Functional hydrogels in cardiovascular therapy: Design, applications and clinical challenges (Review)

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Abstract. Cardiovascular disease (CVD) is the leading cause of mortality worldwide, and conventional treatments (such as pharmacotherapy, stents and bypass surgery) have limited capacity to repair damaged cardiovascular tissue. Hydrogels, as biocompatible three-dimensional network materials, demonstrate potential for the treatment of CVD. The present review summarizes functional hydrogels for CVD treatment, including their preparation, applications, current challenges and future perspectives. Hydrogel materials comprise natural polymers, synthetic polymers and composite systems, each with distinct advantages and limitations: Natural polymers offer good biocompatibility but exhibit poor mechanical strength; synthetic polymers provide tunable properties but lack inherent bioactivity; composites combine the advantages of both but are more complex to manufacture. Stimuli-responsive hydrogels respond to environmental cues and enable on-demand therapeutic delivery. In terms of clinical applications, hydrogels have potential for post-infarction myocardial repair, vascular regeneration, heart valve repair and regeneration and heart failure management. They serve as scaffolds, as well as cell and drug delivery carriers. Nevertheless, hydrogels face challenges in clinical translation, including safety, long-term biocompatibility, mechanical and electrical compatibility with host tissue, thrombogenicity, large-scale manufacturing, integration with standard care and regulatory approval. In the future, hydrogel systems are may evolve toward stimuli-responsive, self-regulating, adaptive and personalized designs, integrate with emerging therapeutic strategies (such as gene therapy, cell therapy, and RNA-based therapeutics) and be used in conjunction with existing medical devices (stents, vascular grafts, pacemakers, and ventricular assist devices), thereby becoming an important platform for cardiovascular regenerative therapy.

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Contents

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, accounting for ~18 million deaths annually (1,2). This broad category includes coronary artery disease, myocardial infarction (MI), cerebrovascular disease (stroke), heart failure (HF) and valvular disorders, all of which impose health and economic burdens (3). Despite advances in pharmacological therapies and interventional procedures (stents, bypass surgery and mechanical valves), conventional treatments primarily manage symptoms without fully restoring damaged cardiac tissue. A challenge is that the adult human heart and vasculature possess limited intrinsic regenerative capacity (4). Following MI, lost cardiac muscle is replaced by non-contractile fibrotic scar tissue rather than newly formed myocardium. This impairs cardiac function and often leads to adverse remodeling and chronic HF (5-7). Traditional therapies, such as reperfusion through percutaneous coronary intervention, pharmacotherapy with β-blockers and angiotensin-converting enzyme (ACE) inhibitors and mechanical circulatory support devices, improve acute survival but do not

restore lost myocardium (8). Heart transplantation remains the gold-standard treatment for end-stage HF, however, it is limited by donor organ scarcity (9,10). In vascular disease, interventions such as angioplasty and surgery address occluded arteries but typically fail to regenerate a functional endothelium or prevent long-term restenosis (5). Prosthetic heart valves and vascular grafts are lifesaving, however, artificial materials may provoke thrombosis, necessitate lifelong anticoagulation or cannot accommodate somatic growth (7). There is a pressing need for novel therapeutic strategies that repair or regenerate cardiovascular tissue rather than merely treat symptoms.

To overcome these limitations in cardiac repair, strategies derived from tissue engineering and regenerative medicine have been developed (11). Hydrogels are biocompatible three-dimensional (3D) networks composed of hydrophilic polymers, characterized by their capacity to retain water, which results in a soft, tissue-mimicking material (12-14). Through adjustment of their composition and structural properties, hydrogels can be engineered to replicate the native extracellular matrix (ECM), including its key characteristics (high water content, biocompatibility and elasticity), thereby providing support for cell differentiation and maturation (15-17). Unlike rigid permanent implants, hydrogels are typically biodegradable, which allows them to integrate into host tissue and be replaced by native tissue. Early generations of hydrogels [polyacrylamide or poly(2-hydroxyethyl methacrylate) (HEMA) gels] were used in medicine as passive materials, such as contact lenses and wound dressings, however, other functional hydrogels extend beyond passive roles (13,14). These advanced hydrogels are bioactive or stimuli-responsive and are designed to interact with the biological environment in specific ways, such as delivering drugs or cells, responding to local stimuli (pH, enzymes or temperature) to release therapeutic agents or presenting biochemical cues that direct cell behavior (18). Functional hydrogels can serve as injectable scaffolds to repair infarcted myocardium, as coatings for stents or grafts to improve performance or as engineered tissue constructs (patches, valves or vessels) that integrate with host tissue. Because hydrogels are typically minimally invasive (injectable or catheter-deliverable) and highly tunable (their mechanical properties, degradation kinetics and biofunctionality can be precisely controlled through material design), they offer unique solutions to challenges that traditional rigid implants or systemic drug therapy cannot adequately address (19). The present study aimed to summarize the fabrication of functional hydrogels, along with their intrinsic properties and therapeutic applications in CVD, the current challenges in this field and future research directions. A schematic overview of the synthesis and applications of functional hydrogels in cardiovascular therapy is illustrated in Fig. 1.

2. Fabrication of functional hydrogels

Hydrogels used in cardiovascular applications are formulated from a wide variety of polymers, which are broadly classified as natural, synthetic or composite materials (20,21). Hydrogels consist of crosslinked polymer chains that form a water-swollen network; natural polymers offer good biocompatibility and bioactivity, synthetic polymers provide tunable mechanical properties and reproducibility and composite systems combine these advantages (22). Hybrid approaches and stimuli-responsive designs are employed to achieve optimal performance (12).

Hydrogels from natural polymers. Natural polymer hydrogels are derived from biological macromolecules and typically resemble the composition of the native ECM. Examples include proteins (collagen, gelatin, fibrin and keratin) and polysaccharides [hyaluronic acid (HA), alginate, chitosan and agarose] (23-27). These materials intrinsically mimic the native matrix by providing ligands for cell adhesion and enzymatic degradation sites that facilitate tissue remodeling. Natural hydrogels are typically biocompatible and bioactive, meaning that cells recognize and interact with them favorably. However, they typically exhibit inferior mechanical strength (compared with synthetic hydrogels), batch-to-batch variability and a risk of immunogenicity if not adequately purified.

Proteins. Collagen type I, the most abundant protein in the mammalian ECM, is found in skin, bone, tendon and myocardium and readily forms hydrogels through the self-assembly of its triple-helical monomers. Collagen gels exhibit intrinsic cell-binding motifs and undergo degradation by collagenase, which makes them cytocompatible. They have been used in tissue engineering and 3D cell culture (19). However, their limitations include low stiffness and the potential for xenogeneic immune responses unless properly processed (decellularization or pepsin digestion to decrease antigenicity) (19). Chemical cross-linkers (such as glutaraldehyde) can reinforce collagen gels, although this may compromise biocompatibility (5). Collagen hydrogels have demonstrated efficacy in cardiac repair. McLaughlin *et al* (28) demonstrated that collagen hydrogel treatment decreases methylglyoxal adduct formation within cardiomyocytes and enhances contractile function in the infarct border zone in a mouse model of MI (Fig. 2A-D). Histological analysis has revealed increased myocardial salvage and reduced fibrosis in the border zone (Fig. 2E-I) (28). Gelatin is a denatured form of collagen produced through partial hydrolysis. It retains numerous collagen bioactive sequences but is easier to handle because it forms gels upon cooling, a property known as thermal reversibility (13). Gelatin hydrogels are biocompatible and can be formulated to deliver growth factors. For example, heparin-binding growth factors can be incorporated to promote vascularization in engineered tissue (11). Because gelatin is derived from collagen, it represents a promising material for cardiac repair. Although its mechanical strength is limited, gelatin is typically chemically modified (for example, gelatin methacrylate) to enable cross-linking and enhance mechanical rigidity (13).

Fibrin is a natural clotting polymer formed through thrombin-mediated cleavage of fibrinogen. Fibrin gels polymerize rapidly at physiological temperature and can be obtained autologously from the patient blood plasma (5). They support cell infiltration and ECM deposition because fibrinolytic enzymes degrade the gel (29,30). Fibrin has clinical applications as a surgical sealant (11). Fibrin injection into infarcted rat hearts enhances cell engraftment and myocardial perfusion, resulting in smaller infarct size and improved cardiac output (31). However, fibrin has limitations, including rapid degradation and relatively weak mechanical strength;

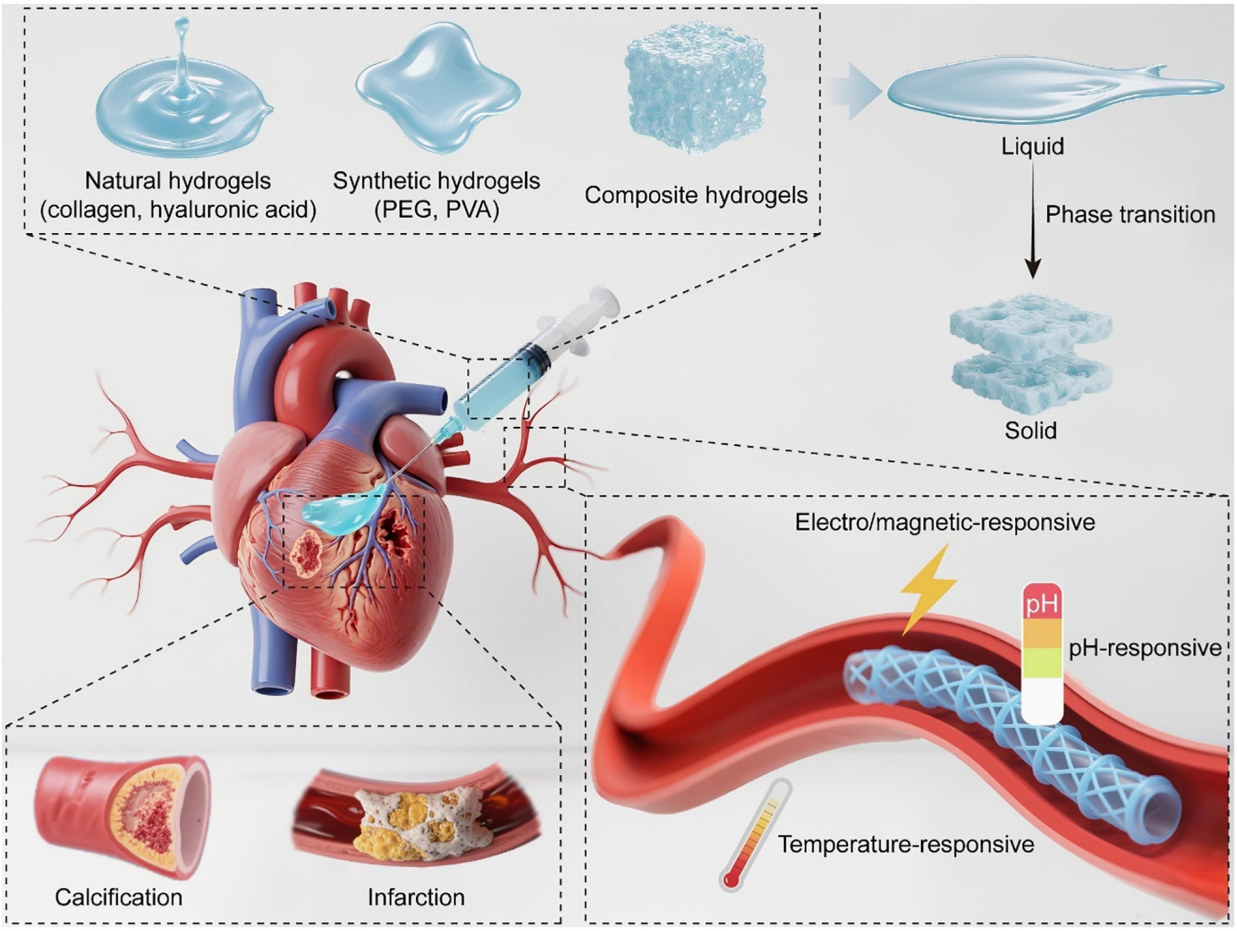

Figure 1. Synthesis and application of hydrogels in cardiovascular therapy. PEG, poly(ethylene glycol); PVA, poly(vinyl alcohol).

therefore, it may not provide sustained structural support unless reinforced or combined with other materials (30). Nonetheless, fibrin exhibits good biocompatibility, as it mimics the native wound-healing process. Fibrin-based heart valve scaffolds generated through injection molding of cell-laden fibrin have also been investigated (15).

Polysaccharides. HA is a glycosaminoglycan that is abundant in connective tissue and heart valves. HA hydrogels are enzymatically degradable by hyaluronidase and are non-immunogenic because HA is a natural component of the human ECM. However, unmodified HA is mechanically weak and fragile, necessitating chemical modification (such as methacrylation or thiol modification) or cross-linking to achieve sufficient mechanical stability for cardiovascular application (13). HA has been well-documented to contribute to wound healing and angiogenesis (14,18,32). Ding *et al* (32) developed an injectable hydrogel based on methacrylate-modified HA, which rapidly gels following ultraviolet irradiation via the Michael addition reaction (Fig. 3A). The aforementioned study demonstrated that this hydrogel suppresses cell apoptosis, increases the M2-to-M1 macrophage ratio, promotes angiogenesis, decreases infarct size and improves cardiac function (Fig. 3B) (32). In another study, application of a cross-linked HA patch to the heart increased ventricular wall thickness and vascular formation, highlighting the potential of HA hydrogels in cardiac regeneration (11).

Alginate, a polysaccharide derived from seaweed, forms hydrogels through ionic cross-linking with divalent cations (such as Ca^{2+}). Alginate hydrogels are biocompatible, inexpensive and readily gel *in situ* by injection of a soluble alginate solution followed by a calcium-containing solution (33). They are non-immunogenic and non-thrombogenic, and their mild gelation conditions, along with the ease of encapsulating cells or drugs, make them suitable for cardiovascular application (33,34). Unmodified alginate is not enzymatically degraded in humans; the gels gradually dissociate through ion exchange of Ca^{2+} with the surrounding environment, which may compromise long-term stability. To address this limitation, alginates are partially oxidized to enable slow hydrolytic degradation or covalently cross-linked to enhance structural stability (34). Lee *et al* (35) presented findings from the first clinical trial evaluating the feasibility and safety of Algisyl-LVR™, a hydrogel composed of sodium and calcium alginate (LoneStar Heart Inc.), for the treatment of HF associated with dilated cardiomyopathy. During injection, mechanical stress disrupts the dynamic cross-links formed via Ca^{2+} coordination, causing the hydrogel to transition into a liquid state that facilitates catheter delivery. Once injected into the myocardium, the stress is relieved, and dynamic cross-linking is re-established (35).

Chitosan is derived from chitin, which is found in crustacean shells, through deacetylation. It is a cationic polysaccharide that forms hydrogels via ionically triggered

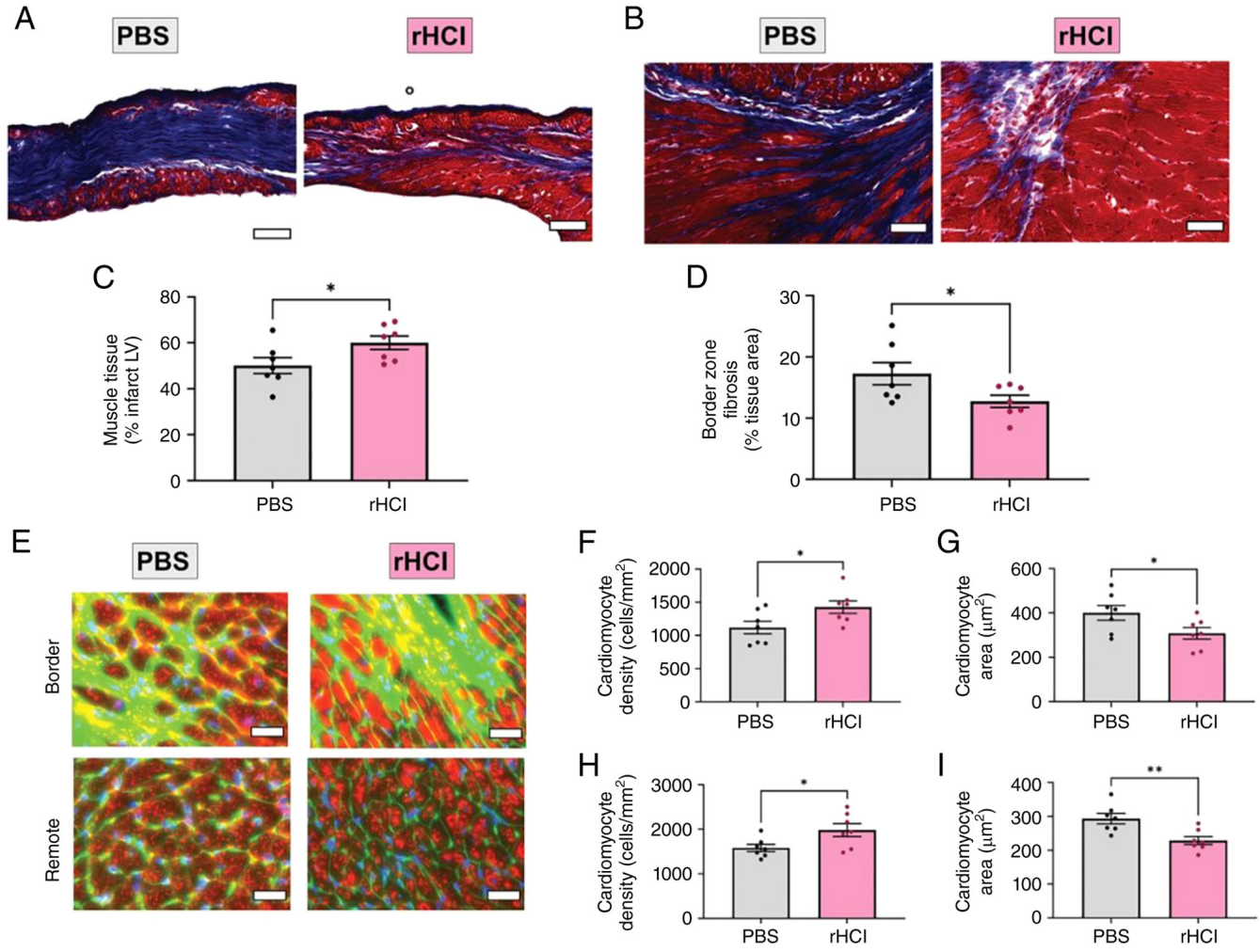

Figure 2. Myocardial salvage is improved following treatment with rHCI hydrogel. At 7 days post-myocardial infarction induction in mice, rHCI hydrogel or PBS was injected into the border zone myocardium. Hearts were harvested 28 days post-treatment for histological analysis. (A) Masson's trichrome staining of infarct regions. (B) Masson's trichrome staining of border zone myocardium. (C) Quantification of myocardial salvage in the infarct region. (D) Quantification of fibrosis in the border zone. Scale bar, 50 μm. (E) Representative immunofluorescence of cardiomyocytes (cardiac troponin I, red) and cell borders (wheat germ agglutinin, green). Scale bar, 25 μm. (F) Quantification of cardiomyocyte density in the infarct border zone.(G) Quantification of cardiomyocyte cross-sectional area in the infarct border zone.(H) Quantification of cardiomyocyte density in the remote myocardium.(I) Quantification of cardiomyocyte cross-sectional area in the remote myocardium. *P<0.05, **P<0.01. Adapted with permission from (28). Copyright 2022, John Wiley and Sons. rHCI, recombinant human type I collagen; LV, left ventricular.

gelation when mixed with β-glycerophosphate. Chitosan structure resembles that of glycosaminoglycans and it is biocompatible, with mild antibacterial properties. It dissolves in acidic solutions and forms gel as the pH or the temperature rises (36). For cardiac applications, thermosensitive chitosan hydrogels (liquid formulations that remain injectable at room temperature but solidify into a gel at body temperature) are particularly attractive because they can be delivered by catheter (36). Chitosan can be chemically modified [by conjugation with arginine-glycine-aspartic acid (RGD) peptides or growth factors] to enhance cell adhesion and therapeutic efficacy (12).

