted bone regeneration, mechanical shear forces will cause low cell retention and damage the membrane of cells during the injection. Another complication is the lack of a 3D structure to support the transplantation, viability, and different functions of the injected cells [38]. To solve these problems, Zhao et al. proposed a strategy that entrapped BMSCs and growth factors in GelMA microspheres using microfluidics-assisted technology (**Fig. 3A**) [5]. This research demonstrated that GelMA microspheres could support the survival, proliferation, and migration as well as osteogenic differentiation of BMSCs. These GelMA microspheres can also support the release of BMP-2 and promote the formation of bone. In another study, Celikkin et al. explored the effect of GelMA concentration on scaffold mineralization in the presence of BMSCs. The authors demonstrated that 5% GelMA concentration has higher and more homogenous calcification than 10% as the softer substrates promoted MSC attachment on the scaffolds [40]. To further improve GelMA degradation and mechanical properties, Wang et al. incorporated photo-crosslinked poly (ethylene glycol) diacrylate (PEGDA) into GelMA. By controlling the ratio of GelMA and PEGDA, GelMA 30%/PEGDA 5% (w/v) hydrogel maintained its shape for more than four weeks, whereas pure GelMA hydrogel has been completely degraded [39]. Kwon et al. developed GelMA/bioglass nanoparticles and proved that the bioglass-laden GelMA cryogels were useful for bone healing. These cryogels can induce osteogenic differentiation of human turbinate mesenchymal stromal cells (hTMSCs) and have strong mechanical strength. The 2.5 w/w% bioglass nanoparticles incorporated in GelMA induced the best bone formation both *in vitro* and *in vivo* [62]. In recent research, Liu et al. produced biomimetic CaPs/GelMA composite nanofibers by electrospinning promoting angiogenesis and osteogenesis. This structure has good mechanical properties, favorable biocompatibility, and excellent cytocompatibility. They also found that CaPs promote the osteogenic differentiation of MC3T3-E1 cells and angiogenesis of human umbilical vein endothelial cells (HUVECs) [63]. To sum up, by incorporating the GelMA with different growth factors, the combination of polymer and organic components can make this hydrogel a potential candidate for bone tissue engineering.