Other natural materials. Several other natural materials have niche applications. Agarose, an algae-derived polysaccharide, forms gels upon cooling, and its pore size is altered by adjusting agarose concentration. Agarose is used as a cell-encapsulation matrix and for drug delivery (13). Kim *et al* (37) developed a low gel temperature agarose by incorporating β-cyclodextrin into ethylenediamine-modified agarose and demonstrated that this modified gel enables sustained release of a thermosensitive drug. Keratin-based hydrogels, derived from hair or wool proteins, leverage keratin self-assembling fibrous structure. They retain bioactive motifs associated with hair follicle development and demonstrate pro-angiogenic effects without eliciting inflammation. Matrigel, a complex ECM extract derived from tumor cells, has been used as an injectable scaffold for stem cell delivery to the heart (19). Studies (17,18) have shown that it preserves ventricular geometry and enhances vascularization. However, Matrigel non-human origin and batch-to-batch variability preclude its clinical use.

Overall, natural hydrogels typically exhibit excellent bioactivity and cytocompatibility because their biochemical components resemble those of native tissue (15). Cells typically attach, migrate and function more readily on natural matrices. For example, a collagen or fibrin patch applied to an infarct can recruit cells and support novel tissue formation more effectively than numerous synthetic materials (3). However, purely natural hydrogels often possess limited

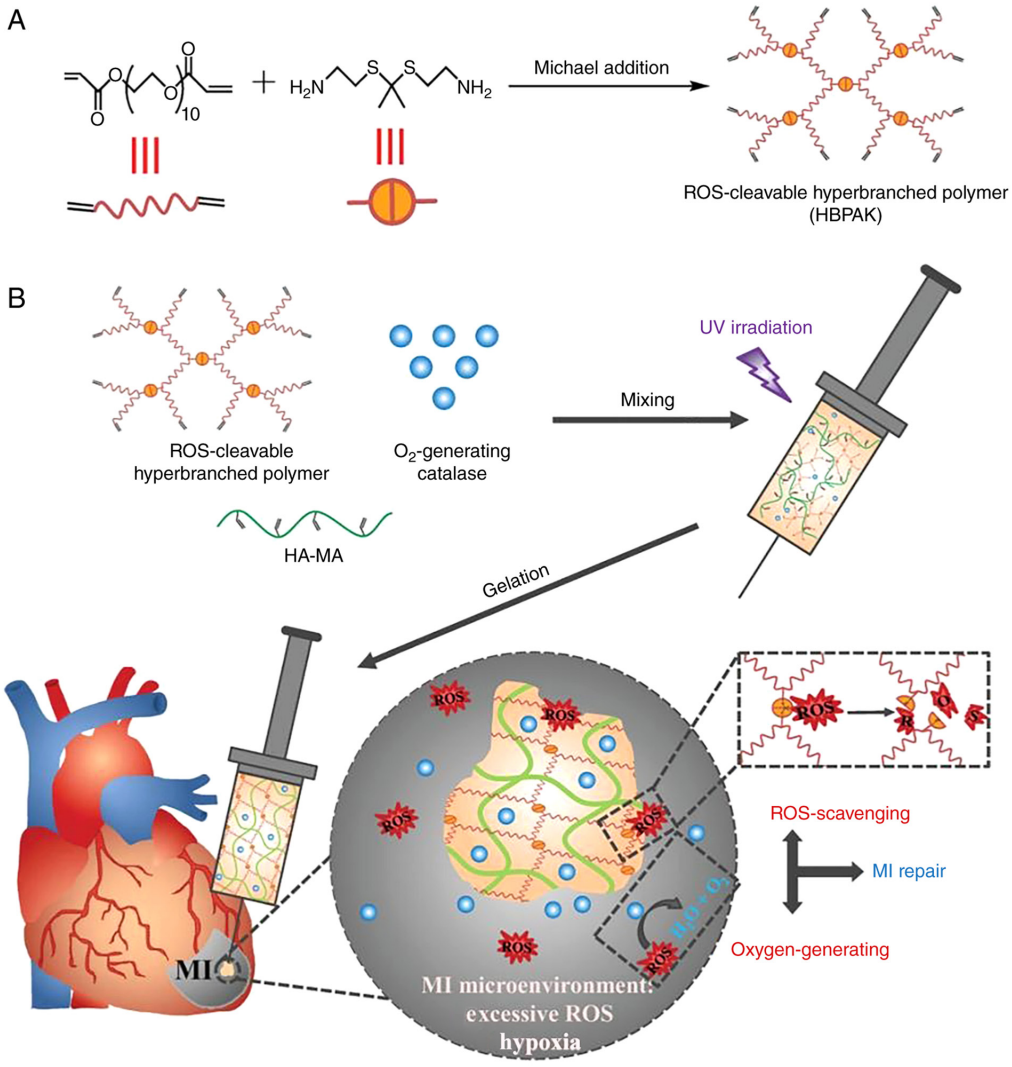

Figure 3. Structure and working principles of ROS-scavenging and O2 generating injectable hydrogel for rat MI treatment *in vivo* (A) Synthesis route of HBPAK (hyaluronic acid-based polymer) via Michael addition reaction. (B) Schematic of the injectable ROS-scavenging and oxygen-generating hydrogel and its mechanism for rat MI treatment *in vivo*. The hydrogel simultaneously reduces reactive oxygen species and supplies oxygen to the ischemic myocardium, thereby suppressing cardiomyocyte apoptosis, promoting M2 macrophage polarization and enhancing angiogenesis. Adapted with permission from (32). Copyright 2020, John Wiley and Sons. HBPAK, hyaluronic acid-based polymer; ROS, reactive oxygen species; MI, myocardial infarction; HA-MA, hyaluronic acid methacrylat; UV, ultraviolet.

mechanical strength and structural stability. They tend to be soft and prone to rapid degradation. In a beating heart or a high-pressure artery, a mechanically weak hydrogel may not withstand physiological forces over time (5). Thus, although natural polymers establish a biologically favorable microenvironment, they typically require modification or reinforcement for load-bearing cardiovascular applications.

Synthetic polymer hydrogels. Synthetic hydrogels are formed from synthetic polymers such as poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA) and polyacrylate (38-40). A key advantage of synthetic polymers is their tunability and reproducibility: Molecular weight, cross-link density and chemical functional groups can be precisely controlled, resulting in consistent batch-to-batch properties (5,15). Synthetic hydrogels can be engineered to exhibit a range of stiffness, degradation rate and network architectures to meet specific application requirements. They also tend to be chemically inert and non-immunogenic in their pure form. However, unlike natural polymers, most synthetic polymers lack inherent bioactive cues; cells do not readily recognize or adhere to them (13). Therefore, biofunctionalization is typically required. For example, peptides such as RGD can be grafted onto synthetic polymer backbones to promote cell adhesion (13).

PEG. PEG, also known as poly(ethylene oxide), is a hydrophilic polymer approved by the U.S Food and Drug Administration (FDA) for medical applications (41). It resists protein adsorption and is typically biologically inert, which decreases non-specific immune reactions. PEG hydrogels are typically formed by cross-linking multi-armed PEG molecules functionalized with acrylates, thiols or other reactive groups to generate a polymeric network. By adjusting PEG molecular weight or incorporating degradable linkers, such as ester bonds or peptide sequences, between PEG chains, the mechanical strength and degradation rate of the gel can be controlled (5). A notable advantage of PEG lies in its tunable architecture and well-defined chemical composition. Researchers engineer

PEG hydrogels with specific pore sizes, stiffness and gelation kinetics. In its unmodified form, PEG does not support cell adhesion; cells typically remain rounded in pure PEG hydrogels. However, incorporation of ECM motifs (RGD peptides or heparin to facilitate growth factor binding) enables PEG hydrogels to become bioactive (5). In cardiac tissue engineering, PEG-based hydrogels have been investigated as scaffolds for engineered heart valves and cell delivery. Crocini *et al* (42) employed photo-clickable thiol-ene PEG hydrogels for 3D cell culture of adult mouse cardiomyocytes. These PEG hydrogels serve as versatile and biocompatible scaffolding materials, with precisely adjustable stiffness that enables them to mimic both physiological and pathological microenvironmental conditions. Compared with conventional cell culture systems, adult cardiomyocytes encapsulated within PEG hydrogels exhibit prolonged survival and preserved the integrity of their sarcomeric and T-tubular structures (42). The mechanical properties of PEG hydrogels are tunable, allowing formulations that are very soft for injectable applications or more rigid and elastomeric for load-bearing cardiac patches (43). Moreover, PEG can be combined with natural polymers (for example, through PEGylation of proteins such as fibrin or collagen) to create composite hydrogels that retain bioactivity while improving structural stability (5).

PVA. PVA is a synthetic, water-soluble polymer that forms hydrogels, typically through repeated freeze-thaw cycles or chemical cross-linking (40). It produces transparent, rubber-like hydrogels with good mechanical integrity and was among the earliest hydrogel materials used in medicine. PVA hydrogels are biologically inert, and few cells adhere to them without modification, however, they are non-toxic and chemically stable (22). PVA is used in cardiac applications, including the fabrication of heart valve leaflet models and vascular graft coatings, because of its flexibility and mechanical strength. Recent studies have developed nanocomposite PVA hydrogels reinforced with nanoparticles or nanofibers to enhance mechanical performance (41,44). Although unmodified PVA lacks cell-instructive cues, it can be functionalized (with gelatin or RGD peptides) to improve cell-material interactions (5). Mannarino *et al* (44) developed a composite hydrogel consisting of PVA coated with poly(acrylic acid) (PAA), which was subjected to heat treatment to form a physically cross-linked network. The mechanical properties and swelling behavior of the hydrogel are modulated by adjusting the heat input and duration of thermal exposure, thereby increasing the cross-link density of the matrix. In an *in vitro* study using a simulated aging model over 162.6 days, the composite hydrogel retained its mechanical properties and surface functionality following accelerated aging. When evaluated in an *in vitro* blood loop model, the PVA/PAA composite hydrogel exhibited a 97% decrease in platelet adhesion (44). Additionally, it demonstrated a slower thrombosis-induced occlusion rate at the catheter tip, in contrast to commercially available catheter products. Ultimately, this thromboresistant hydrogel shows potential as a biomaterial for vascular access application, with the goal of improving patient outcomes. PVA hydrogels can be loaded with drugs or growth factors and have been investigated as drug-eluting coatings for stents or cardiac implants (45,46). Hu *et al* (47) developed an injectable hydrogel composed of phenylboronic acid-grafted carboxymethyl cellulose and PVA for the localized delivery of curcumin and recombinant human collagen type III to the infarcted myocardium in a rat MI model. This hydrogel improves cardiac function, increases left ventricular (LV) wall thickness, decreases infarct size, attenuates cardiomyocyte apoptosis and decreases inflammation.

Polyacrylates and poly(HEMA). Hydrogels based on PAA or poly(HEMA) are classical synthetic materials that have been widely used in contact lenses and biomedical implants. PAA is hydrophilic and pH-responsive, exhibiting increased swelling at higher pH due to deprotonation of its carboxyl groups; this property has been exploited in drug delivery systems (36). Although these polymers are not commonly used alone in cardiac tissue engineering because of their limited bioactivity, they demonstrate the concept of stimuli-responsive synthetic hydrogels. By copolymerizing acrylic monomers with other functional monomers, responsiveness to pH or temperature can be induced (12). Poly(N-isopropylacrylamide) (PNIPAM) is a synthetic polymer that undergoes a thermal phase transition at ~32˚C. It is soluble below this temperature and forms a gel above it (13). PNIPAM-based hydrogels are used to develop injectable systems that solidify at body temperature, conceptually similar to the chitosan/β-glycerophosphate system but fully synthetic. One limitation of PNIPAM is that its degradation products, if the polymer is not fully cross-linked, exhibit limited biocompatibility; therefore, PNIPAM is often combined with biodegradable segments or formulated as microgels to minimize potential accumulation (13).

Self-assembling peptides and other polymers. Certain synthetic hydrogels bridge the distinction between natural and synthetic. For example, peptide-based hydrogels are fabricated from short synthetic peptides that spontaneously self-assemble into fibrous networks (such as the RADARADARADARADA peptide forms a β-sheet hydrogel) (13). Although these materials are synthetic in origin, they are biological in composition because they consist of amino acids. They have been investigated for myocardial repair because they present a nanofibrous architecture resembling collagen and incorporate bioactive sequences (5). Polyphosphazenes, a class of inorganic-organic polymers, can be engineered to be biodegradable and have been evaluated as hydrogel matrices for tissue engineering. Polyurethane and polyester urethane hybrids have also been formulated as hydrogels, referred to as elastic hydrogels, to provide rubber-like elasticity for cardiac patches. Synthetic systems offers advantages, such as electrical conductivity when doped with conductive polymers or high toughness in double-network hydrogels composed of two interpenetrating polymer networks (12).

In general, synthetic hydrogels provide greater control over material properties and typically exhibit superior mechanical robustness compared with natural hydrogels. They do not inherently support cell attachment or tissue integration, however, this limitation can be addressed through composite design (blending synthetic and natural polymers) or by conjugating bioactive molecules (5). Numerous contemporary hydrogel systems are hybrid in composition. For example, a PEG backbone can be functionalized with cell-adhesive peptides

or combined with collagen or chondroitin sulfate (48). Such composite hydrogels aim to integrate the biofunctionality of the native ECM with the mechanical tunability of synthetic polymers. An example is PEGylated fibrin or PEG-collagen composites, in which the synthetic component slows degradation and increases mechanical strength, whereas the natural component preserves cytocompatibility (49,50). Table I summarizes key differences between natural and synthetic hydrogel materials in cardiovascular therapy.

Composite and stimuli-responsive hydrogels. A trend in hydrogel research is the development of stimuli-responsive (smart) hydrogels that undergo physicochemical changes in response to specific environmental triggers (5,13,16). In cardiovascular therapy, dynamic behavior is desirable because it enables minimally invasive delivery, on-demand drug release and adaptation to the changing post-infarction microenvironment (11). For example, a hydrogel may remain in a liquid state during injection but undergo gelation within the warm myocardium, or a drug-loaded matrix may release its therapeutic payload when it detects elevated levels of inflammatory cytokines at an injury site. By incorporating stimuli-responsive components, hydrogels enable on-demand therapeutic delivery and adapt to patient-specific conditions in real time (5).

Thermo-responsive hydrogels. Thermo-responsive hydrogels exploit the temperature difference between room temperature during injection and body temperature during gelation, enabling catheter-based delivery with rapid *in situ* gelation. This temperature-triggered transition allows therapeutic action to be aligned with the acute to subacute phases of cardiac injury. PNIPAM is a thermo-responsive polymer that exhibits solution-to-gel (sol-gel) transition at ~32˚C (13). By copolymerizing PNIPAM with other monomers, the transition temperature is adjusted to physiological temperature. Other approaches include blending polymers that undergo temperature-induced assembly, such as chitosan combined with β-glycerophosphate, which gels upon warming, or Pluronic F127, a PEG-poly(propylene oxide) block copolymer that is liquid at low temperature and forms a gel at ~37˚C. Duan *et al* (51) prepared a thermosensitive injectable hydrogel (PFSgel) synthesized from Pluronic F127 and sodium alginate (Fig. 4A). The poloxamer-alginate blend exists as a liquid solution) at room temperature and undergoes gelation *in vivo* (Fig. 4C). When loaded with PEDF and injected around an atherosclerotic arterial lesion, it forms a local depot that gradually releases the therapeutic agent and decreases plaque neovascularization and progression in mice by inhibiting MMP2/MMP9 and CD31 signaling pathways (Fig. 4B).

A thermo-responsive PLEL triblock copolymer hydrogel has also been developed that undergoes rapid sol-gel transition at body temperature. When sprayed or injected onto the injured epicardial surface, it forms a conformal and fouling-resistant barrier that prevents postoperative cardiac adhesion during the critical early healing phase (52). Another thermo-responsive system based on Pluronic F127 has been engineered to encapsulate HA-modified zeolitic imidazolate framework-8 nanoparticles loaded with shikonin/Cu^{2+} complexes, enabling sustained drug retention at the myocardial injection site following ischemia-reperfusion injury (53).

pH-responsive hydrogels. Following MI, sustained ischemia and hypoxia lead to a decrease in local pH, creating a spatially and temporally defined acidic microenvironment that evolves with disease progression (6). pH-responsive hydrogels exploit this dynamic change to achieve targeted, stage-specific therapeutic delivery (3) PAA hydrogels exhibit increased swelling at neutral-to-basic pH because deprotonated carboxylate groups repel one another. In CVD, this pH-responsive behavior can be harnessed because ischemic tissue typically becomes acidic (3). Alimirzaei *et al* (54) reported the fabrication of two pH-sensitive chitosan hydrogels and evaluated them as cell carriers and cardiac scaffold materials for infarcted myocardial regeneration. An injectable pH-responsive micellar system has been developed by encapsulating a small-molecule glycogen synthase kinase-3β inhibitor [(2'Z,3'E)-6-bromoindirubin-3'-oxime(BIO) within a PEG-polycaprolactone (PCL) matrix and integrating it with adipose-derived stem cells in Matrigel (55). Under acidic conditions simulating the post-MI microenvironment, micelles undergo accelerated degradation, triggering BIO release and mitigating reactive oxygen species (ROS)-induced injury (55). A pH-responsive conductive hydrogel composed of PVA, oxidized sodium alginate, borax, tannic acid and a vanadium-based MXene (a class of 2D transition metal carbides/nitrides) nanozyme has also been engineered. Under acidic conditions that mimic the ischemic microenvironment, the hydrogel exhibits enhanced nicotinamide adenine dinucleotide (NADH) oxidation activity, enabling sustained release of the nanozyme and restoration of the NAD^+/NADH redox balance (56).

Enzyme-responsive hydrogels. MMPs, particularly MMP-2 and MMP-9, are notably upregulated in the infarcted myocardium during the inflammatory and early remodeling phases. Their expression peaks within days after injury and declines as healing progresses. This positions MMPs as ideal endogenous triggers for on-demand therapeutic delivery aligned with the dynamic requirements of cardiac repair (57). Researchers have designed hydrogels containing cross-links cleavable by MMP-2 or MMP-9, which are abundant proteases in post-MI tissue (13,57,58). Such MMP-responsive hydrogels degrade in synchrony with the remodeling process, potentially releasing embedded therapeutics, such as growth factors or antifibrotic agents, at sites where MMP activity is elevated (57,58). Pereira *et al* (59) employed a biscysteine MMP-cleavable peptide as a cross-linking agent and fabricated a pectin-based hydrogel via a photo-click reaction: The fabricated hydrogel degraded in the presence of type II collagenase, suggesting its potential for *in vivo* enzymatic degradation (59). An MMP-2-responsive cardiac ECM (c-ECM) hydrogel has also been engineered to enable sequential release of pro-angiogenic and vascular-stabilizing factors (60). A collagen-binding vascular endothelial growth factor (VEGF) is incorporated directly into the c-ECM matrix, whereas an angiopoietin-1 (Ang-1) mimetic peptide is conjugated through an MMP-2-cleavable linker (60). As MMP-2 levels progressively increase, the enzyme cleaves the peptide linker, releasing the mimetic peptide to promote vascular maturation. For heart valve applications, an MMP-responsive hydrogel system encapsulating microRNA-93 (miR-93)-loaded

Table I. Natural and synthetic hydrogels for cardiovascular application.

Hydrogel source	Primary components	Strengths	Limitations	Degradation rate	Clinical translation status	Uses in CVD
Natural-derived	Collagen, gelatin, fibrin, hyaluronic acid, alginate, chitosan	Biocompatible; inherent cell adhesion ligands and enzymatic degradability; promote cell functions (migration, angiogenesis)	Lower mechanical strength without reinforcement; batch variability (derived from tissue); risk of immunogenicity if xenogeneic	Enzymatic (collagenase, hyaluronidase, plasmin); typically weeks to months	Phase I/II (alginate, ECM hydrogels); preclinical	Collagen/gelatin for cardiac patches; fibrin for cell delivery in MI; alginate injectables for MI and HF; HA in tissue-engineered valves
Synthetic-derived	PEG, PVA, poly(acrylates), PNIPAM	Highly tunable mechanical and chemical properties; reproducible and pure (manufactured under controlled conditions); generally non-immunogenic	Bio-inert (lack cell recognition sites); hydrophobic degradation byproducts possible depending on polymer (acidic monomers)	Hydrolytic or via engineered cleavable linkers; months to years	Mostly preclinical; PEG-based devices approved for other indications; PVA in clinical use as coatings	PEG-based injectable hydrogels for MI and heart valves; PVA scaffolds for small-diameter vascular grafts; PNIPAM thermo-gels for minimally invasive delivery
Composite/hybrid	PEG-collagen conjugates, fibrin + synthetic polymer interpenetrating network	Improved mechanics and stability; preserved bioactivity; versatile design to meet complex requirements (mechanical strength and biological function)	More complex to manufacture (multiple components); need to balance degradation rates of each component; regulatory approval can be harder for multi-component products	Tunable via component ratios; typically weeks to months	Preclinical; early clinical (cell-loaded composites)	PEGylated collagen hydrogels for valve engineering (retain collagen biofunction, added strength); collagen-chitosan blends for cardiac patches (enhanced mechanical integrity)

CVD, cardiovascular disease; ECM, extracellular matrix; HA, hyaluronic acid; HF, heart failure; MI, myocardial infarction; PEG, poly(ethylene glycol); PNIPAM, poly(N-isopropylacrylamide); PVA, poly(vinyl alcohol).

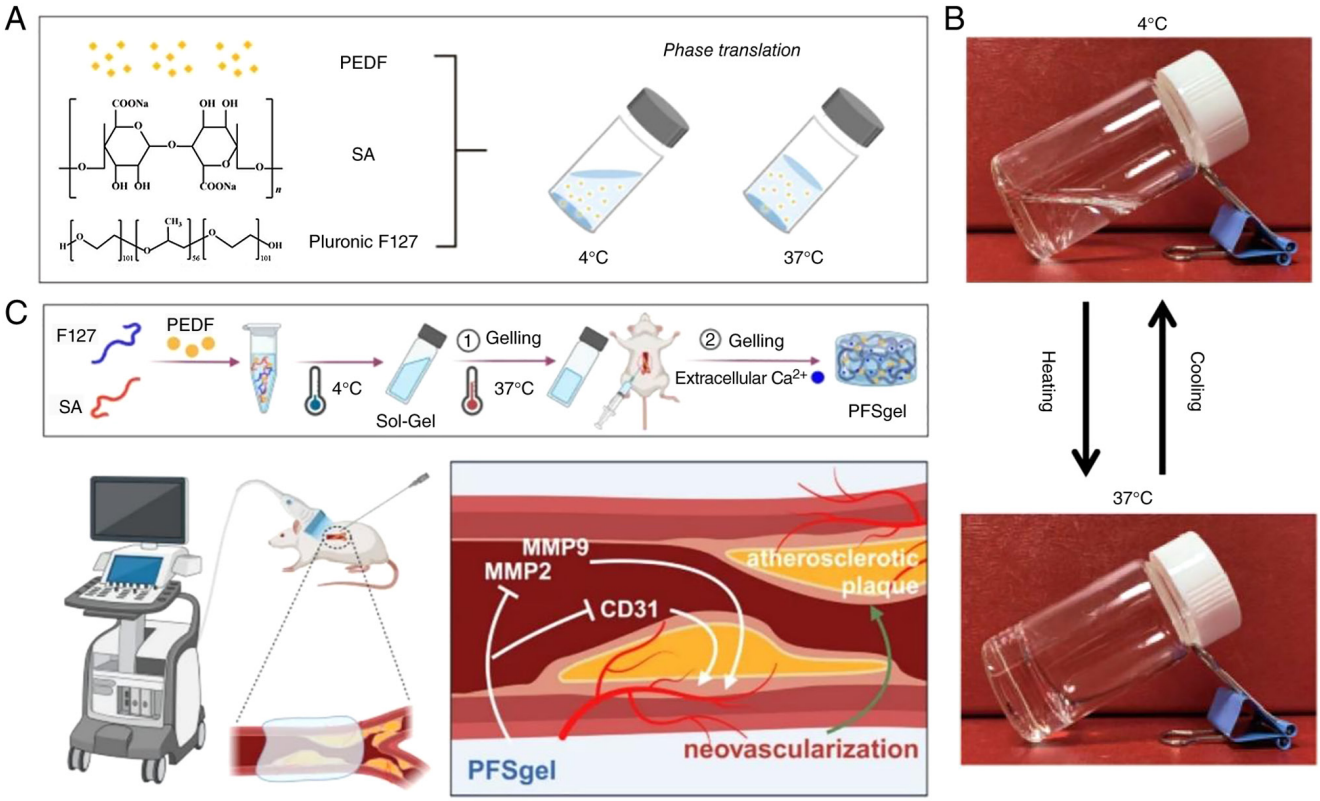

Figure 4. Thermosensitive injectable PFSgel for atherosclerosis treatment. (A) PFSgel comprises PEDF, SA and F127. (B) Fluid-to-colloid transition of PFSgel upon warming to 37˚C. (C) PFSgel undergoes solution-to-gel transition at body temperature in the presence of extracellular Ca^{2+}. Ultrasound-guided perivascular injection forms a local depot that releases PEDF, which inhibits VEGFA-dependent neovascularization via suppression of MMP2/MMP9 and CD31 signaling, thereby decreasing plaque progression. Adapted from (51). PFS, PEDF-F127-SA; F127, poloxamer 407; PEDF, pigment epithelium-derived factor; SA, sodium alginate.

nanoparticles has been developed. Following MMP-mediated degradation, the nanoparticles are released and internalized by infiltrating macrophages, where miR-93 induces M2 polarization and promotes constructive remodeling of decellularized valve scaffolds (61).

Electrical, light and magnetic responsiveness. Because the heart is an electrically active organ, electro-responsive hydrogels that alter their properties in response to an applied electric field represent an emerging area of research (5). Although at an early stage of development, conductive or piezoelectric hydrogel composites incorporating graphene, gold nanowires or conductive polymers such as polypyrrole have been investigated for cardiac patch applications to enhance electrical signal propagation across scar tissue (41,43). Light-responsive hydrogels, which rely on photodegradable linkers or light-induced conformational changes, are being explored for externally regulated drug release (5,62). An injectable hydrogel containing light-sensitive bonds and photodegradable components, composed of PEG and heparin-derived polymers, effectively encapsulates fibroblast growth factor-2 (FGF-2) (62). The biological activity of FGF-2 following encapsulation is comparable to that pre-encapsulation and the hydrogel modulates its release profile. Magnetic field-responsive hydrogels typically incorporate magnetic nanoparticles and can be manipulated or heated under an external magnetic field; such systems may enable targeted thrombosis therapy or localized hyperthermia for the ablation of atherosclerotic plaque cells (12).

Composite hydrogels. To harness the strengths of natural and synthetic components, numerous composite hydrogels have been developed (13,17). In composite systems, a natural polymer, living cells or nanoparticles, may be embedded within a synthetic polymer matrix, or a synthetic component may be incorporated into a natural matrix (5). This strategy can produce materials that balance biofunctionality with mechanical robustness (12). For example, combining type I collagen with glycosaminoglycans or a synthetic polymer such as PEG can enhance mechanical integrity while preserving cell-supportive surfaces (16). Composite hydrogels are applied in heart valve engineering, where a biological scaffold, such as a decellularized valve matrix, may be reinforced with a secondary synthetic polymer network to improve durability (48). In vascular graft design, the luminal surface of synthetic grafts [expanded polytetrafluoroethylene (ePTFE) tubes) is coated with a thin hydrogel layer to create a more biomimetic and endothelial cell-supportive interface (63). One study reported the bonding of a hydrogel lining to the interior of an ePTFE graft, which promotes endothelialization without compromising mechanical strength (63). Similarly, nanocomposite hydrogels, in which inorganic nanoparticles or nanofibers are dispersed within the polymer network, have attracted increasing attention (64-66). Incorporation of silica nanoparticles, clay nanosheets or carbon-based nanomaterials reinforce the hydrogel matrix and, in some cases, introduce additional functionality such as electrical conductivity or growth factor binding (13). For cardiac tissue engineering,

embedding electrically conductive nanomaterials, including graphene, gold nanowires or MXene nanosheets, within a polymeric gel can generate electroconductive hydrogels that facilitate electrical signal propagation and may improve synchronization with myocardial contraction (64). Consequently, the incorporation of conductive biomaterials is key for enhancing the physiological relevance of *in vitro* bioengineered cardiac tissue models. These composite systems aim to mitigate post-MI arrhythmias by promoting integration with the cardiac electrical conduction network (64-66).

Additional stimuli, such as oxidative stress characterized by elevated ROS levels in infarcted regions and alterations in mechanical strain associated with changes in loading conditions, have also been explored (67). Overall, stimuli-responsive hydrogels introduce an additional functional dimension by enabling spatiotemporal control of therapeutic activity. By integrating multiple components or incorporating distinct responsive mechanisms, these hydrogels concurrently satisfy the mechanical requirements of cardiac tissue and the biological requirements necessary to support regeneration (3,11).

3. Application of functional hydrogels in CVD

Hydrogels have been applied across cardiovascular diseases, including MI, heart failure, vascular atherosclerosis and heart valve disease, typically as components of regenerative medicine or targeted therapeutic strategies (5,15,31,51).

Treatment of MI. MI, commonly referred to as a heart attack, results from occlusion of a coronary artery, leading to ischemia and necrosis of cardiac muscle tissue (68,69). The primary goals of post-MI therapy are to preserve cardiac function, promote myocardial regeneration and prevent adverse ventricular remodeling (3,6). Standard post-MI management, including reperfusion therapy and pharmacological agents such as ACE inhibitors and β-blockers, aims to limit infarct size and decrease cardiac workload, however, these interventions do not restore lost myocardium (7,31). Functional hydrogels have been investigated as a multifaceted strategy for cardiac repair, serving as structural scaffolds, therapeutic delivery platforms and supportive biomaterials that actively promote myocardial regeneration (5,11).

Injectable hydrogels for cardiac repair. One of the most direct approaches involves injection of a hydrogel or hydrogel precursor into the infarcted myocardium, typically via intracardiac administration, either surgically or through catheter-based delivery (33). Following administration, the hydrogel forms a bulking scaffold within the scarred region. This intervention confers an immediate mechanical benefit by increasing ventricular wall thickness and decreasing wall stress on the remaining myocardium. Finite element modeling and preclinical animal studies have demonstrated that intramyocardial injection of biomaterials attenuates ventricular dilation and preserves physiological geometry, thereby improving cardiac pump function (3). For example, an injectable HA-based hydrogel with optimized stiffness provides mechanical support and results in reduced infarct expansion in treated hearts compared with controls (70). Beyond passive mechanical reinforcement, injectable hydrogels serve as 3D scaffolds that permit cell infiltration (13). Ideally, the material undergoes gradual degradation and is replaced by newly formed tissue, such as vascularized myocardium, rather than persistent fibrotic scar tissue (16).

A variety of materials have been evaluated as injectable cardiac hydrogels. Natural polymers, including collagen, fibrin and alginate, were among the earliest candidates investigated (11,17). Collagen injections in animal models improves cardiac function, potentially by providing a provisional matrix that facilitates cardiomyocyte alignment and limits increases in ventricular wall stress (28). Leveraging its capacity to form stable gels through ionic cross-linking, calcium-cross-linked alginate injected into rat and porcine MI models increases wall thickness and improves ejection fraction (EF) (3,34). These effects are attributed to a combination of mechanical reinforcement and pro-angiogenic bioactivity. This strategy has progressed to clinical evaluation as the IK-5001 hydrogel (BioLineRx) (33). In a first-in-human study, intracoronary administration of this alginate hydrogel shortly following MI was demonstrated to be feasible and safe (33). Another injectable hydrogel, VentriGel (Ventrix, Inc), is derived from decellularized porcine c-ECM (71). It is supplied as a lyophilized cardiac matrix powder that is reconstituted and administered as a liquid, followed by *in situ* gelation within the myocardium. VentriGel retains native cardiac ECM biochemical cues and, in preclinical studies, recruits endogenous cells and promotes novel myocardial tissue formation (19,71). A Phase I clinical trial evaluating catheter-based delivery of VentriGel in patients following MI demonstrated safety and preliminary signs of functional improvement, including increased exercise capacity and trends toward improved cardiac function, particularly in patients treated >1 year after MI (71). These findings represent important translational milestones, demonstrating that catheter-based hydrogel therapy is feasible and safe in human patients.

Cell delivery and myocardial tissue engineering. A notable application of hydrogels in MI therapy is their use as cell delivery vehicles. Numerous cell types, including mesenchymal stem cells (MSCs), adipose-derived SCs, bone marrow-derived mononuclear cells, induced pluripotent SC (iPSC)-derived cardiomyocytes and cardiac progenitor cells, have been investigated for cardiac regeneration (3). Delivery of these cells within a hydrogel enhances their retention and survival in the myocardium compared with injection in saline alone (20). The hostile post-MI microenvironment, characterized by inflammation, oxidative stress, and ECM disruption, causes the majority of injected cells to undergo apoptosis or be rapidly cleared (31). Hydrogels provide a protective and adhesive microenvironment that promotes cell retention and supports cell viability. For example, a chitosan-based hydrogel conjugated with survival-promoting peptides increases the engraftment of transplanted cardiomyocytes and enhances neovascularization in the infarcted region (72). Similarly, fibrin-based patches loaded with SCs demonstrated higher cell survival rates and greater improvements in cardiac function compared with cell transplantation alone (24). Hydrogels can be pre-seeded with cells and implanted as cardiac patches. In this approach, cells are cultured within or on the hydrogel scaffold *in vitro*, typically under dynamic mechanical stimulation

to promote tissue maturation, and the resulting cell-laden construct is surgically applied to the infarcted myocardium. Such tissue-engineered cardiac patches, fabricated using scaffolds composed of collagen, fibrin or synthetic polymers, have demonstrated partial remuscularization of injured myocardium in animal models (64).