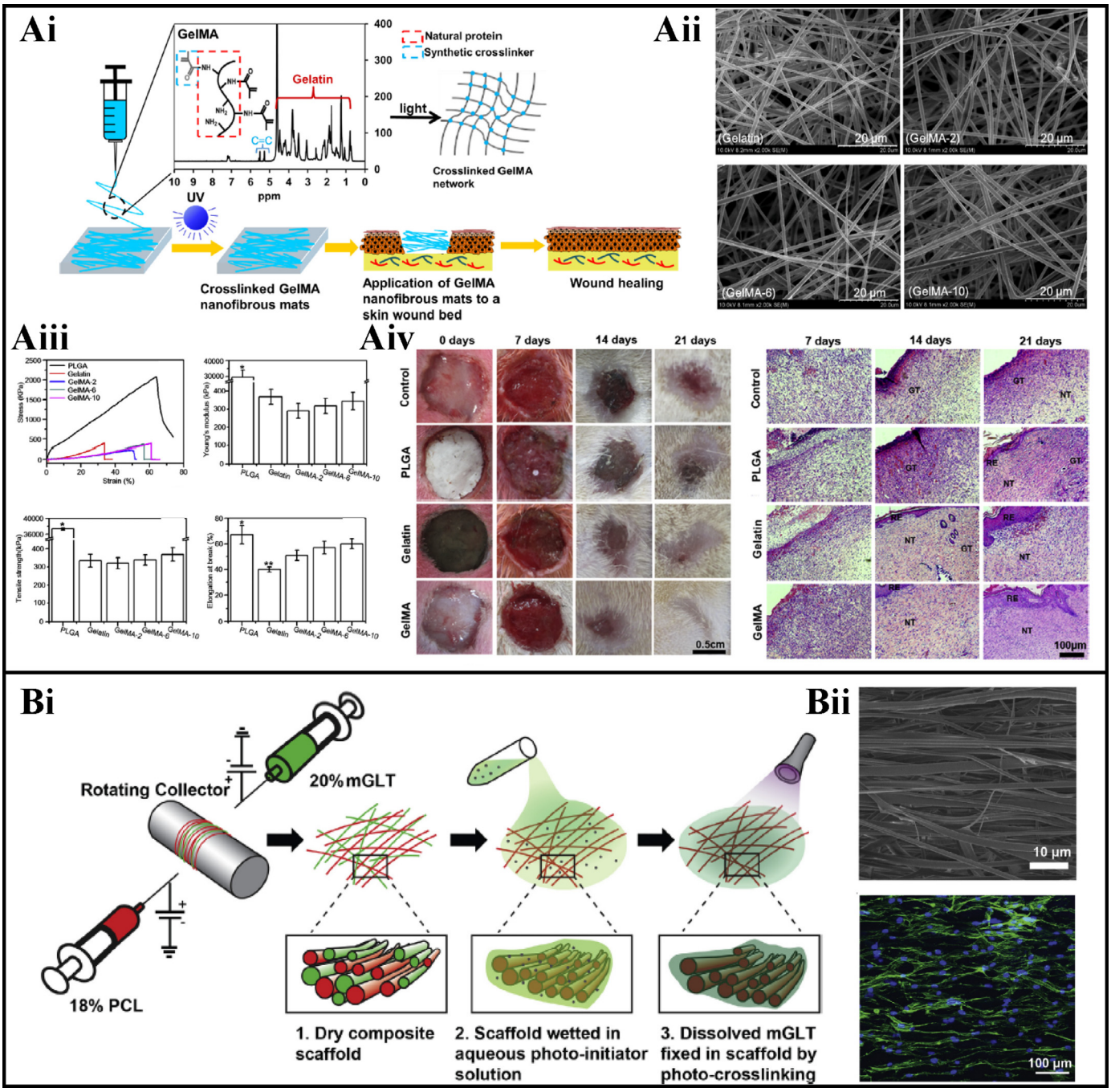

Fig. 2. A. Construction of electrospun GelMA membrane for wound healing. (Ai) Schematic showing the fabrication and application into a wound bed. (Aii) SEM images showing the morphology of electrospun GelMA scaffolds. (Aiii) Mechanical properties of engineered PLGA, gelatin, and GelMA fibers. (Aiv) *In vivo* wound healing using different electrospun scaffolds. Images reproduced from ref. [23] with permission from Elsevier. B. Construction of PCL and GelMA as a 3D biomimetic scaffold. (Bi) Schematic showing the preparation of composite scaffold. (Bii) Formation of tendon-like features on the multi-layered electrospun scaffold. Images reproduced from ref. [37] with permission from Elsevier . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.1.4. Cartilage regeneration

GelMA hydrogels have also been widely used for cartilage regeneration based on their adjustable mechanical properties, which could simulate the natural cartilage matrix. Meanwhile, the excellent biocompatibility of GelMA allows for stem cell adhesion, proliferation, and chondrogenic differentiation. In one study, Visser et al. proposed an endochondral bone regeneration system by combining the GelMA, MSCs, and cartilage-derived matrix (CDM) particles, which could provide MSCs with a high diffusion rate and facilitate matrix formation. They found that the presence of CMD could enhance the mineralized bone, which surrounded hypertrophic cartilage clusters *in vivo*. This result indicates that relevant-size endochondral bone constructs could be formed in the GelMA hydrogel system [41]. To increase the mechanical properties of GelMA, the same team used melt electrospinning to fabricate GelMA/PCL microfibrous network, whose stiffness exhibited a 54-fold increase and showed similar stiffness and elasticity with articular cartilage tissue (**Fig. 3B**) [36]. For composite structure design, Han et al. fabricated a GelMA/polyacrylamide (PAM) biohybrid hydro-