A study (72) reported the development of a self-healing, electrically conductive injectable hydrogel based on chitosan-graft-aniline tetramer for cardiac therapy. Owing to its decreased viscosity under shear stress, allowing easy injection) and self-healing properties, this hydrogel enables minimally invasive administration and provides a protective niche for transplanted cells. In a rat model, it exhibits favorable injectability, controllable cell release and complete biodegradation within 45 days, underscoring its potential as a cell delivery platform for cardiovascular therapy (72).

Growth factor and drug delivery. Hydrogels serve as versatile drug delivery platforms in the infarcted myocardium. Instead of systemic administration, therapeutic agents are incorporated into a hydrogel and delivered locally to the injury site, thereby achieving high local concentrations while minimizing systemic adverse effects (3,5). A range of cargos has been investigated, including small-molecule agents such as anti-inflammatory and antioxidant compounds, cytokines and growth factors, nucleic acids and extracellular vesicles (EVs) (11). The structural characteristics of the hydrogel regulate release kinetics, either through diffusion-driven release mediated by water uptake and swelling or through degradation-triggered release mechanisms (57).

Delivery of pro-angiogenic factors to promote neovascularization within the infarcted region is key for supporting regenerating myocardium. VEGF and basic FGF (bFGF) are well-established angiogenic proteins with short biological half-lives when administered in free form. Encapsulation within a hydrogel enables sustained release over days to weeks (73). In a representative study, a fibrin-based hydrogel patch releasing VEGF was applied to infarcted rat hearts (51). Over a 4 week period, it increases capillary density in the infarct border zone and improves cardiac function compared with controls. The hydrogel ensures prolonged local retention of VEGF, allowing it to exert therapeutic effects during the key healing phase. Similarly, dual delivery of an angiogenic peptide, N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) and the chemokine stromal cell-derived factor-1α (SDF-1α) from an injectable hydrogel enhances angiogenesis and promotes SC recruitment to the infarcted myocardium, resulting in decreased infarct size and improved LV function in a mouse MI model (73,74).

Another strategy involves modulation of inflammation and prevention of cardiomyocyte death during the acute phase of MI. Immediately following infarction, waves of inflammatory cells, including neutrophils and macrophages, infiltrate the injured myocardium and may cause collateral tissue damage through oxidative stress and protease release (64). Hydrogels have been loaded with anti-inflammatory agents, such as IL-10, glucocorticoids or non-steroidal anti-inflammatory drugs (NSAIDs), to locally attenuate this inflammatory response. For example, an injectable peptide hydrogel carrying an NSAID and iron oxide nanoparticles has been evaluated for targeting macrophages in atherosclerotic cardiac tissue, demonstrating decreased inflammatory markers and promotion of a reparative macrophage phenotype (75). In MI, a hydrogel-based platform may similarly deliver immunomodulatory agents to promote macrophage polarization from a pro-inflammatory M1 to a pro-reparative M2 phenotype, thereby limiting secondary tissue injury. One approach incorporates microparticles releasing IL-10 within a cardiac patch, resulting in decreased fibrosis and improved cardiac function in a rat MI model (34).

Hydrogels encapsulate antifibrotic or anti-remodeling agents. During post-infarction healing, excessive fibrosis and ventricular dilation contribute to progressive cardiac dysfunction (7). The peptide Ac-SDKP inhibits cardiac fibroblast activation. Firoozi *et al* (76) synthesized a RADA-SDKP hydrogel composed of a self-assembling gel-forming core sequence (RADA) and a bioactive motif (SDKP), providing structural flexibility through dynamic self-assembly to facilitate injectability. Following transplantation of the hydrogel, LVEF is improved. This functional improvement is associated with a marked reduction in fibrotic tissue deposition, enhanced microvascular density and attenuation of the inflammatory response within the infarcted region (76). Similarly, tissue inhibitors of metalloproteinases have been delivered via MMP-responsive hydrogels to locally counteract MMP-mediated ECM degradation that contributes to ventricular wall thinning (77).

Timing of therapeutic delivery can be modulated through hydrogel design. Physiological requirements of the heart evolve over time following MI, progressing through inflammatory, proliferative and remodeling phases (64). Hydrogels provide the capacity for temporally controlled release profiles (for example, immediate release of an anti-apoptotic agent to preserve jeopardized cardiomyocytes, followed by delayed release of a growth factor to stimulate regenerative processes). Multiphase hydrogel systems have been engineered to achieve sequential delivery (62). For example, a two-component hydrogel system has been developed in which one component rapidly releases SDF-1α to recruit progenitor cells, while the second component enables sustained release of VEGF to promote neovascularization (73). This staged delivery approach enhances cardiac repair in a mouse MI model.

Gene therapy and exosome delivery. Beyond proteins and cells, hydrogels are explored as platforms for localized gene therapy in the myocardium (78). Plasmid DNA, mRNA or viral vectors encoding regenerative factors can be incorporated into hydrogel matrices to enable sustained and site-specific gene delivery (21,78). An injectable biocompatible hydrogel capable of facilitating efficient delivery of a nanocomplex composed of graphene oxide (GO) and the pro-angiogenic VEGF-165 gene demonstrates therapeutic potential for myocardial repair (Fig. 5A) (78). Exosomes (nanoscale EVs secreted by cells that contain miRs and proteins) have attracted attention as cell-free therapeutic agents (79-81). Exosomes attenuate apoptosis and promote cardiac repair in a manner comparable with their parent cells (79-81). However, freely injected exosomes are rapidly cleared from the myocardium. Encapsulation within hydrogels prolongs their retention at the injury site (82). Improved retention of exosomes in injured myocardium has been demonstrated using an injectable shear-thinning gel (STG) loaded with EVs (82) (Fig. 5B-D). The STG shows

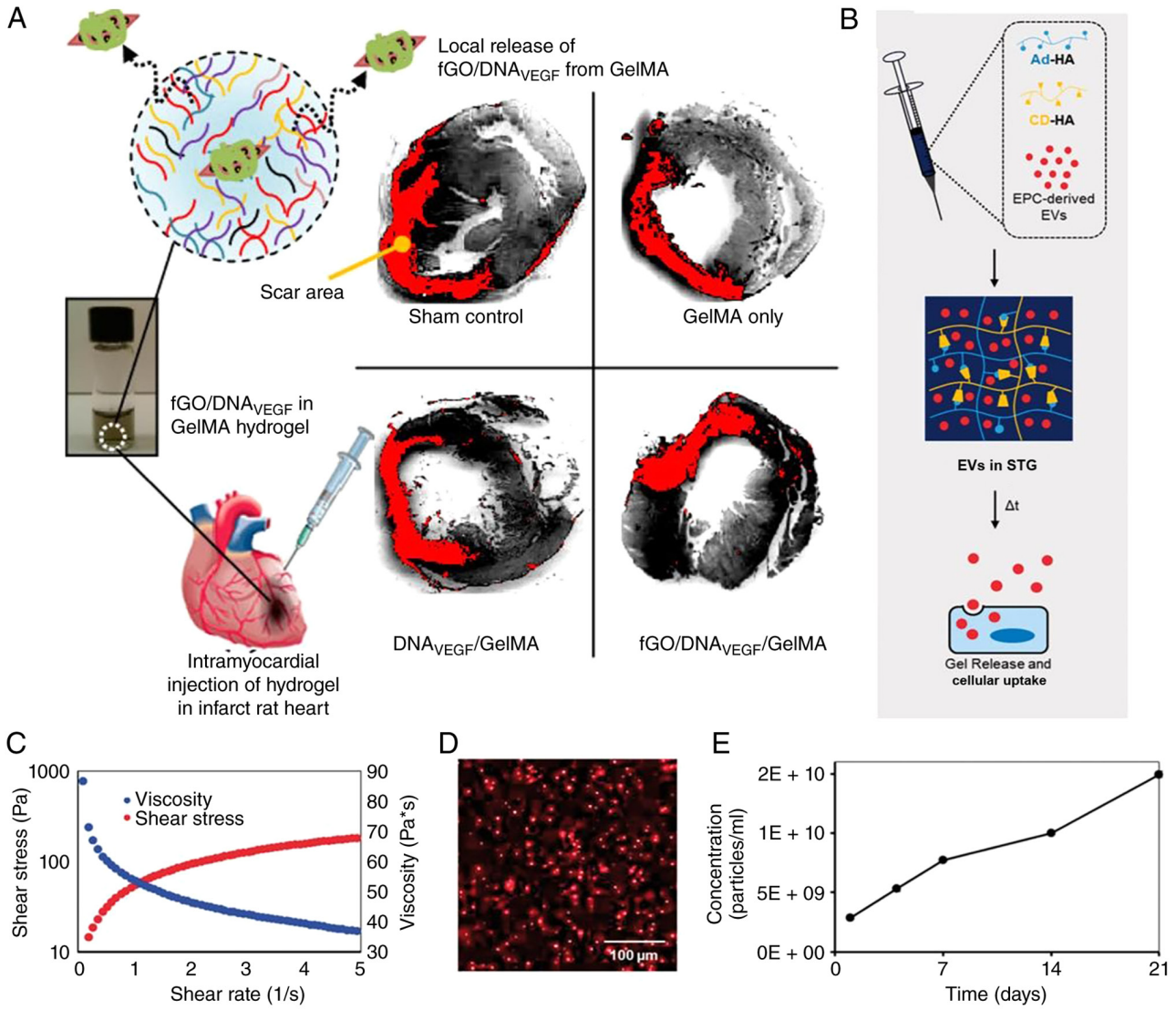

Figure 5. Hydrogel-based delivery systems for gene and exosome therapy in myocardial repair. (A) Schematic of an injectable GO/hydrogel-based angiogenic gene delivery system carrying the VEGF-165 gene. The GO nanocomplex enhances transfection efficiency and the hydrogel enables sustained local gene release for cardiac repair. Adapted from (78) (open access). STG for EV delivery. (B) EVs are mixed with CD-HA and Ad-HA, which form a supramolecular gel via guest-host chemistry. (C) Under syringe shear stress, the gel shear-thins to allow injection; upon strain cessation, it rapidly re-assembles at the myocardial injection site, entrapping EVs. (D) Confocal microscopy showing even distribution of CM-DiI-labeled EVs within the STG. (E) Cumulative EV release profile over 21 days, demonstrating steady particle release and cellular uptake. Adapted from (82). Copyright 2018, Oxford University Press. fGO, functionalized graphene oxide; STG, shear-thinning gel; EV, extracellular vesicle; CD, cyclodextrin; HA, hyaluronic acid; Ad, adamantane; GeIMA, gelatin methacryloyl; EPC, endothelial progenitor cell.

even distribution of EVs within the gel matrix (Fig. 5D) and sustained EV release over 21 days (Fig. 5E), which collectively enhances myocardial function, improves hemodynamic parameters and increases neovascularization (82). Furthermore, exosomes derived from human adipose-derived SCs, gelatin and laponite are combined to formulate a shear-thinning nanocomposite hydrogel (nSi Gel) as an injectable carrier of the stem cell secretome, which increases vascular density surrounding the myocardium, improves cardiac function and decreases scar formation (83). These findings demonstrate how hydrogels function as reservoirs for advanced biological agents, such as nucleic acids or EVs, ensuring localized therapeutic activity rather than rapid systemic dispersion.

Epicardial patches and cardiac tissue engineering. In addition to injectable systems, hydrogels have been developed in patch form for application to the epicardium, the outer surface of the heart, overlying the infarcted region (84). These patches may be acellular or seeded with therapeutic cells. The underlying concept is to provide a scaffold that covers the damaged myocardium, promotes tissue regeneration from the epicardial surface inward and serves as a mechanical restraint to limit adverse ventricular dilation (5). Epicardial patches have been fabricated from synthetic polymers, such as degradable polyester meshes embedded within hydrogel matrices, as well as from naturally derived ECM sheets (17,64). Patch-based approaches cover a broader area and accommodate larger numbers of cells or higher drug loads, however, they typically require surgical implantation. Consequently, minimally invasive strategies, including thoracoscopic placement or catheter-based attachment techniques, are under investigation (5). In addition, epicardial priming through placement of

bioactive materials on the cardiac surface has been explored to stimulate recruitment of endogenous progenitor cells from the pericardial space (64). Hydrogels that can be applied by painting or spraying onto the epicardium are in development, with some formulations incorporating mucoadhesive properties to enhance adhesion to the moist cardiac surface (52). Furthermore, hydrogel-based patches can be prevascularized or engineered with microchannel architectures to facilitate oxygen and nutrient diffusion, supporting cell survival following implantation. A 3D bioprinted cardiac patch composed of a PEG hydrogel has been fabricated with an internal microchannel network (64). When loaded with MSCs and implanted in a mouse MI model, the microchannel-containing patch results in greater vascular ingrowth and superior functional recovery compared with a solid patch, underscoring the importance of internal architecture (34). Wang *et al* (85) established a rabbit MI model and administered an epicardial injection of a hydrogel incorporating bone marrow-derived mesenchymal stem cells (BMSCs). Compared with control groups, retention of BMSC grafts within the infarcted myocardium is prolonged, an effect attributed to the properties of the α-cyclodextrin (CD)/PEG-b-polycaprolactone-(dodecanedioic acid)-polycaprolactone-PEG (MPEG-PCL-MPEG) hydrogel system. The transplanted BMSCs contribute to restoration of cardiac function, as evidenced by increased vascular density in the infarct border zone (85). Although the long-term therapeutic efficacy of this approach requires further investigation, the α-CD/MPEG-PCL-MPEG hydrogel, characterized by its cytoprotective properties, improves LV function and attenuates adverse LV remodeling (85).

Vascular regeneration and repair. Vascular diseases, particularly atherosclerosis affecting arterial vessels, contribute to life-threatening conditions such as coronary artery and peripheral arterial disease and stroke (1,2). Conventional treatments include bypass graft surgery using either autologous vessels or synthetic grafts and percutaneous angioplasty with stent implantation to restore luminal patency in occluded arteries (5). Although these interventions are typically effective in the short term, they present notable limitations. Synthetic small-diameter grafts (for arteries <6 mm) exhibit high failure rates due to thrombosis or intimal hyperplasia, defined as excessive neointimal tissue formation (18). Stents may undergo restenosis or induce chronic inflammatory responses. Functional hydrogels offer strategies for engineering artificial blood vessels, enhancing integration and healing of vascular implants and treating vascular pathologies such as atherosclerosis (45,63).

Tissue-engineered vascular grafts (TEVGs). The development of TEVGs has long been an objective, particularly for small-diameter arteries (≤6 mm), such as coronary or peripheral vessels (86). Conventional synthetic grafts, typically composed of PET or ePTFE, perform adequately in large-diameter applications but demonstrate high failure rates in small-caliber vessels due to thrombosis and intimal hyperplasia (86). Clinical outcomes for large-diameter grafts (>6 mm) have been satisfactory, with reported patency rates of up to 95% at 5 years (87). By contrast, the aforementioned study reported a patency rate of 30% for small-diameter grafts (<6 mm) (87). Additional investigations have documented patency rates ranging from 0 to 25% in canine and rabbit models after implantation periods of weeks to months (88-90).

Hydrogels serve as scaffold materials capable of forming the structural matrix of bioengineered vascular grafts (16). One strategy involves fabrication of a tubular hydrogel scaffold (optionally reinforced with supportive materials) that can be seeded with vascular cells and matured into a functional vessel. Natural hydrogels, such as collagen or fibrin, have been molded into tubular configurations for this purpose (24,46). These materials provide a favorable microenvironment for smooth muscle and endothelial cells to deposit ECM components and organize into a vessel wall. However, hydrogel-only tubes typically exhibit insufficient mechanical strength, particularly in terms of burst pressure, during the early implantation phase (63). To address these limitations, strategies have been developed in cardiovascular tissue engineering, including the use of diverse scaffold types, such as natural and synthetic polymers (91-93), as well as decellularized xenografts and homografts (94-96), in combination with different cell sources, including valvular interstitial cells (97,98), BMSCs (99) and progenitor cells obtained from peripheral blood or amniotic fluid (100-102). In addition, 3D bioprinting techniques have been employed to fabricate vessel-like constructs using hydrogel-based bioinks laden with cells, enabling the creation of defined multilayered wall architectures (45). Another strategy involves cell sheet engineering, in which cell monolayers cultured on temperature-responsive hydrogel surfaces are detached as intact sheets and wrapped into tubular structures. Although the final graft does not contain a hydrogel component, this approach relies on PNIPAM, a thermoresponsive hydrogel, to enable enzyme-free harvesting of cell sheets (103). These cell sheet-based grafts have demonstrated promising outcomes in small animal models (45,85,103).

Hydrogels serve a more direct role in fully synthetic TEVGs through the development of hybrid graft materials. One design involves electrospinning a blend of biodegradable polymer fibers with an incorporated hydrogel component to enhance graft compliance and facilitate cell infiltration (104). Another approach involves chemically bonding a hydrogel layer to the luminal surface of a porous synthetic graft, thereby creating a bioactive interface that promotes endothelialization (63). This inner hydrogel layer can be functionalized with bioactive agents such as heparin to reduce thrombogenicity, or VEGF to stimulate endothelial cell recruitment. In a study by Chen *et al* (105), a small-diameter polyethylene terephthalate graft was coated on its luminal surface with a heparin-containing hydrogel. In a rabbit carotid artery implantation model, this modification results in decreased thrombosis and more rapid formation of a functional endothelial lining compared with uncoated grafts (105). A key objective in TEVG development is to promote host-mediated remodeling and repopulation of the graft with autologous cells, effectively transforming the construct into a living vascular tissue (86). Hydrogels, owing to their cytocompatible and bioactive properties, are well-suited to support this process. For example, a bioinspired small-diameter vascular graft incorporated a hydrogel derived from decellularized arterial matrix on the luminal surface, providing biochemical cues that

accelerate endothelial coverage following implantation (106). Establishment of a confluent endothelium is key for long-term graft patency, as it suppresses thrombosis and pathological smooth muscle cell proliferation (86).

Promotion of endothelialization and hydrogel coatings for stents. In vascular intervention, such as percutaneous angioplasty with stent implantation, a challenge is the host response to the implanted stent (107). Drug-eluting stents incorporate antiproliferative agents (sirolimus or paclitaxel) within a polymer coating to suppress excessive smooth muscle cell proliferation and thereby prevent restenosis, however, these agents may also delay endothelial healing (107). Ideally, a stent should inhibit neointimal hyperplasia and rapidly achieve coverage by a functional endothelial layer, thereby mimicking the behavior of a native artery and decreasing the risk of thrombosis. Hydrogel-based coatings are being investigated to create pro-healing stent surfaces. One approach involves nitric oxide (NO)-releasing hydrogel coatings applied to stents (105). A tough NO-eluting (NOE) hydrogel coating has been designed for sustained NO release (Fig. 6A). Following stent deployment in porcine coronary arteries (Fig. 6B), digital subtraction angiography shows that the NOE coating prevents severe restenosis observed in control stents (Fig. 6C; yellow arrow). Histological analysis (Fig. 6D) and luminal surface imaging at 2 weeks and 3 months (Fig. 6E) confirms that the NOE coating decreases neointimal hyperplasia and thrombosis. Confocal microscopy (Fig. 6F) reveals rapid and complete endothelialization ($CD31^+$ cells) on the NOE-coated stents (105). Another strategy employs antibody-functionalized hydrogels, such as those conjugated with anti-CD34 antibodies, to capture circulating endothelial progenitor cells and accelerate endothelialization (106). Zwitterionic hydrogels, characterized by resistance to non-specific protein adsorption, have also been utilized as coatings to reduce platelet adhesion while selectively promoting endothelial cell attachment (104). In one study, a zwitterionic hydrogel loaded with VEGF was applied to a heart valve prosthesis to enhance endothelialization and decrease calcification; this may also be applicable to vascular stents (108). For bioresorbable stents composed of biodegradable metals, such as magnesium, or biodegradable polymers, hydrogel coatings modulate degradation kinetics and improve the tissue-device interface. In one study, magnesium alloy stents were coated with a fucoidan-containing hydrogel, which enhanced hemocompatibility and promoted endothelial cell colonization during gradual metal degradation (109). Fucoidan, a sulfated glycosaminoglycan with anticoagulant properties, contributes to localized inhibition of thrombosis and inflammation (109).

Hydrogel-based strategies for atherosclerosis treatment. Atherosclerosis, characterized by the accumulation of lipid-rich plaques within arterial walls, underlies numerous cardiovascular events, including MI and stroke (1,2). Although risk factor modification and systemic pharmacotherapy, such as statins and anti-inflammatory agents, remain the cornerstone of management, attention has been directed toward localized therapeutic strategies aimed at stabilizing or regressing high-risk plaques (75). Hydrogels serve as promising platforms in this context, particularly as injectable depots that can be delivered to vulnerable plaque sites for localized drug release (110).

One strategy targets intraplaque neovascularization, a hallmark of advanced atherosclerotic lesions. Fragile microvessels that develop within plaques are prone to rupture, leading to intraplaque hemorrhage and contributing to plaque instability. In a recent study, a thermosensitive hydrogel composed of poloxamer 407 and alginate was employed to deliver PEDF, an endogenous inhibitor of pathological angiogenesis, to atherosclerotic plaques (51). The formulation remained in a liquid state during catheter-based administration and gelled at physiological temperature, forming a localized drug reservoir at the plaque site. Sustained release of PEDF decreases intraplaque neovessel density and plaque progression in a mouse model of atherosclerosis (51). Treated plaques exhibited smaller lipid cores and thicker, more stable fibrous caps, indicating enhanced lesion stabilization. This approach demonstrates how hydrogel-based delivery systems can localize therapeutics that would lack plaque specificity if administered systemically (110).

Hydrogels have been investigated as vehicles for delivering agents that modulate plaque-associated inflammation (75). For example, an injectable peptide hydrogel incorporating an anti-inflammatory agent (naproxen) and a ferrofluid for magnetic targeting was developed to treat atherosclerotic plaques by promoting macrophage polarization toward a reparative phenotype. In principle, a hydrogel could be directed to the lesion site using an external magnetic field via embedded Fe_3O_4 nanoparticles and provide sustained local drug release (75). Similarly, another group developed a filamentous nanofiber hydrogel depot for prolonged delivery of anti-inflammatory nanoparticles, resulting in sustained suppression of inflammatory markers in an experimental model of atherosclerosis (110). Gene and RNA-based therapeutic delivery to plaques using hydrogel systems has also been explored (66,78). For example, administration of small interfering RNA (siRNA) or miR targeting pro-atherogenic genes in macrophages or vascular smooth muscle cells may modulate plaque progression (78). Hydrogels shield such nucleic acids from enzymatic degradation and enhance their local retention within the plaque microenvironment (62,78). Preliminary studies employing DNA-loaded hydrogels to modulate macrophage signaling pathways in arterial tissue have demonstrated decreased pro-inflammatory cytokine expression (78,110,111). Although these strategies remain largely at the preclinical stage, they represent a paradigm shift toward localized resolution of plaque pathology. While intramural hydrogel injection into the arterial wall may appear invasive, such delivery could be integrated into existing angioplasty procedures or implemented via specialized catheter systems. This localized therapeutic approach has the potential to complement systemic pharmacotherapy by targeting high-risk plaques individually (107,110).

Heart valve repair and regeneration. Heart valve disease typically necessitates valve replacement (112), with conventional options including mechanical and bioprosthetic valves (Fig. 7A and B). To the best of our knowledge, however, all currently available prosthetic devices are associated with limitations that increase the risk of morbidity and mortality. For

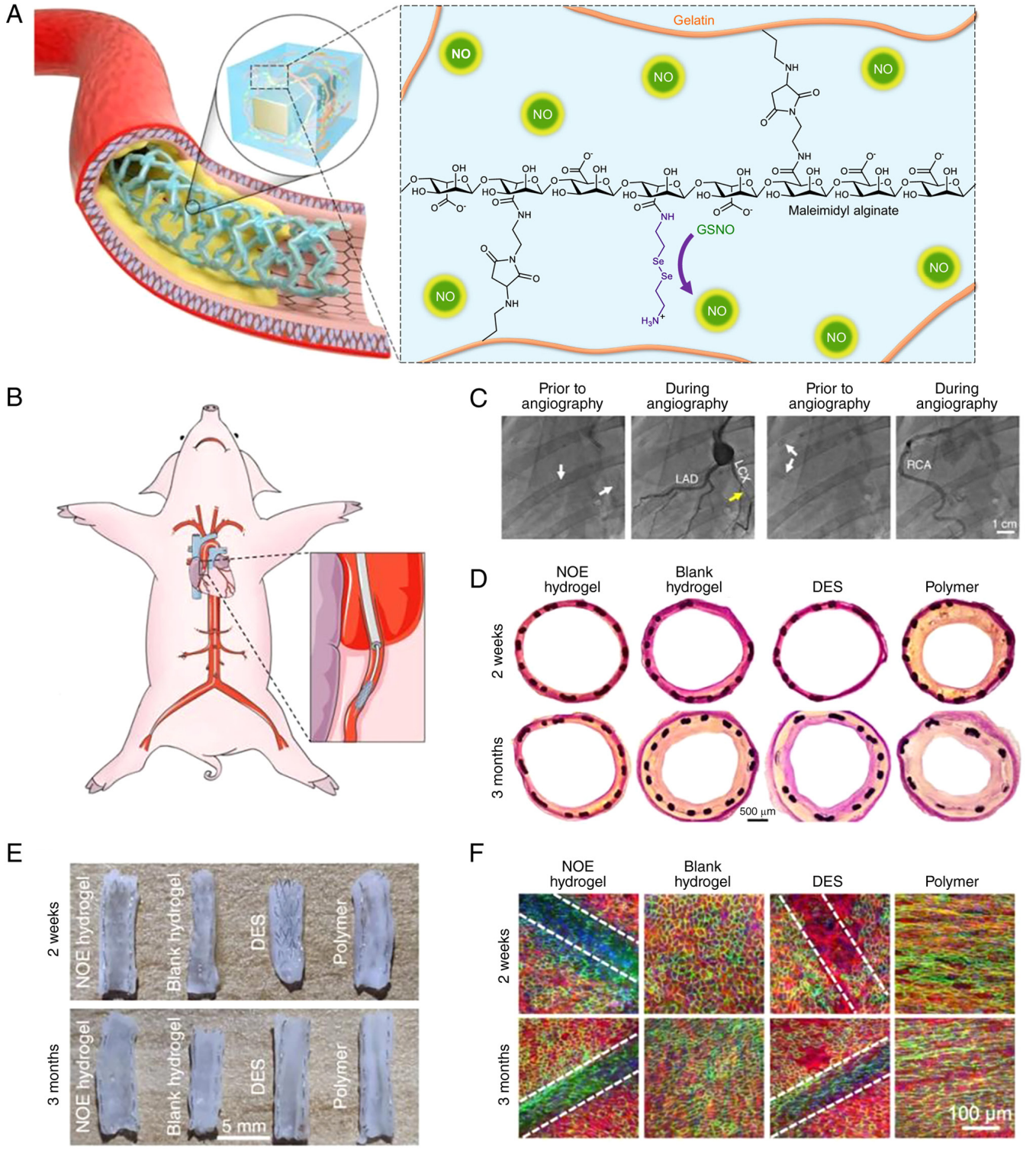

Figure 6. NOE hydrogel coating for vascular stents. (A) Design of the NOE hydrogel with sustained NO release capability. (B) Schematic of stent deployment in porcine coronary arteries. (C) Digital subtraction angiography before harvest. White arrows indicate implanted stents; yellow arrow shows severe restenosis in a polymer-coated control stent. (D) Cross-sections of stented arteries following van Gieson staining. (E) Luminal surface images at 2 weeks and 3 months post-deployment. (F) Confocal laser-scanning microscopy showing endothelialization on stents (dashed lines); blue, cell nuclei; green, CD31 (endothelial marker), red, F-actin. NOE coating promotes rapid and complete endothelial coverage. Adapted from (105) (open access). Blank, control; NOE, nitric oxide-eluting; GSNO, S-nitrosoglutathione; DES, drug-eluting stent.

example, mechanical valves are associated with thromboembolic events and hemorrhagic complications, thereby requiring lifelong anticoagulation therapy (113). Bioprosthetic valves demonstrate limited long-term durability due to structural degeneration, calcification and fibrotic remodeling and they may also provoke immunogenic responses (114-116). To the best of our knowledge, no existing valve replacement strategy fully overcomes these limitations, rendering tissue-engineered heart valves (TEHVs) (Fig. 7C) an appealing therapeutic alternative for affected patients (117-121).

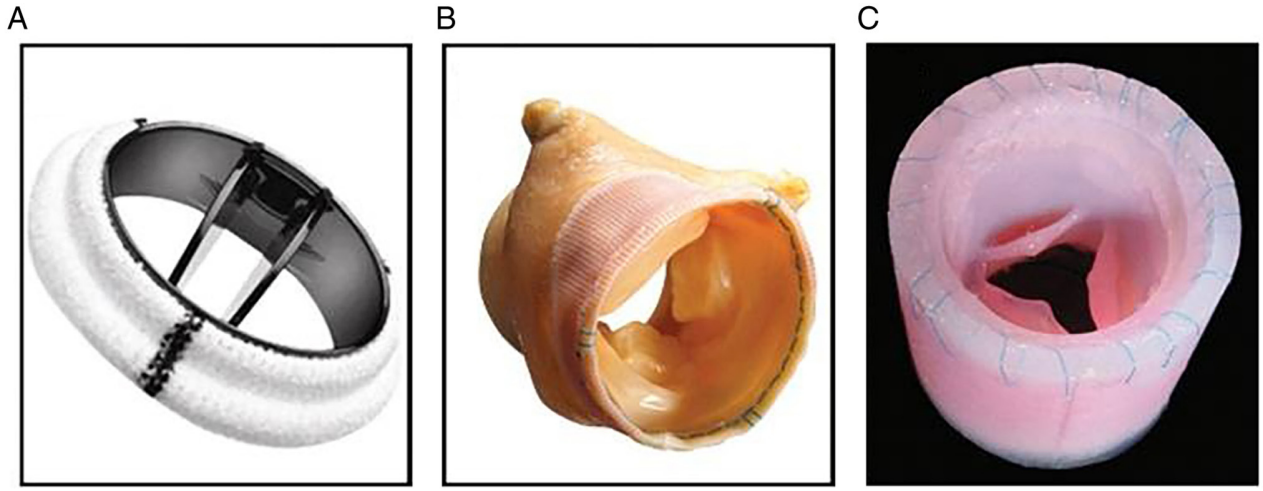

Figure 7. Heart valve prostheses. (A) Mechanical heart valve (durable but requires lifelong anticoagulation). (B) Biological (bioprosthetic) heart valve (better hemocompatibility but limited durability due to calcification and degeneration). (C) Living, fibrin-based tissue-engineered tri-leaflet heart valve (regenerative potential, capable of remodeling but still under preclinical/early clinical development). Adapted from (15,121). Copyright 2007, Elsevier.

Hydrogels are attractive materials in heart valve engineering owing to their high water content, biocompatibility and ability to mimic the compliant connective tissue of native valve leaflets, and they can be seeded with cells capable of remodeling the construct (122-124). Native valve leaflets exhibit a trilayered architecture, comprising collagen fibers that provide tensile strength, proteoglycans that confer shock absorption and elastin that enables elastic recoil (115). Pure hydrogels, such as collagen or fibrin, replicate certain characteristics (for example, softness and pliability) but may lack sufficient mechanical strength to withstand repetitive cyclic loading during valve opening and closing (24). Consequently, hydrogel application in TEHVs typically involves composite designs or the use of hydrogels as cell carriers within a mechanically robust framework (15). One strategy employs a decellularized valve matrix as the primary scaffold, which preserves native architecture and mechanical integrity, followed by infusion or coating with a cell-or growth factor-laden hydrogel (5). The hydrogel facilitates reseeding of the decellularized scaffold with autologous endothelial and valvular interstitial cells and can fill microstructural defects. Hydrogels such as gelatin methacrylate or HA-based formulations have been used to impregnate decellularized porcine valves, generating hybrid constructs that support cellular infiltration while maintaining cusp flexibility (25). Another research direction focuses on fabricating synthetic or hybrid valve scaffolds incorporating hydrogels. Li *et al* (125) developed a PEG/poly(sulfobetaine methacrylate)] dual-network hydrogel coating on decellularized heart valves (Fig. 8A). Following implantation, the hydrogel coating provides sufficient flexural stiffness and fatigue resistance to withstand mechanical cycling, while facilitating endothelial cell coverage and ECM remodeling (Fig. 8B) (125). Hydrogel coatings mitigate calcification of bioprosthetic valves. For example, a zwitterionic hydrogel coating loaded with heparin and VEGF demonstrates reduced calcific deposition and enhanced endothelialization in a rabbit animal model (106).

Four-dimensional (4D) bioprinting, where printed constructs are designed to undergo controlled structural changes over time, may enable the fabrication of hydrogel-based valves that mature in response to physiological forces (123,124). A valve could be printed in a predefined geometry with cells embedded within a hydrogel matrix; as the cells synthesize ECM components and the hydrogel degrades, the construct may transition into a mechanically functional configuration shaped by bioreactor-mediated conditioning (121). Conditioning engineered valves in a pulsatile flow bioreactor enhances collagen alignment and improves mechanical strength (15). Hydrogels serve a key role in these strategies by providing an initial structural template that is progressively replaced by newly formed tissue.

4. Cell and molecular mechanisms of hydrogel-tissue interactions in CVD

Functional hydrogels modulate cardiovascular tissue repair through precise regulation of cell behavior and molecular signaling pathways (5,16).

Pro-angiogenic mechanisms. Hydrogels promote vascularization through coordinated biochemical signaling and mechanotransductive pathways (126,127). VEGF-loaded HA nanobubble/Pluronic F127 diacrylate) hydrogels activate PI3K/Akt signaling, thereby enhancing endothelial cell migration and proliferation (126). Spatially heterogeneous platelet-rich plasma (PRP) fibrin hydrogels direct 3D vasculogenesis via the integrin β1/phosphorylated focal adhesion kinase/phosphorylated myosin light chain pathway and stabilize vascular endothelial-cadherin/β-catenin junctions (127). UCL-TRO-1938, a PI3Kα activator delivered from alginate hydrogels, stimulates angiogenesis in a temporally controlled manner during the acute ischemic phase (128). Moreover, c-ECM hydrogels enable sequential release of VEGF and Ang-1 mimetic peptides in response to MMP-2, thereby promoting the formation of mature and functional blood vessels (60).