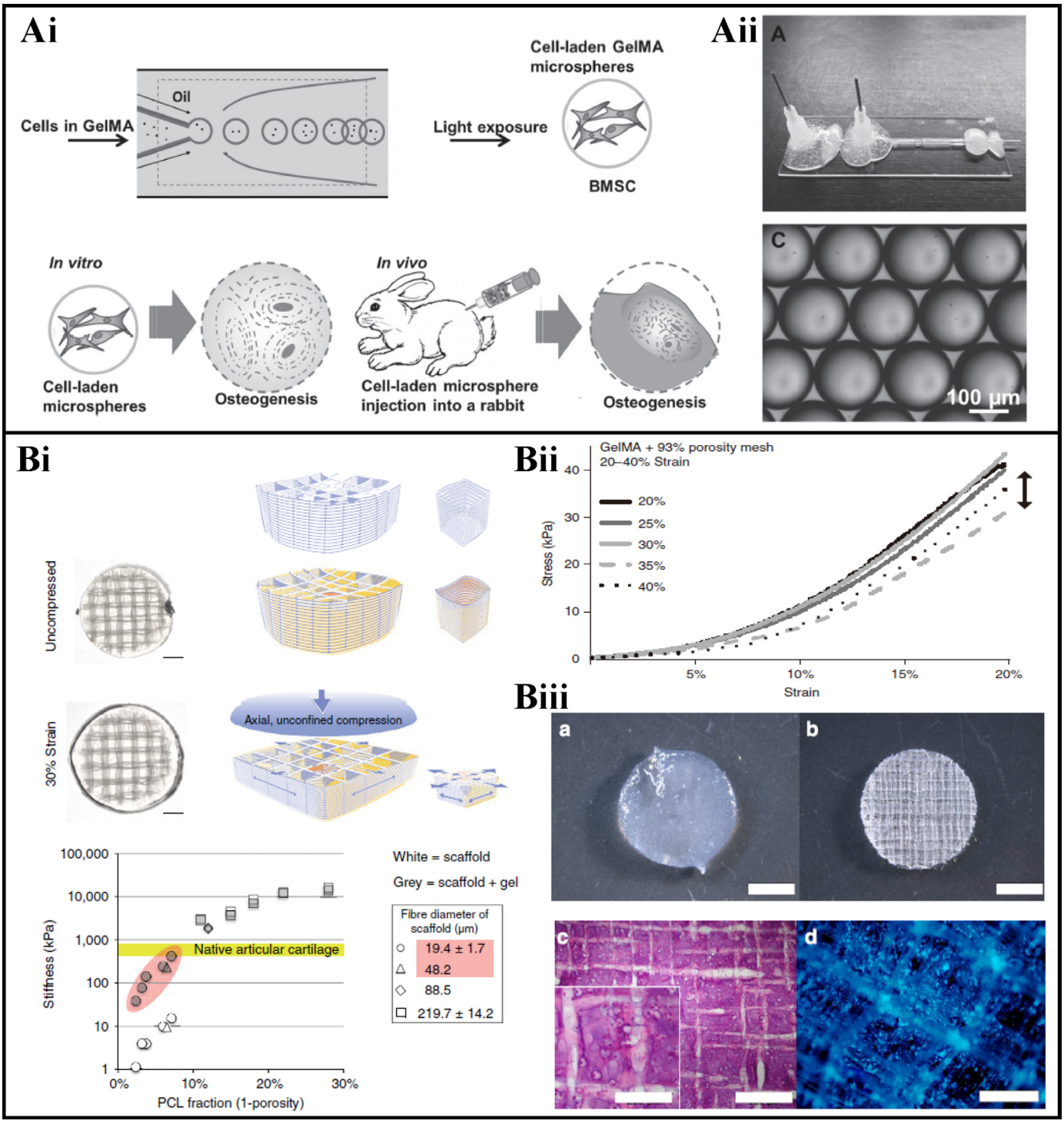

Fig. 3. A. Construction of cell-laden microspheres for bone regeneration. (Ai) Schematic of BMSC-laden GelMA microspheres and their application *in vivo* osteogenic differentiation. (Aii) Fabrication of GelMA microspheres by microfluidic device and the morphology of the GelMA droplet. Images reproduced from ref. [5] with permission from Wiley. B. Construction of 3D printing PCL and GelMA composite scaffolds for cartilage regeneration. (Bi) The mechanism of hydrogel reinforcement with organized high-porosity scaffolds and the mechanical property of scaffold/gel composites compared with native articular cartilage. (Bii) The compressive force for PCL/GelMA scaffolds under different strains (20% to 40%). (Biii) Microscopy images of PCL/GelMA gel scaffold and the Haematoxylin/eosin (H&E) and DAPI staining of the chondrocytes seeded on scaffolds. Images reproduced from ref. [36] . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

gel. Compression strength, elasticity, degradation rate, and release of growth factors were all improved in this hydrogel. The *in vitro* and *in vivo* experiments of this biohybrid hydrogel showed that it could maintain chondrocytes' phenotype while transforming growth factor beta-2 (TGF-β2) loaded hydrogel can repair the defect for cartilage [42].