Anti-inflammatory mechanisms. Hydrogels reshape the cardiac immune microenvironment through modulation of conserved

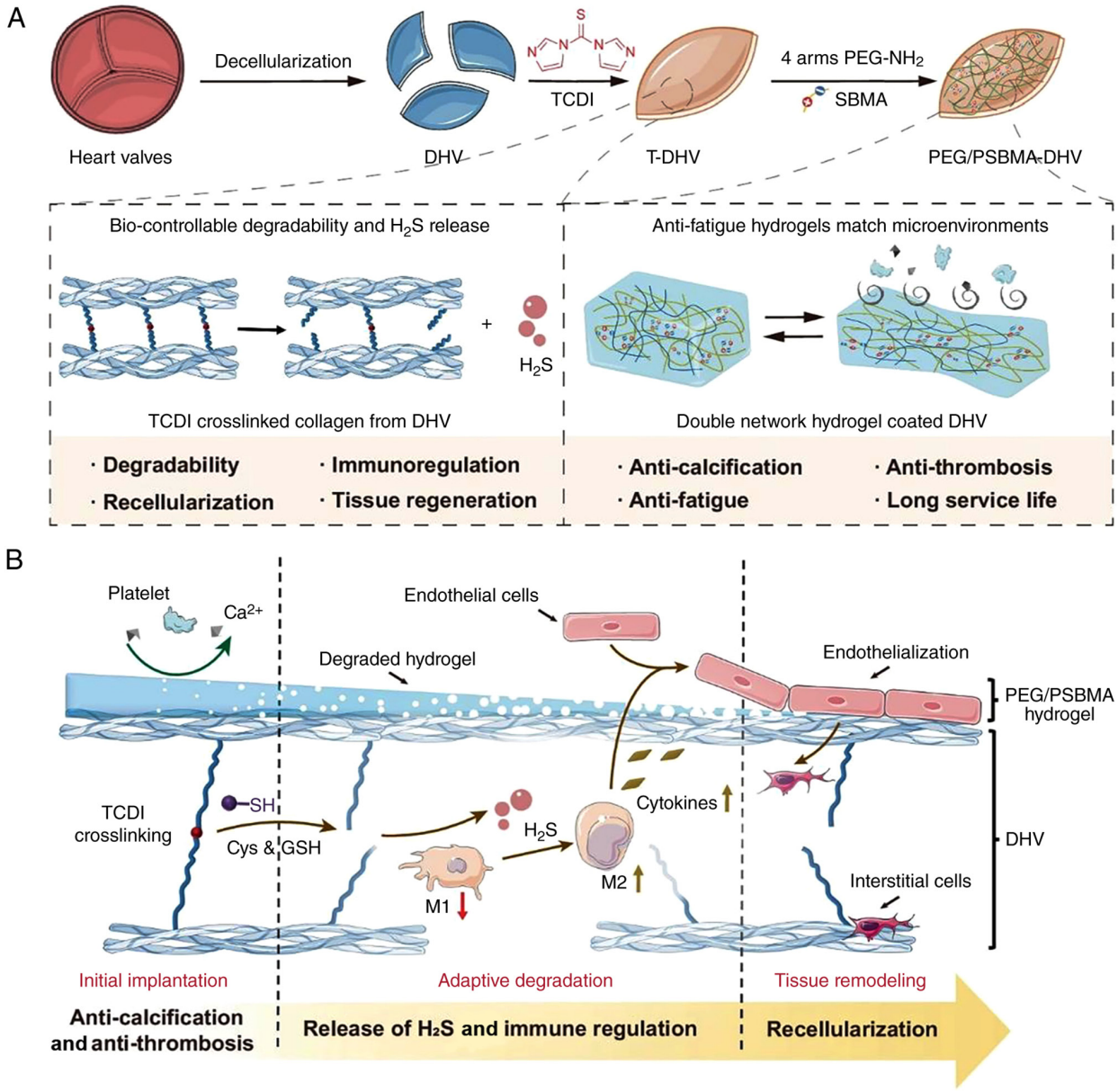

Figure 8. PEG/PSBMA dual-network hydrogel coating for heart valve regeneration. (A) Schematic overview of the fabrication and structure of PEG/PSBMA-coated DHV. Created with BioRender.com. (B) Functional mechanism of PEG/PSBMA-DHV. The hydrogel coating provides sufficient flexural stiffness and fatigue resistance to withstand repetitive mechanical cycling, while simultaneously promoting endothelial cell coverage and extracellular matrix remodeling, thereby enabling adaptive valve regeneration *in vivo*. Adapted from (125) (open access). PEG, poly(ethylene glycol); PSBMA, poly(sulfobetaine methacrylate); T-DHV, TCDI-crosslinked decellularized heart valve; TCDI, 1,1'-thiocarbonyldiimidazole.

anti-inflammatory and antioxidant signaling pathways. MXene-PVA hydrogels activate AMPK/Nrf2/Keap1 signaling to enhance ROS clearance and suppress NF-κB activity, while promoting macrophage polarization toward a reparative M2 phenotype (129). Similarly, ROS-responsive adhesive hydrogels releasing andrographolide derivatives, NLRP3 inhibitor-loaded folic acid-HA-mesoporous silica nanoparticles and gelatin methacrylate/gelatin norbornene hydrogel patches promote M2 polarization independent of exogenous cytokine supplementation (130,131). MMP-responsive hydrogels enable on-demand IL-4 plasmid delivery to suppress post-MI inflammation, whereas p38-responsive supramolecular hydrogels inhibit p38 mitogen-activated protein kinase signaling to attenuate oxidative stress and inflammatory responses (132,133). Furthermore, thermosensitive hydrogels delivering thiamet-G enhance M2 polarization via signal transducer and activator of transcription 6 O-GlcNAcylation (134). Annexin A1-loaded alginate hydrogels modulate macrophage polarization through the AMPK-mTOR axis (135), while exosome-laden hydrogels regulate PI3K/Akt/mTOR, Hippo, TGF-β, HIF-1 and FoxO signaling pathways to facilitate cardiac repair (136). Collectively, these findings underscore the capacity of hydrogels to modulate the cardiac immune microenvironment through multiple convergent molecular mechanisms.

Anti-fibrotic mechanisms. Hydrogels mitigate maladaptive cardiac fibrosis through multiple complementary mechanisms. Co-delivery of the MMP-2 inhibitor CTT (a cyclic peptide) and bFGF inhibits fibroblast-to-myofibroblast differentiation (137).

ROS-responsive hydrogels releasing anti-IL-11 antibodies reduce scar thickness and border zone expansion by suppressing fibroblast activation (138). Furthermore, injectable alginate composite hydrogels enabling pH-responsive release of bone morphogenetic protein-9 effectively suppress TGF-β mediated fibroblast activation and myocardial fibrosis by antagonizing maladaptive ECM deposition (128). Similarly, a ROS-responsive hydrogel system (superoxide inhibitor, and FT011/liposome-quercetin-thioketal ROS-responsive linker; S1&FT/Lipo-QCFT) sequentially releases the superoxide production inhibitor S1QEL1.1 and tannic acid to attenuate early oxidative injury and promote M2 macrophage polarization, followed by sustained release of the anti-fibrotic agent FT011 to counteract TGF-β1-induced fibrosis and prevent adverse ventricular remodeling (139). Notably, injectable conductive hydrogel patches (GRAXe, a gelatin-base MXene-containing ROS-responsive conductive patch with asymmetric adhesion) integrate ROS-responsive degradation, MXene-mediated electrical conductivity and asymmetric tissue adhesion to restore electromechanical coupling while decreasing fibrotic remodeling (140).

Mechanisms of conductive hydrogels regulating cardiac electrical signal propagation. Conductive hydrogels restore cardiac electrical signal propagation by re-establishing electrophysiological continuity, modulating connexin 43 (Cx43)-dependent gap junctions, stabilizing ion channel function and decreasing electrical heterogeneity across fibrotic infarcted tissue (5). Studies have demonstrated that polypyrrole-chitosan conductive hydrogels bridge electrically isolated cardiomyocyte clusters, synchronize calcium transients and improve conduction velocity across cryoinfarcted myocardium (141-147). *In vivo* administration shortens QRS duration and restores longitudinal conduction, whereas *ex vivo* scar tissue exhibits a three- to four-fold increase in electrical signal amplitude compared with controls, confirming restoration of conductive pathways (141). Injectable conductive hydrogels composed of polypyrrole/PAA and loaded with cardiomyocyte-derived exosomes enhance electrical coupling by upregulating Cx43 expression and improving sarcomeric organization, while concurrently modulating SIRT1/p53 signaling to attenuate oxidative stress and electrical instability (142). *In vivo*, these hydrogels normalize action potential and calcium transient duration and decrease arrhythmia inducibility and electrical resistivity within infarcted tissue. MXene-based conductive hydrogel patches with intrinsic ROS-scavenging capacity and electroconductive properties increase Cx43 expression and enhance electrical signal amplitude in the infarct zone, thereby synchronizing cardiomyocyte contraction through restoration of gap junction communication (143). Their conductivity approximates that of native myocardium, enabling physiological electroconductive restoration . Injectable GO-based conductive hydrogels capable of sustained NO release also provide tissue-matched electrical conductivity. These systems preserve electrical signal propagation, enhance endothelial network formation and maintain electrophysiological stability by reducing ROS-mediated electrical disruption (144). Printable PVA-glutaraldehyde/PEDOT [poly(3,4-ethylenedioxythiophene) (PEDOT) conductive patches efficiently transmit electrical signals to adult cardiomyocytes without introducing notable conduction resistance, demonstrating safe *in vivo* performance and preservation of electrocardiographic parameters (145). Ionic-conductive PEDOT/poly(ionic liquid) hydrogels enhance Cx43 and α-actinin expression, thereby restoring intercellular electrical coupling and decreasing infarct-associated electrical heterogeneity (146). Aniline tetramer-grafted conductive supramolecular hydrogels preserve Cx43 expression in the infarct border zone, maintaining gap junction integrity, improving electrical communication and attenuating adverse ventricular remodeling (147).

5. Challenges

While functional hydrogels hold promise, critical issues must be addressed to ensure their safe and effective translation into routine cardiovascular therapies (5). These challenges range from material-associated concerns (biocompatibility and stability) to practical and economic considerations (scalability and regulatory approval) (5,13). A comprehensive understanding of these barriers and the development of strategies to overcome them is an active focus of ongoing research (5).

Identifying promising candidates and their limitations. ECM-derived hydrogels represent one of the most promising platforms owing to their intrinsic bioactivity. A principal advantage of ECM-derived hydrogels is their capacity to modulate the host inflammatory response and promote tissue regeneration, rather than merely providing passive mechanical support (71). However, their limitations include batch-to-batch variability inherent to biologically sourced materials, low mechanical strength compared with synthetic counterparts and regulatory complexity associated with xenogeneic products (60,71). Alginate-based hydrogels exhibit good biocompatibility and have been extensively investigated for mechanical reinforcement of the infarcted ventricle (3,8). Preclinical studies have demonstrated increased wall thickness, decreased wall stress, and improved cardiac function (33,35). Nevertheless, a major limitation of alginate hydrogels is their lack of intrinsic bioactivity. As non-degradable or slowly degrading materials, they primarily provide mechanical support without actively stimulating tissue regeneration (33,35). Fibrin-based hydrogels have been employed as cell delivery vehicles because of their rapid gelation, biocompatibility and capacity to support cell infiltration and ECM deposition (24). Preclinical studies have demonstrated enhanced cell engraftment and angiogenesis (24,30,31). However, rapid degradation and limited mechanical strength restrict their application as standalone scaffolds in load-bearing cardiac environments (31). Collagen and gelatin-based hydrogels support cardiomyocyte function and have demonstrated efficacy in decreasing infarct size and improving contractility in preclinical models (11,28,70). However, their low stiffness and rapid enzymatic degradation necessitate chemical crosslinking or composite formulation to achieve adequate mechanical stability, which may compromise biocompatibility (5,28). HA hydrogels exhibit immunomodulatory properties, including promotion of M2 macrophage polarization and angiogenesis (32). Although promising for myocardial repair, unmodified HA is mechanically weak

and structurally fragile, requiring chemical modification to enhance mechanical stability, thereby increasing manufacturing complexity (32). Synthetic hydrogels offer tunability and reproducibility, with precisely controllable mechanical properties, degradation kinetics and network architectures. Despite these advantages, most synthetic hydrogel systems remain confined to preclinical development (13). Their intrinsic bioinertness prevents effective cell recognition and adhesion, thereby limiting tissue integration and remodeling unless biofunctionalized with adhesive ligands, such as RGD peptides, or incorporated growth factors (41,45). Conductive composite hydrogels incorporating graphene, gold nanowires or MXene nanosheets represent an emerging frontier in cardiac applications, with the objective of enhancing electrical signal propagation across scar tissue and decreasing arrhythmogenic susceptibility (141,143). Preclinical studies have demonstrated improved electrical integration and synchronized myocardial contraction (141,143). However, concerns regarding nanomaterial-associated cytotoxicity, long-term biocompatibility and fabrication complexity constrain their clinical translation.

The divergent outcomes observed across hydrogel platforms suggest that optimal cardiovascular therapy may require integration of multiple functional attributes. This informs future research priorities and underscores that no single platform currently satisfies all therapeutic requirements in cardiovascular medicine. To facilitate direct quantitative and qualitative comparison, the key efficacy endpoints and safety outcomes of major hydrogel platforms are summarized in Table II.

Translational insights from comparative analysis. Discrepancies between preclinical and clinical outcomes arise from multiple contributing factors. In addition to efficacy considerations, several critical challenges must be addressed to ensure safe and effective clinical translation, including immune response, biodegradation control, long-term mechanical stability, thrombogenicity and scalability (5,12,148).

Immune response. Comprehensive biocompatibility evaluation in animal models and *in vitro* systems is essential prior to clinical application (148-150). Hydrogels derived from xenogeneic sources carry a theoretical risk of immunogenicity. Decellularization decreases this risk by removing cell components and debris, thereby promoting constructive tissue remodeling rather than immune rejection (151). VentriGel demonstrates no serious immune-associated adverse events, supporting the biocompatibility of decellularized ECM products &1). Nevertheless, each newly developed material must undergo rigorous immunotoxicological assessment. Strategies include incorporation of immunomodulatory cues within hydrogel matrices to promote immune tolerance, as well as the use of autologous or allogeneic sources to eliminate xenogeneic-associated risks (132,148). Synthetic hydrogels may elicit inflammatory responses if degradation yields irritant byproducts, particularly in the case of certain polyester-based systems [such as poly(lactic acid), poly(glycolic acid) and poly(lactic-co-glycolic acid)] (13). Ensuring degradation products are biologically inert and readily metabolized or excreted represents a key design consideration. This challenge may be mitigated by optimizing degradation kinetics and incorporating buffering components, however, the balance between material persistence and degradation must be tailored to each specific application.

Biodegradation control. Control of biodegradation is key to balance mechanical support and tissue remodeling in cardiovascular hydrogels. Premature degradation leads to early loss of structural support before myocardial repair is complete, whereas slow degradation impedes native tissue ingrowth, disrupts electromechanical integration and increases the risk of chronic inflammation or foreign-body reactions. Therefore, degradation kinetics must be tailored to align with the repair timeline of infarcted myocardium (13,16). Recent advances (128,152) have enabled programmable degradation through modulation of crosslinking density, incorporation of stimuli-responsive cleavable bonds, or design of composite networks with controlled erosion profiles. Increased crosslinking density typically slows degradation by limiting water penetration and enzymatic accessibility, thereby extending hydrogel persistence (152). Degradation byproducts must be chemically inert, non-toxic and readily metabolized or excreted to prevent chronic inflammation, local acidosis or tissue injury. Consequently, contemporary cardiac hydrogels increasingly favor natural polymers or synthetic systems engineered to yield neutral, biocompatible metabolites (13). Recent studies (138,139) emphasize the importance of dynamic mechanical matching during degradation. Gradual decrease in hydrogel stiffness should parallel recovery of native tissue mechanics to prevent pathological loading or functional decline. Collectively, rational control of degradation rate, mechanism and byproduct biocompatibility is key for the safe and effective application of hydrogel-based cardiac therapies (12,152).

Long-term mechanical stability under dynamic cardiovascular conditions. The beating heart and pulsatile vasculature impose cyclic mechanical loading that may result in material fatigue, fracture or functional deterioration. Hydrogels must therefore exhibit not only appropriate initial stiffness but also sufficient fatigue resistance and viscoelastic properties that approximate those of native tissue (5,64). Stiffness matching represents a foundational strategy: Hydrogels can be engineered to approximate native myocardial stiffness, thereby minimizing abnormal stress transmission to the surrounding myocardium (153). Beyond static stiffness, viscoelastic design is key. Hydrogels exhibiting stress relaxation that mimics the time-dependent mechanical behavior of native tissue promote cell spreading, proliferation and ECM deposition, which are key for functional integration and repair (154). In addition to intrinsic material durability, a hydrogel patch or injectable formulation must integrate with the myocardial wall and deform synchronously during each cardiac cycle. If the material is excessively stiff, the adjacent myocardium may experience abnormal mechanical loading; conversely, if it is overly compliant, it may fail to provide adequate structural support. Achieving mechanical integration with dynamic cardiac tissue remains challenging (64,67). Early-generation polymeric restraint devices, for example, restricted diastolic filling. Although hydrogels are inherently soft and deformable, offering an advantage in this context, their mechanical contribution evolves as degradation progresses. Designers

Table II. Clinical and preclinical outcomes of hydrogel platforms.

Platform	Composition	Indication	Delivery method	Phase/status	Preclinical findings	Clinical findings	Safety/AEs	Discrepancy analysis
Algisyl-LVR™ (LoneStar Heart Inc.)	Calcium alginate	Advanced HF	Intramyocardial injection	Phase II (AUGMENT-HF)	Porcine IHF model demonstrates increased LVEF, stroke volume and infarct wall thickness and decreased myofiber stress; preserved sphericity index; preserved downregulation of stress-associated miRNAs	Increased LVEF; decreased LVEDD, KCCQ quality of life and 6MWD & peak VO_2; improved NYHA class	30-day mortality, 0%; no device-associated SAEs; no arrhythmogenicity; decreased NSVT; no thrombosis or immune reaction	Preclinical: Structural and functional benefits are robust and consistent; clinical: Clear functional improvements; modest limited improvement in ventricular dilation and wall thickness compared with robust preclinical findings); species difference: Preclinical studies used healthy, genetically uniform swine with induced ischemic heart failure, whereas clinical patients have advanced heart failure with multiple comorbidities, which may affect the therapeutic response; clinical delivery in advanced, chronic HF vs. preclinical in subacute IHF; open-surgical delivery in clinical vs. preclinical model limits comparability
IK-5001 (BL-1040) (BioLineRx)	Sodium alginate + calcium gluconate	Post-STEMI	Intracoronary infusion	Phase II (PRESERVATION-I)	Rat MI model: Decreased LV dilatation, preserved scar thickness preserved, increased LVFS/FAC; porcine MI model: Adverse LV remodeling prevented; decreased	6 mo primary endpoint, negative; no notable decrease in ventricular dilation; preserved LVEF and LV volume (no further deterioration);	No device-associated SAEs; no death, stroke, thrombosis or arrhythmia; 3.7% HF; 3.7% renal failure (not device-associated); no coronary flow impairment	Delivery route mismatch (preclinical, direct intramyocardial injection; clinical, intracoronary infusion, low retention); timing difference: Clinical delivered 2-5 d post-PCI; preclinical treated at

Table II. Continued.

Platform	Composition	Indication	Delivery method	Phase/status	Preclinical findings	Clinical findings	Safety/AEs	Discrepancy analysis
					infarct expansion; increased wall thickness; preserved LVEF	decreased NT-proBNP; increased 6MWD; MLHFQ improved		1-2 weeks; revascularization effect: Clinical patients all received PCI; preclinical models usually without reperfusion; preclinical showed robust reverse remodeling; clinical only showed stabilization
VentriGel (Ventrix, Inc)	Decellularized porcine cardiac ECM	Post-MI	Transendocardial injection	Phase I	Rat MI: Preserved EF, decreased ESV/EDV, fibrosis, hypertrophy and apoptosis; increased viable cardiomyocyte islands, angiogenesis and c-kit^{+} progenitor cells; improved metabolism; modulated immune microenvironment; Porcine MI: Increased cardiac muscle content and global/regional function; decreased fibrosis; no arrhythmia or embolization	Safety and feasibility established; 3-6 mo, increased 6MWD; increased LVEF; decreased LVESV; benefit strongest in >1 yr chronic MI	No device-associated serious AEs, arrhythmia, thrombosis or immune response; one case of mild transient fever	Timing mismatch: Preclinical treated at subacute MI; clinical treated in chronic phase (regenerative window closed); disease severity: Rodent/porcine models uniform vs. human heterogeneous comorbidities; Phase I underpowered; efficacy outcomes (LV end-systolic Volume, LV end-diastolic volume) were not statistically significant

d, days; ECM, extracellular matrix; EDV, end-diastolic volume; ESV, end-systolic volume; FAC, fractional area change; IHF, ischemic heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; MI, myocardial infarction; miRNA, microRNA; MLHFQ, Minnesota Living with Heart Failure Questionnaire; mo, months; NSVT, non-sustained ventricular tachycardia; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SAE, serious adverse event; STEMI, ST-segment elevation myocardial infarction; VO_2, oxygen consumption; 6MWD, 6-min walk distance; yr, years.

must therefore anticipate shifts in myocardial workload as the hydrogel resorbs. Premature degradation may lead to loss of structural support before tissue healing is complete, whereas excessively delayed degradation may impede physiological remodeling. Alignment of degradation half-life with the myocardial recovery timeline is key (155); for example, an ideal hydrogel for MI repair may degrade over 3-6 months, coinciding with scar maturation (31). Electrical compatibility is also critical. An implanted hydrogel should not interfere with cardiac electrical conduction or contractile synchrony. Although a highly insulating hydrogel may induce a conduction block if it forms a substantial mass, clinical injections are typically small and distributed within native tissue and to the best of our knowledge, no increase in arrhythmic events has been reported to date (156). Nevertheless, studies (7,156) monitor patients for potential proarrhythmic effects [using magnetic resonance imaging (MRI) and electroanatomic mapping]. Conductive hydrogels incorporating conductive nanomaterials (such as graphene, gold nanowires or MXene) or electrically conductive polymers have been developed to restore electrical coupling across scar tissue (141,143). Preclinical studies (141-143) have demonstrated enhanced Cx43 expression, decreased arrhythmogenic susceptibility and improved synchronization of cardiomyocyte contraction. Collectively, achieving long-term mechanical and electrical stability under dynamic cardiovascular conditions requires an integrated design strategy that balances stiffness, viscoelasticity, degradation kinetics and electrical compatibility. By tailoring these properties to the specific biomechanical and electrophysiological demands of the target tissue, as well as the temporal course of healing, functional hydrogels provide durable support that promotes native cardiac repair.

Thrombogenicity. Thrombogenicity is a key concern for any intravascular application of hydrogels or for materials that come into direct contact with blood. Although numerous hydrogels (alginate or PEG) are considered relatively hemocompatible, clinical experience from the Humacyte human acellular vessel trial demonstrated that even human ECM-based grafts may thrombose when flow dynamics are disturbed (157). In the Symvess trauma study, peri-implantation anticoagulation was administered to mitigate thrombotic risk (158). For future hydrogel-based vascular devices, surface modification strategies may be necessary to maintain long-term patency. Heparin or heparin-mimetic coatings decrease platelet adhesion and activation, as demonstrated in heparin-coated ePTFE grafts and stent coatings (159). NO-eluting hydrogels and mechanically robust NO-releasing hydrogel coatings applied to stents attenuate neointimal hyperplasia and thrombosis in porcine models by leveraging the antiplatelet and anti-smooth muscle proliferative effects of NO (105). Zwitterionic hydrogel coatings exhibit enhanced antifouling properties and decrease thrombogenicity of decellularized swim bladder matrices used for bioprosthetic heart valves (160). Hydrogels incorporating fucoidan, a sulfated glycosaminoglycan with anticoagulant properties, are applied as coatings for magnesium alloy stents, improving hemocompatibility and promoting endothelial cell colonization (109). In cardiac applications such as injectable hydrogels, delivery techniques must avoid the introduction of air bubbles or particulate contaminants that could result in embolization. Clinical protocols developed to date, including hydrogel filtration and meticulous catheter-based delivery techniques, have prevented embolic complications (33,71), however, these procedures require standardization as therapies advance toward broader clinical implementation.

Scalability and manufacturability of hydrogel products. Complex hydrogel systems, particularly those incorporating biological components, present challenges for consistent large-scale production. Batch-to-batch variability in biologically derived materials, such as differences in ECM composition among donor lots, directly influence therapeutic performance. For scale-up of composite and multi-component hydrogels, advances in continuous manufacturing technology, including microfluidic systems, automated mixing and dispensing platforms and 3D bioprinting, are enabling reproducible large-scale production with improved quality control (13,19). These platforms permit precise regulation of component ratios, crosslinking kinetics and final product homogeneity, thereby mitigating the inherent variability associated with multi-component formulations (161-163). Sterilization constitutes a notable translational barrier for cardiovascular hydrogels because of their high water content, thermosensitivity and susceptibility to structural degradation under conventional sterilization conditions. Most hydrogels cannot tolerate autoclaving or dry-heat sterilization, as elevated temperatures may induce premature gelation, network disruption, polymer hydrolysis or loss of thermoresponsive properties (164). Alternative terminal sterilization strategies are required but must be rigorously validated to preserve mechanical integrity, biocompatibility and drug release characteristics (150,164). Gamma irradiation and electron beam irradiation have been investigated for heat-sensitive hydrogels, however, radiolysis of water generates ROS, which can cause polymer chain scission, crosslinking imbalance, decreased mechanical strength and accelerated degradation (164). Ethylene oxide sterilization enables low-temperature processing; however, it requires prolonged degassing to eliminate cytotoxic residues and is incompatible with highly hydrated formulations. Hydrogen peroxide plasma sterilization decreases residual toxicity but may induce oxidative damage to polymer networks. Supercritical carbon dioxide sterilization has emerged as a promising low-temperature, residue-free alternative that preserves hydrogel structure, mechanical properties and biocompatibility while achieving high sterility assurance levels (164). For injectable and *in situ*-forming hydrogels, sterile filtration of prepolymer solutions prior to crosslinking is a practical and widely implemented approach, provided that all components are amenable to filtration and aseptic processing conditions are maintained. Lyophilized (freeze-dried) hydrogel formulations enable terminal sterilization of dry solids before reconstitution, thereby decreasing moisture-mediated degradation during sterilization and storage (164). No universal sterilization strategy exists; selection must be tailored to polymer composition, crosslinking chemistry, water content and therapeutic payload, with rigorous validation of sterility, structural integrity, mechanical performance and biocompatibility. Achieving good manufacturing practice compliance is also essential. Regulatory approval requires controlled

cleanroom environments, validated cleaning protocols and comprehensive quality control of composition, mechanical properties, gelation behavior and sterility. Taken together, these considerations underscore that scalability is an integral component of hydrogel design, requiring the integration of robust material engineering with validated manufacturing processes to enable reproducible, off-the-shelf production of functional hydrogels for cardiovascular applications.

Integration with standard care. Any novel therapy must complement, rather than replace, established treatments unless it demonstrates a clear clinical advantage. For patients with MI, reperfusion therapy (percutaneous coronary intervention) and contemporary guideline-directed medical therapy are life-saving interventions and the cornerstone of management (6,7); hydrogel injection may serve as an adjunct strategy aimed at improving ventricular remodeling. Accordingly, clinical trials must demonstrate incremental benefit beyond optimal standard-of-care therapy (8,31,37). This necessitates sufficiently powered studies to detect, for example, additional improvements in LVEF or decreased HF-associated hospitalizations. Similarly, in patients with HF, hydrogel-based therapy may be administered in combination with established pharmacological and device-based treatments (34). The multimodal nature of HF management complicates attribution of therapeutic effects, making it challenging to isolate the independent contribution of the hydrogel intervention unless trials are rigorously designed and appropriately controlled (5,34).

Regulatory and clinical adoption challenges. Hydrogel-based therapies typically straddle the boundary between medical devices and biologics, rendering regulatory classification complex (150). FDA has categorized certain formulations (hydrogels incorporating cells such as mesenchymal stem cells or hydrogels containing bioactive factors like growth factors) as combination products, particularly when they incorporate cells or bioactive factors (150). Comprehensive safety and efficacy data are required as these therapies represent relatively new treatment modalities. Clinicians may also exercise caution in adopting such technologies until robust evidence from Phase III clinical trials demonstrates clear clinical benefit (71). Practical considerations influence adoption. Interventional cardiologists may require specialized training to deliver hydrogels safely via catheter-based techniques and cardiac surgeons must become familiar with handling hydrogel materials during operative procedures. In addition, reimbursement pathways must be defined, as these therapies may initially incur notable costs due to manufacturing complexity (5,150).

6. Conclusion

Although synthetic hydrogels provide tunable mechanical properties and high reproducibility, their long-term *in vivo* fate, including degradation products, chronic inflammatory responses, and potential toxicity, remains insufficiently characterized. Most preclinical studies (5,13,64) have reported outcomes over weeks to months, however, cardiovascular applications require durability over years. Future investigations should prioritize systematic evaluation of degradation kinetics, long-term biocompatibility and sustained functional performance in large-animal models over extended timeframes. Attention should be directed toward the accumulation of degradation byproducts and their potential off-target effects.

Current hydrogel therapies largely follow a 'one-size-fits-all' paradigm. However, patient-specific factors, including age, comorbidity, infarct geometry, scar composition and inflammatory status, may influence therapeutic response. Advances in high-resolution imaging modalities (cardiac MRI and computed tomography), biomarker profiling and 3D bioprinting may enable the development of patient-tailored hydrogels with customized mechanical properties, degradation rates and bioactive payloads. Further research is required to establish rational design algorithms that integrate patient-derived data with material selection strategies and determine whether personalized hydrogels confer superior outcomes compared with standardized formulations in preclinical models.

Hydrogels represent promising platforms for localized delivery of next-generation biologics, including mRNA, siRNA and CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9) gene-editing components (78,165). For example, hydrogel-mediated delivery of mRNA encoding cardioprotective factors may overcome the short half-life and off-target effects associated with systemic administration. Similarly, hydrogels may facilitate spatiotemporally controlled CRISPR-based genome editing to correct disease-associated genes, such as silencing profibrotic genes in cardiac fibroblasts, or to enhance endogenous repair pathways. Proof-of-concept studies in clinically relevant animal models are needed to establish safety, efficacy and optimal delivery parameters. Addressing these knowledge gaps may accelerate the translation of functional hydrogels and help realize their full potential in cardiovascular regenerative medicine.

The design space for functional hydrogels, encompassing polymer composition, crosslinking density, degradation rate, mechanical properties and bioactive payloads, is vast and multidimensional. Conventional trial-and-error approaches are typically time-consuming and inefficient. Machine learning and artificial intelligence (AI) offer transformative potential to accelerate hydrogel development. By training algorithms on existing datasets that associate hydrogel physicochemical properties with biological outcomes, AI models predict optimized formulations for specific clinical applications, propose novel polymer combinations and elucidate structure-function relationships. When coupled with high-throughput screening platforms and automated synthesis technologies, AI-guided design may shorten development timelines and reveal previously unrecognized interactions (161-163).

Advances in 3D bioprinting enable fabrication of complex, patient-specific hydrogel constructs with precise control over architecture, cell distribution and biomechanical properties (45). For cardiac repair, bioprinted patches can be designed to match individual infarct geometry mapped using cardiac MRI and incorporate aligned microchannels that guide cardiomyocyte orientation and vascular ingrowth. Beyond therapeutic applications, hydrogel-based organ-on-a-chip platforms incorporating patient-derived iPSC-derived cardiomyocytes, endothelial cells and fibroblasts provide powerful tools for preclinical evaluation. These microphysiological systems recapitulate key features of the cardiac microenvironment, enabling rapid assessment of hydrogel mechanical

behavior, drug release kinetics and cellular responses prior to translation into animal studies (49).

Hydrogels are expected to increasingly function as delivery platforms for next-generation therapeutics. Beyond conventional growth factors, hydrogels encapsulate and locally release viral vectors, such as adeno-associated virus and lentiviral vectors encoding therapeutic genes, thereby enabling sustained and localized transduction while minimizing systemic exposure (66). For cell-based therapy, hydrogels provide a protective microenvironment that enhances survival, retention and functional integration of transplanted cells, including MSCs, iPSC-derived cardiomyocytes and cardiac progenitor cells (72). Emerging strategies integrate both modalities, employing hydrogels to deliver gene-edited cells or cells engineered to secrete therapeutic factors. The tunable physicochemical properties of hydrogels permit spatiotemporal control over cell release, differentiation signals and paracrine activity, thereby maximizing therapeutic efficacy.

The next generation of hydrogels may exhibit enhanced responsiveness and dynamic interaction with the physiological environment. Multi-responsive hydrogels capable of sensing and reacting to multiple cues, including pH, enzymatic activity, ROS and mechanical strain, may enable on-demand, feedback-controlled therapy. 4D hydrogel materials, which undergo programmed structural or functional changes over time, may facilitate sequential therapeutic staging, for example, initially promoting angiogenesis followed by stimulation of myocardial regeneration. Such adaptive materials more closely recapitulate the dynamic behavior of native tissue compared with conventional static hydrogels.

Hydrogels may combine with established cardiovascular devices to enhance therapeutic performance. For example, hydrogel coatings applied to stents or vascular grafts can improve hemocompatibility, promote endothelialization and enable localized delivery of antirestenotic agents. Hydrogels incorporated into balloon angioplasty catheters may simultaneously dilate stenotic arteries and deliver therapeutic compounds directly into the vessel wall. In HF management, hydrogels injected around the inflow cannula of left ventricular assist devices may promote myocardial recovery within the mechanically unloaded environment. These integrated strategies leverage the complementary strengths of biomaterials and device-based interventions while mitigating their individual limitations.

As understanding of patient heterogeneity advances, hydrogel-based therapies may be tailored to individual characteristics. This personalization may involve adjusting hydrogel composition according to inflammatory profile, selecting degradation kinetics that correspond to individual healing dynamics or incorporating autologous cells or PRP. With advances in imaging technologies and 3D bioprinting, fully personalized cardiac patches (custom-shaped to conform to infarct geometry and incorporating patient-derived cells) may become clinically feasible. Although technically complex, these approaches are progressing and associated costs may decline as scalable manufacturing technologies mature.

As clinical evidence accumulates, optimal timing and patient selection criteria for hydrogel-based interventions may increasingly refined. Future treatment protocols may define specific indications, for example, hydrogel injection on day 5 post-MI in patients with infarct size exceeding a defined threshold and inflammatory biomarkers within a specified range. Integration of hydrogel therapy into standard-of-care algorithms requires large-scale clinical trials demonstrating incremental benefit beyond optimal medical management. Nevertheless, the potential advantages, namely, true tissue regeneration rather than symptomatic palliation, justify continued investigation.

Functional hydrogels may become a key component of cardiovascular regenerative therapy, either as standalone modalities or in combination with pharmacological agents, cell-based therapy, gene-editing technologies and implantable devices. The ongoing convergence of materials science, bioengineering, computational modeling and clinical medicine suggests that interventions such as myocardial regeneration, bioengineered living valves and reversal of fibrotic remodeling may become clinically attainable, with functional hydrogels serving as both structural scaffolds and biological modulators. The progress from foundational laboratory concepts to early-phase clinical trials provides a platform for future translation. As remaining scientific, regulatory and manufacturing challenges are systematically addressed, hydrogel-based interventions may transition from experimental applications to integrated components of mainstream clinical cardiology and cardiac surgery, offering patients restorative therapeutic options.