To overcome the poor mechanical properties and brittleness of GelMA, Gan et al. incorporated ODMA into the chain of GelMA. The addition of ODMA reduces the density of GelMA chains and adds sacrificial physical crosslinking into the hydrogel, which makes this scaffold tough and resilient. Also, the catechol groups of ODMA provide this scaffold with

a high affinity for cells. This novel scaffold is more suitable for cartilage regeneration than the traditional brittle hydrogel network due to its good biocompatibility and mechanical properties [43]. BMSCs' differentiation is also an important factor that should be considered. Chen et al. fabricated a GelMA-based poly (ethylene glycol) (PEG), gelatin, and heparin (PGH) multi-composite scaffold to guide chondrogenesis of BMSCs and maintain their cartilaginous phenotype. They demonstrated that PGH and GelMA hydrogels could regulate BMSC differentiation and regenerate cartilaginous interfacial tissues *in situ* [64]. Overall, the mechanical properties of the GelMA-based cartilage grafts should ideally be optimized to regulate BMSCs' differentiation.

3.1.5. Vascular regeneration

Current approaches in developing vascular networks are carried out using natural hydrogels. However, most natural hydrogels have poor mechanical properties. GelMA, with adjustable mechanical properties, has a wide range of applications to build the 3D vascular network. In one study, Chen et al. proved that GelMA hydrogels could support human progenitor cell-based vascular network formation. They also showed that the controllable physical properties of GelMA were adjusted by the degree of methacrylation, which can be used to tune the extent of vascular formation. GelMA containing 49.8% methacrytion possesses softer properties, which is more favorable for promoting vascular formation, compared with GelMA containing 73.2% methacrylation (**Fig. 4A**) [44]. Combining GelMA with drug release can further improve its vascular formation performance. For example, Chen et al. fabricated a GelMA hydrogel to provide a sustained and steady release of desferrioxamine. This hydrogel network provides an environment suitable for cell growth and upregulates the expression of HIF-1α, which is significant for blood vessel formation [45]. Due to the photo-crosslinkable and tunable rheological properties of GelMA, it can also act as a bioink to fabricate the complex and functional 3D vascular mimicking structure. For instance, Jia et al. used GelMA, sodium alginate, and poly (ethylene glycol)-tetraacrylate (PEGTA) as the bioink to 3D-print biologically relevant, highly organized, and perfusable vessels with significant potential in engineering large-scale vascularized tissue constructs [46]. Although bioprinting has made significant progress, the printing of multi-layered tubular tissues such as vessels remains a challenge. Pi et al. showed that the multichannel coaxial extrusion system (MCCES) that used GelMA, alginate, and 8-arm polyacrylate as bioink could bioprint multi-layered tubular tissues in only one single step [47]. Meanwhile, GelMA hydrogel with good hydrophilicity and natural cell-binding motifs could provide a suitable microenvironment for cell adhesion and proliferation. In addition to 3D printing technology, the combination of electrospinning and GelMA has many applications in vascular tissue engineering. Coimbra et al. made PCL/GelMA coaxial electrospun fibers to provide good mechanical properties and biocompatibility together. This kind of core/shear structure induced an increasing biological performance of the materials while interacting with blood with reduced hemolysis and thrombosis [65]. Hassanzadeh et al. formed a self-assembly GelMA hydrogel with a chitin nanofibrous system. This system can realize the coculture of HUVECs and hBMSCs in the self-assembled microstructures and enable these cells to adhere, proliferate, and align on the construct to finally form a stable vascular system [66]. Controllable physical properties enable GelMA to be fabricated into different forms of scaffolds, such as a hydrogel, 3D printed scaffold, electrospun fibers. The good biological performance of these scaffolds enables GelMA to have good application potential in vascular regeneration.

3.1.6. Other tissues

GelMA hydrogel is used for another tissue engineering, such as cardiovascular and neural engineering. Due to the limited electrical conductivity and mechanical property of cardiac biomaterials, Shin et al. designed a reduced graphene oxide-laden GelMA myocardial tissue constructs that showed stronger contractility and a faster rate of spontaneous beating. This structure provides a high-fidelity model for research on cardiovascular engineering [67]. In another study, Bejleri et al. bioprinted a customizable cardiac ECM hydrogel (cECM)-laden 3D patch using GelMA, human cardiac progenitor cell (hCPCs), and cECM as the bioink. The hCPCs in the bioink maintained over 75% viability, and the cardiogenic gene expression is increased by 30 folds in the cECM-incorporated GelMA compared with the pure one. This cardiac patch showed strong vascularization and presented the potential for improved differentiation and angiogenesis in cardiovascular healing (**Fig. 4B**) [55]. For neural tissue regeneration, Dursun et al. fabricated a nerve guide, which is an instrument bridging the proximal and distal ends of the injured nerve by hybridizing different ratios of GelMA hydrogel and poly (2-hydroxyethylmethacrylate) (pHEMA). They found that GelMA-pHEMA (5:5) with porosity (15–70%), pore size (10–35 μm), water content (42–92%), and mechanical strength (65–710 kPa) are suitable for Schwann cells' attachment and proliferation. The hybrid hydrogel, as the outer part of the nerve guide, displayed excellent nerve guiding ability for surrounding injured nerves [68]. Through modification with distinctive characteristics, combination with different compositions, and fabrication via novel techniques, GelMA-based material systems present a broader range of applications in tissue engineering.

3.2. Drug delivery

To acquire better tissue engineering functionality, drug delivery is often combined with hydrogel systems to improve drug delivery efficiency and reduce drug side effects. GelMA has been applied as a drug delivery vehicle in different forms. In one study, Serafim et al. fabricated GelMA/PAA hybrid hydrogels with porous structures. These scaffolds include controllable cell affinity, swelling ratio, mechanical properties, porosity, and biodegradability. Also, the ratio between GelMA and PAA could control the drug release kinetics. With the increase of GelMA ratio, the drug release is decreased due to increasing hydrogel crosslinking density. Adjusting different hydrogels' ratios is one of the effective strategies to control drug release [69]. GelMA hydrogels with chitosan microspheres (CM-SIN) were used by Chen et al. in osteoarthritis treatment. The sinomenium encapsulated by chitosan and GelMA hydrogel was delivered intra-articularly to activate autophagy and effectively ameliorate cartilage matrix degradation, implicating a promising strategy for treating osteoarthritis [48]. Moreover, GelMA can be fabricated as microparticle drug delivery systems. Li et al. developed a novel synergistic and sustained GelMA/poly (lactic-co-glycolic acid) (PLGA) microparticle drug delivery system using microfluidics technology. GelMA aqueous solution and PLGA oil solution are the raw materials of the microfluidic double emulsion templates. These microparticles could avoid the loaded drugs' burst release and extend the release time to longer than 500 h with the degradation of the biopolymer layer [49]. Microneedle is a novel technology for drug delivery. Luo et al. reported a controllable GelMA based microneedle (MN), which was used for doxorubicin (DOX) drug delivery. This microneedle effectively goes through the stratum corneum layer of rat skin. By adjusting the range of photo-crosslinking, the DOX release is controllable at specific sites. GelMA-based MN patch exhibits a gradual release of the loaded DOX, especially at higher crosslinking degrees (30 s and above) (**Fig. 5A**) [50]. Besides, Dong et al. achieved a simple, accurate, and consecutive fluorescence-based approach to monitoring the degradation of GelMA *in vivo* by the non-invasive tracking methods using up-conversion nanoparticles [51]. Overall, GelMA with proven biocompatibility can provide controllable drug release to achieve a safer and more efficient drug release.

3.3. Organ-on-a-chip

Organ-on-a-chip (OOAC) is a multi-functional cell culture chip that mimics the activities, mechanics, and physiological responses of the whole organs and organ systems. GelMA hydrogels can be considered

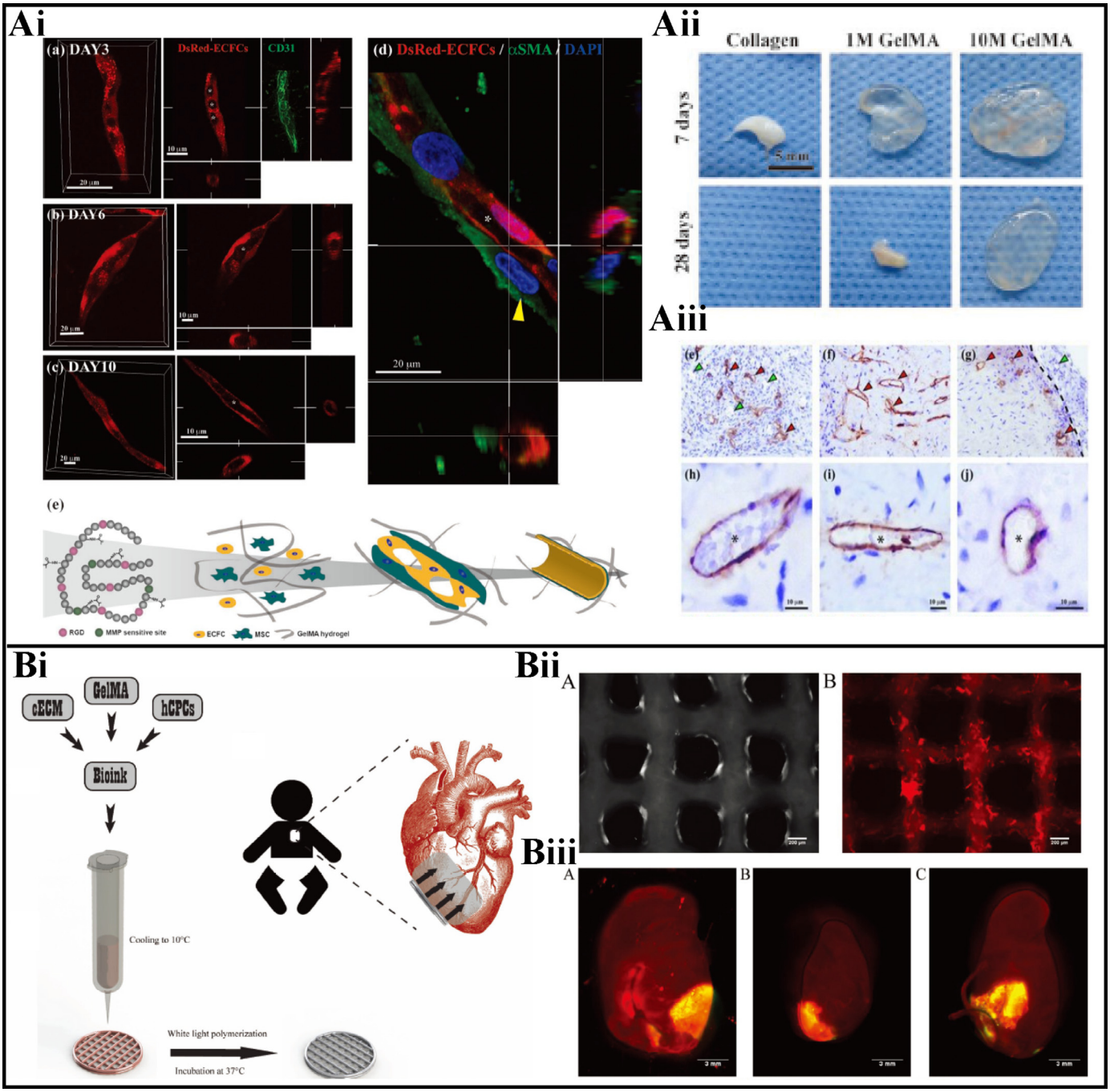

Fig. 4. A. Construction of 3D GelMA hydrogel for vascular regeneration. (Ai) Formation of blood-derived endothelial colony-forming cells in GelMA hydrogel. (Aii) Macroscopic views of explanted GelMA. (Aiii) Immunohistochemistry staining of the human CD31 (red arrowheads) in *vivo* formation of functional vascular networks. Images reproduced from ref. [44] with permission from Wiley. B. Construction of 3D printing hybrid GelMA cell-laden cardiac patch for heart repair. (Bi) Schematic of the preparation of hCPC, decellularized cECM, and GelMA 3D printing patch and the application. (Biii) *In vivo* patch retention with different implantation methods. Images reproduced from ref. [55] with permission from Wiley . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

raw materials for fabricating artificial organs [52]. The important contribution to the field is liver-on-a-chips, which can mimic the native liver microenvironment and contribute to drug testing, disease modeling, and tissue engineering *in vitro*. Recently, Wu et al. developed a liver support system by integrating GelMA and hepatocytes into a decellularized liver matrix. The system provides both a biomimetic environment and mechanical support for hepatic functions. The biomechanical support provided by GelMA ensures high engraftment of cells, which plays essential role in converting ammonia (ammonia concentration reduces by 45%) into urea and helps prevent hepatic encephalopathy [53]. Also, OOAC could be applied to study tumor disease development. Lu et al. developed a tumor-on-a-chip to mimic the tumor microenvironment (TME) by a microfluidics-based 3D dynamic culture system. They used the GelMA decellularized liver matrix (DLM) as the raw biomaterials. Under flow conditions, the cell viability is maintained, and the hepatocyte functions are also enhanced. Moreover, this tumor-on-a-chip is drug responsive to acetaminophen and sorafenib. Based on these results, this TME biomimetic tumor-on-a-chip has proved its potential for pathological

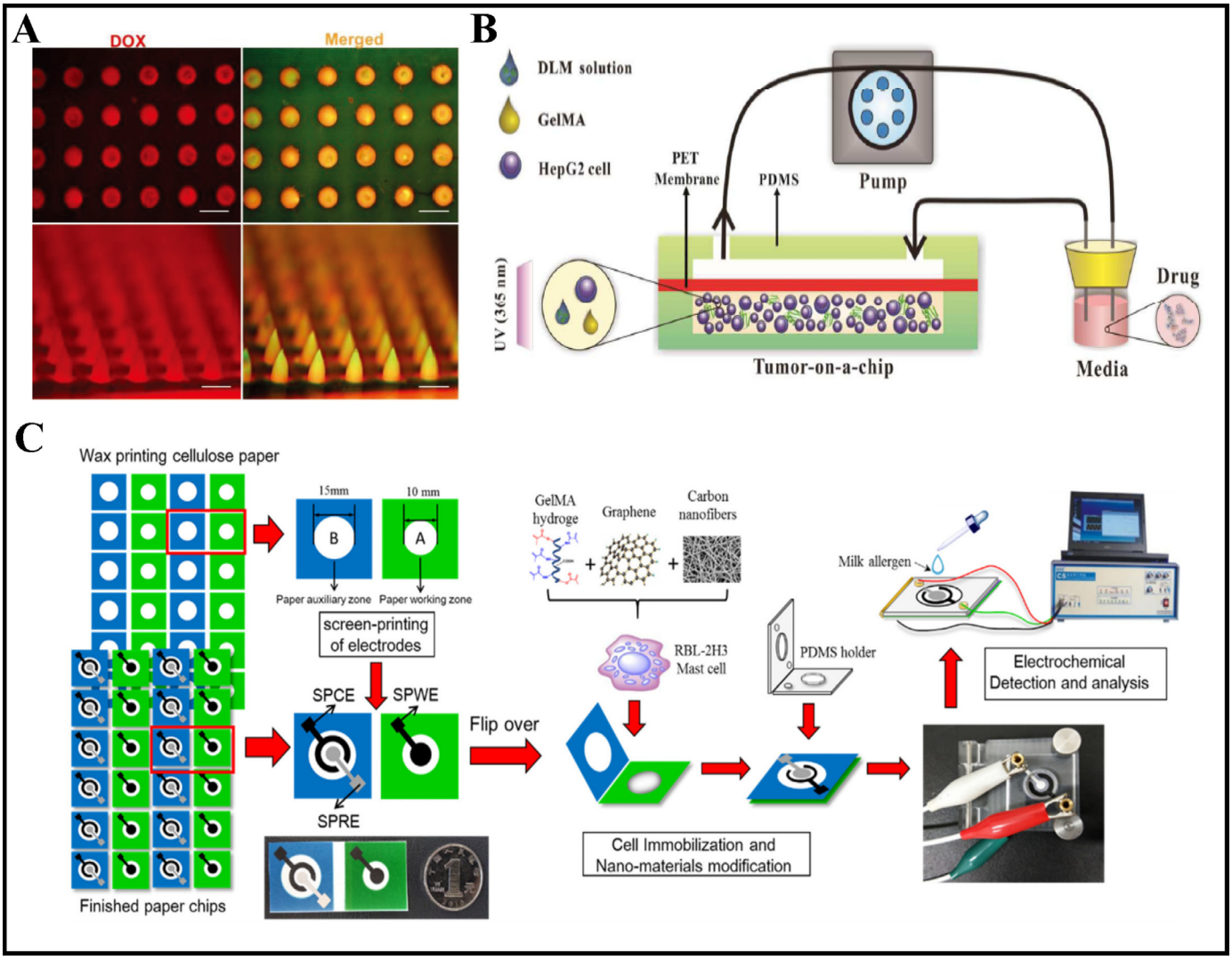

Fig. 5. A. Representative fluorescent microscope images of doxorubicin-loaded GelMA microneedles. Images reproduced from ref. [50] with permission from Wiley. B. Schematic of the decellularized liver matrix-based liver tumor-on-a-chip and its application for drug toxicity testing. Images reproduced from ref. [54] with permission from the Royal Society of Chemistry. C. Schematic of the fabrication and assay procedure of the electrochemical mast cell-based paper sensor for determining the major milk allergen casein. Images reproduced from ref. [56] with permission from Elsevier.

and pharmacological studies (**Fig. 5B**) [54]. 3D-printed OOAC can be more sensitive to the microenvironment of cell manipulating and drug testing. Yi et al. have shown that 3D printing technology can control the spatial distribution and layer by layer package for cells, ECM, and other biomaterials precisely. This technology could establish highly reliable and useful drug-screening platforms with heterogeneity, presenting desired 3D cellular arrangements and tissue-specific functions [70].

3.4. Biosensor

The biosensor is an analytical device used to detect a certain chemical or biological component. Jiang et al. fabricated a low-cost, disposable cell-based paper biosensor for milk allergen casein. In this paper, the biosensor was modified by GelMA, carbon nanofiber, and graphene, which has high conductivity, stability, and convenient properties [56]. Also, GelMA has been used in electrochemical biosensors for detecting DNA hybridization. By modifying the pencil graphite electrode with GelMA, Topkaya et al. fabricated a new DNA hybridization indicator with higher sensitivity to recognize minimal quantities of oligonucleotides as low as 10–12 mol. Intrinsic oxidation signals of GelMA are significantly changed when interacting with different oligonucleotides. It presents a much higher signal suppression of 93% compared with just 50% of bare pencil graphite electrodes, significantly enhancing the detection capability [57]. Recently, GelMA also shows its application potential in wearable biosensors. Li et al. have designed a wearable tactile sensor using micro-structured GelMA as the core dielectric layer. The resultant sensor is biocompatible, transparent, and highly sensitive. Because of the outstanding mechanical and electrical properties, the GelMA tactile sensor performs at a higher pressure sensitivity of 0.19 kPa^{-1} and a lower detection limit to 0.1 Pa, compared with other hydrogel-based sensors [71]. As more research is done, more promising advantages and applications of GelMA in the field of biosensors will be uncovered.

4. Conclusion

GelMA hydrogel is featured with robustly adjustable physical properties such as mechanical, degradation, and swelling properties, which can be achieved by varying the degree of MA substitution, GelMA concentration, and incorporation of various other hydrogels or nanofillers. With the aid of advanced fabrication technologies, including bioprinting, microfluidics, electrospinning, and micromolding, it can be fabricated into

different formats, including micro/nanopatterns, micro/nanospheres, micro/nanofibers, and 3D tissue scaffolds or models for drug screening and disease modeling. Due to its promising biocompatibility and tunable physicochemical properties, GelMA hydrogel now has extensive applications in research of tissue engineering, drug delivery, organ-on-a-chip, and biosensors.

Despite the significant advances of its fabrication technique and its widespread use in different biomedical domains, GelMA hydrogel still has several insufficiencies and requires further investigations. (1) As a bioink, pure GelMA has too low viscosity to achieve high-resolution 3D printing or even has no printability at low concentration. While the concentration influences the mechanical property of the GelMA hydrogel, researchers have to balance between mechanical property and printability of the materials. An alternative strategy is to add a viscosity-enhancing modifier, such as alginate, to improve the printability without changing the GelMA hydrogel's concentration. Conversely, this problem could be solved by the improvement of 3D printers in the future. For instance, a nozzle that can cool the GelMA bioink during extrusion may enhance its printability since GelMA possesses a higher viscosity at a low temperature. (2) Although pure GelMA hydrogel possesses excellent biocompatibility, it is too soft to provide enough mechanical strength in some applications, such as bone regeneration grafts. One possible solution is to build a frame with a stronger material, for instance, polylactic acid (PLA). The PLA frame can be filled with and wrapped in GelMA hydrogels, forming a mechanically enhanced construct similar to the reinforced concrete in architecture. (3) Meanwhile, the fast degradation rate limits its application in long-term drug delivery systems and increases the potential cytotoxicity due to the rapid elevation of exogenous drug levels *in vivo*. To slow down the hydrogel degradation and drug release, GelMA hydrogel could be synthesized into nanoparticles and incorporated into less degradable materials such as synthetic polymer nanofibers. Hence burst release could be avoided, and the scaffold can achieve long-term drug delivery. At present, many positive results of GelMA's applications were derived from the laboratory. However, it is not guaranteed that large-scale GelMA hydrogels could be fabricated with similar traits for clinical purposes. The size, shape, cross-sectional area, and surface area of the materials could influence their mechanical and biological performances. As a result, more clinical-oriented investigations on GelMA hydrogel are needed in the future in order to facilitate the translational applications of GelMA in medicine.

Declaration of Competing Interest

The authors declare no competing financial interest.

CRediT authorship contribution statement

Yun Piao: Conceptualization, Writing – original draft. **Hengze You:** Writing – review & editing. **Tianpeng Xu:** Writing – review & editing. **Ho-Pan Bei:** Writing – review & editing. **Imanuel Zvi Piwko:** Writing – review & editing. **Yu Yan Kwan:** Writing – review & editing. **Xin Zhao:** Conceptualization, Supervision, Writing – review & editing.

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