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Authors' contributions

ZY and JL conceived the study and wrote the manuscript. ZY edited the manuscript. ZY and LZ constructed figures JL and DZ performed the literature review. CY, DL and YH conceived the study and revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, *et al*: Global burden of cardiovascular diseases and risk factors, 1990-2019: Update from the GBD 2019 study. J Am Coll Cardiol 76: 2982-3021, 2020.
2. Li Y, Cao GY, Jing WZ, Liu J and Liu M: Global trends and regional differences in incidence and mortality of cardiovascular disease, 1990-2019: Findings from 2019 global burden of disease study. Eur J Prev Cardiol 30: 276-286, 2023.
3. Hasan A, Khattab A, Islam MA, Hweij KA, Zeitouny J, Waters R, Sayegh M, Hossain MM and Paul A: Injectable hydrogels for cardiac tissue repair after myocardial infarction. Adv Sci (Weinh) 2: 1500122, 2015.
4. Klaourakis K, Vieira JM and Riley PR: The evolving cardiac lymphatic vasculature in development, repair and regeneration. Nat Rev Cardiol 18: 368-379, 2021.
5. Holme S, Richardson SM, Bella J and Pinali C: Hydrogels for cardiac tissue regeneration: Current and future developments. Int J Mol Sci 26: 2309, 2025.
6. Lüscher TF: Myocardial infarction: Mechanisms, diagnosis, and complications. Eur Heart J 36: 947-949, 2015.
7. Damluji AA, van Diepen S, Katz JN, Menon V, Tamis-Holland JE, Bakitas M, Cohen MG, Balsam LB, Chikwe J; American Heart Association Council on Clinical Cardiology; Council on Arteriosclerosis, *et al*: Mechanical complications of acute myocardial infarction: A Scientific statement from the American heart association. Circulation 144: e16-e35, 2021.
8. Mann DL, Lee RJ, Coats AJ, Neagoe G, Dragomir D, Pusineri E, Piredda M, Bettari L, Kirwan BA, Dowling R, *et al*: One-year follow-up results from AUGMENT-HF: A multicentre randomized controlled clinical trial of the efficacy of left ventricular augmentation with Algisyl in the treatment of heart failure. Eur J Heart Fail 18: 314-325, 2016.
9. Nick C and John HD: Heart transplantation. Surgery (Oxford) 41: 573-579, 2023.
10. Fuchs M, Schibilsky D, Zeh W, Berchtold-Herz M, Beyersdorf F and Siepe M: Does the heart transplant have a future? Eur J Cardiothorac Surg 55 (Suppl 1): i38-i48, 2019.
11. Li P, Hu J, Wang J, Zhang J, Wang L and Zhang C: The role of hydrogel in cardiac repair and regeneration for myocardial infarction: Recent advances and future perspectives. Bioengineering (Basel) 10: 165, 2023.
12. Dong S, An S, Saiding Q, Chen Q, Liu B, Kong N, Chen W and Tao W: Therapeutic hydrogels: Properties and biomedical applications. Chem Rev 125: 8835-8920, 2025.
13. Spicer CD: Hydrogel scaffolds for tissue engineering: The importance of polymer choice. Polym Chem 11: 184-219, 2020.
14. Chaudhary S and Chakraborty E: Hydrogel based tissue engineering and its future applications in personalized disease modeling and regenerative therapy. Beni Suef Univ J Basic Appl Sci 11: 3, 2022.
15. Zhang X, Xu B, Puperi DS, Wu Y, West JL and Grande-Allen KJ: Application of hydrogels in heart valve tissue engineering. J Long Term Eff Med Implants 25: 105-134, 2015.
16. Drury JL and Mooney DJ: Hydrogels for tissue engineering: Scaffold design variables and applications. Biomaterials 24: 4337-4351, 2003.
17. Gomez-Florit M, Pardo A, Domingues RMA, Graça AL, Babo PS, Reis RL and Gomes ME: Natural-based hydrogels for tissue engineering applications. Molecules 25: 5858, 2020.
18. Gutowski P, Guziewicz M, Ilzecki M, Kazimierczak A, Lawson JH, Prichard HL, Przywara S, Samad R, Tente W, Turek J, *et al*: Six-year outcomes of a phase II study of human-tissue engineered blood vessels for peripheral arterial bypass. JVS Vasc Sci 4: 100092, 2022.
19. Kafili G, Kabir H, Jalali Kandeloos A, Golafshan E, Ghasemi S, Mashayekhan S and Taebnia N: Recent advances in soluble decellularized extracellular matrix for heart tissue engineering and organ modeling. J Biomater Appl 38: 577-604, 2023.
20. Zhang J, Guo Y, Bai Y and Wei Y: Application of biomedical materials in the diagnosis and treatment of myocardial infarction. J Nanobiotechnology 21: 298, 2023.
21. Hong SB, Jeong JO and Choi H: Hydrogels in cardiac surgery: Versatile platforms for tissue repair, adhesion prevention, and localized therapeutics. Gels 11: 564, 2025.
22. Kim SJ, Park SJ and Kim SJ: Swelling behavior of interpenetrating polymer network hydrogels composed of poly(vinyl alcohol) and chitosan. React Funct Polym 55: 53-59, 2003.
23. Gould RA, Chin K, Santisakultarm TP, Dropkin A, Richards JM, Schaffer CB and Butcher JT: Cyclic strain anisotropy regulates valvular interstitial cell phenotype and tissue remodeling in three-dimensional culture. Acta Biomater 8: 1710-1719, 2012.
24. Mol A, van Lieshout MI, Dam-de Veen CG, Neuenschwander S, Hoerstrup SP, Baaijens FP and Bouten CV: Fibrin as a cell carrier in cardiovascular tissue engineering applications. Biomaterials 26: 3113-3121, 2005.
25. Masters KS, Shah DN, Leinwand LA and Anseth KS: Crosslinked hyaluronan scaffolds as a biologically active carrier for valvular interstitial cells. Biomaterials 26: 2517-2525, 2005.
26. Flanagan TC, Sachweh JS, Frese J, Schnöring H, Gronloh N, Koch S, Tolba RH, Schmitz-Rode T and Jockenhoevel S: In vivo remodeling and structural characterization of fibrin-based tissue-engineered heart valves in the adult sheep model. Tissue Eng Part A 15: 2965-2976, 2009.
27. Rodriguez KJ, Piechura LM and Masters KS: Regulation of valvular interstitial cell phenotype and function by hyaluronic acid in 2-D and 3-D culture environments. Matrix Biol 30: 70-82, 2011.
28. McLaughlin S, Sedlakova V and Zhang QZ: Recombinant human collagen hydrogel rapidly reduces methylglyoxal adducts within cardiomyocytes and improves borderzone contractility after myocardial infarction in mice. Adv Funct Mater 32: 2204076, 2022.
29. Gorlatov S and Medved L: Interaction of fibrin(ogen) with the endothelial cell receptor VE-cadherin: Mapping of the receptor-binding site in the NH2-terminal portions of the fibrin beta Chains. Biochemistry 41: 4107-4116, 2002.
30. Ahmed TA, Griffith M and Hincke M: Characterization and inhibition of fibrin hydrogel-degrading enzymes during development of tissue engineering scaffolds. Tissue Eng 13: 1469-1477, 2007.
31. Hu W, Yang C, Guo X, Wu Y, Loh XJ, Li Z, Wu YL and Wu C: Research advances of injectable functional hydrogel materials in the treatment of myocardial infarction. Gels 8: 423, 2022.
32. Ding J, Yao Y, Li J, Duan Y, Nakkala JR, Feng X, Cao W, Wang Y, Hong L, Shen L, *et al*: A reactive oxygen species scavenging and O_2 generating injectable hydrogel for myocardial infarction treatment in vivo. Small 16: e2005038, 2020.
33. Frey N, Linke A, Süselbeck T, Müller-Ehmsen J, Vermeersch P, Schoors D, Rosenberg M, Bea F, Tuvia S and Leor J: Intracoronary delivery of injectable bioabsorbable scaffold (IK-5001) to treat left ventricular remodeling after ST-elevation myocardial infarction: A first-in-man study. Circ Cardiovasc Interv 7: 806-812, 2014.
34. Wan H, Sun CW and Zhang JY: Recent advances in implantable hydrogels for treating heart failure. J Appl Polym Sci 139: 53156, 2022.
35. Lee RJ, Hinson A, Bauernschmitt R, Matschke K, Fang Q, Mann DL, Dowling R, Schiller N and Sabbah HN: The feasibility and safety of Algisyl-LVR™ as a method of left ventricular augmentation in patients with dilated cardiomyopathy: Initial first in man clinical results. Int J Cardiol 199: 18-24, 2015.
36. Chaturvedi K, Ganguly K, Nadagouda MN and Aminabhavi TM: Polymeric hydrogels for oral insulin delivery. J Control Release 165: 129-138, 2013.
37. Kim C, Jeong D, Kim S, Kim Y and Jung S: Cyclodextrin functionalized agarose gel with low gelling temperature for controlled drug delivery systems. Carbohydr Polym 222: 115011, 2019.
38. Tseng H, Cuchiara ML, Durst CA, Cuchiara MP, Lin CJ, West JL and Grande-Allen KJ: Fabrication and mechanical evaluation of Anatomically-inspired quasilaminate hydrogel structures with Layer-specific formulations. Ann Biomed Eng 41: 398-407, 2013.
39. Durst CA, Cuchiara MP, Mansfield EG, West JL and Grande-Allen KJ: Flexural characterization of cell encapsulated PEGDA hydrogels with applications for tissue engineered heart valves. Acta Biomater 7: 2467-2476, 2011.
40. Jiang H, Campbell G, Boughner D, Wan WK and Quantz M: Design and manufacture of a polyvinyl alcohol (PVA) cryogel tri-leaflet heart valve prosthesis. Med Eng Phys 26: 269-277, 2004.
41. Xue F, Zhao S, Tian H, Qin H, Li X, Jian Z, Du J, Li Y, Wang Y, Lin L, *et al*: Two way workable microchanneled hydrogel Suture to diagnose, treat and monitor the infarcted heart. Nat Commun 15: 864, 2024.

42. Crocini C, Walker CJ, Anseth KS and Leinwand LA: Three-dimensional encapsulation of adult mouse cardiomyocytes in hydrogels with tunable stiffness. Prog Biophys Mol Biol 154: 71-79, 2020.
43. Zou Y, Li L, Li Y, Chen S, Xie X, Jin X, Wang X, Ma C, Fan G and Wang W: Restoring cardiac functions after myocardial infarction-ischemia/reperfusion via an exosome anchoring conductive hydrogel. ACS Appl Mater Interfaces 13: 56892-56908, 2021.
44. Mannarino MM, Bassett M, Donahue DT and Biggins JF: Novel high-strength thromboresistant poly(vinyl alcohol)-based hydrogel for vascular access applications. J Biomater Sci Polym Ed 31: 601-621, 2020.
45. Matějková J, Kaňoková D and Matějka R: Current status of bioprinting using polymer hydrogels for the production of vascular grafts. Gels 11: 4, 2024.
46. López-Gutierrez J, Ramos-Payán R, Ayala-Ham A, Romero-Quintana JG, Castillo-Ureta H, Villegas-Mercado C, Bermúdez M, Sanchez-Schmitz G and Aguilar-Medina M: Biofunctionalization of hydrogel-based scaffolds for vascular tissue regeneration. Front Mater 10: 1168616, 2023.
47. Hu C, Liu W, Long L, Wang Z, Zhang W, He S, Lu L, Fan H, Yang L and Wang Y: Regeneration of infarcted hearts by myocardial infarction-responsive injectable hydrogels with combined anti-apoptosis, anti-inflammatory and pro-angiogenesis properties. Biomaterials 290: 121849, 2022.
48. Wang K, Zhang J, Li H, Wu J, Wan Q, Chen T, Liu W, Peng H, Zhang H and Luo Y: Smart hydrogel sensors for health monitoring and early warning. Adv Sensor Res 3: 2400003, 2024.
49. Lu J, Pan X, Zhang W, Han J, Chen J, Song M, Xu C, Li X, Wang J and Wang L: Hydrogel sensing platforms for monitoring contractility in in vitro cardiac models. Nanoscale 17: 8436-8452, 2025.
50. Xu Q, Xiao Z, Yang Q, Yu T, Deng X, Chen N, Huang Y, Wang L, Guo J and Wang J: Hydrogel-based cardiac repair and regeneration function in the treatment of myocardial infarction. Mater Today Bio 25: 100978, 2024.
51. Duan Y, Lin J, Yue J, Li Y, Liao J, Sun Y, Wang Q, Duan Y and Li Z: Temperature-sensitive hydrogel inhibits VEGFA-dependent neovascularization in atherosclerosis progression. Sci China Mater 68: 280-291, 2025.
52. Shi K, Li T, Hu X, Chen W, Yu Y, Bei Z, Yuan L, Tong Q, Liu J, Fan Q, *et al*: Injectable and sprayable thermoresponsive hydrogel with Fouling-Resistance as an effective barrier to prevent postoperative cardiac adhesions. Adv Sci (Weinh) 12: e2500731, 2025.
53. Tang J, Li T, He X, Liu Y, Zhou M, Wu M, Li Y, Lan Y, Tan X, Tian J and Li C: A shikonin/Cu2+ coordination complex-encapsulated hydrogel drug depot alleviates myocardial ischemia-reperfusion injury by disrupting energy metabolism-mediated intercellular crosstalk. J Colloid Interface Sci 706: 139580, 2026.
54. Alimirzaei F, Vasheghani FE, Ghiaseddin A, Soleimani M, Pouri and Zeinab NG: pH-sensitive chitosan hydrogel with instant gelation for myocardial regeneration. J Tissue Sci Eng 8: 3, 2017.
55. Kong Y, Wang L, Duan F, Huang C, Qiu Z, Ji RJ, Qiao L, Zhou Y, Cai T, Li YQ, *et al*: Injectable and pH-activated Self-feedback hydrogel encapsulating stem cells for augmented acute myocardial infarction therapy. Adv Healthc Mater 15: e03324, 2026.
56. Chen Y, Liang Y, Shen J, Wang Y, Qiu B, Hou H and Qiu X: A NADH oxidase nanozyme restores redox homeostasis to ameliorate Multi-organ aging and ischemic cardiomyopathy. Research (Wash D C) 8: 0973, 2025.
57. Wu TL and Liu WG: Functional hydrogels for the treatment of myocardial infarction. NPG Asia Mater 14: 9, 2022.
58. Sullivan HL, Liang Y, Worthington K, Luo C, Gianneschi NC and Christman KL: Enzyme-Responsive nanoparticles for the targeted delivery of an MMP inhibitor to acute myocardial infarction. Biomacromolecules 24: 4695-4704, 2023.
59. Pereira RF, Barrias CC, Bártolo PJ and Granja PL: Cell-instructive pectin hydrogels crosslinked via thiol-norbornene photo-click chemistry for skin tissue engineering. Acta Biomater 66: 282-293, 2018.
60. Song S, Yang L, Su K, Wu G, Li N, Wang J, Yu Z and Shi C: Bioactive cardiac ECM hydrogel sequentially released VEGF and Ang-1 mimic peptides to promote the recovery of myocardial infarction. Biomater Adv 180: 214617, 2026.
61. Chen X, Wu Y, Song P, Feng L, Zhou Y, Shi J, Dong N and Qiao W: Matrix Metalloproteinase-responsive controlled release of Self-assembly nanoparticles accelerates heart valve regeneration in situ by orchestrating immunomodulation. Adv Sci (Weinh) 12: e2403351, 2025.
62. Kharkar PM, Scott RA, Olney LP, LeValley PJ, Maverakis E, Kiick KL and Kloxin AM: Controlling the release of small, bioactive proteins via dual mechanisms with therapeutic potential. Adv Healthc Mater 6: 10, 2017.
63. Li Z, Chen E, Parsons J and Turng LS: Design, synthesis, and characterization of polymer-hydrogel composite vascular grafts using double-expanded polytetrafluoroethylene to achieve enhanced mechanical and biological properties. Polym Eng Sci 65: 2893-2908, 2025.
64. Liu Z, Zheng Z, Xie J, Wei H and Yu CY: Hydrogel-based cardiac patches for myocardial infarction therapy: Recent advances and challenges. Mater Today Bio 29: 101331, 2024.
65. Walker BW, Lara RP, Yu CH, Sani ES, Kimball W, Joyce S and Annabi N: Engineering a naturally-derived adhesive and conductive cardiopatch. Biomaterials 207: 89-101, 2019.
66. Wu C, Zhang Y, Xu Y, Long L, Hu X, Zhang J and Wang Y: Injectable polyaniline nanorods/alginate hydrogel with AAV9-mediated VEGF overexpression for myocardial infarction treatment. Biomaterials 296: 122088, 2023.
67. Alvarez-Lorenzo C, Grinberg VY, Burova TV and Concheiro A: Stimuli-sensitive cross-linked hydrogels as drug delivery systems: Impact of the drug on the responsiveness. Int J Pharm 579: 119157, 2020.
68. Streian CG, Novaconi RC, Munteanu IR, Manzur AR, Merce AG, Boca MI, Falnita LS, Dima CN, Merce AP, Pescariu SA, *et al*: Mechanical complications after acute myocardial infarction: A Shock-Stage and Timing-based management framework. J Clin Med 15: 2399, 2026.
69. Bi S, Yu L and Gu Y: Inflammatory signalling pathways and non-coding RNAs in myocardial infarction: Insights into pathogenesis and therapeutic opportunities. Folia Morphol (Warsz) 84: 816-839, 2025.
70. Young JL and Engler AJ: Hydrogels with time-dependent material properties enhance cardiomyocyte differentiation in vitro. Biomaterials 32: 1002-1009, 2011.
71. Traverse JH, Henry TD, Dib N, Patel AN, Pepine C, Schaer GL, DeQuach JA, Kinsey AM, Chamberlin P and Christman KL: First-in-Man study of a cardiac extracellular matrix hydrogel in early and late myocardial infarction patients. JACC Basic Transl Sci 4: 659-669, 2019.
72. Dong R, Zhao X, Guo B and Ma PXL: Self-Healing conductive injectable hydrogels with antibacterial activity as cell delivery carrier for cardiac cell therapy. ACS Appl Mater Interfaces 8: 17138-17150, 2016.
73. Song M, Jang H, Lee J, Kim JH, Kim SH, Sun K and Park Y: Regeneration of chronic myocardial infarction by injectable hydrogels containing stem cell homing factor SDF-1 and angiogenic peptide Ac-SDKP. Biomaterials 35: 2436-2445, 2014.
74. Yi B, Xu Y, Wang X, Wang G Li S, Xu R, Liu X and Zhou Q: Overview of injectable hydrogels for the treatment of myocardial infarction. Cardiovasc Innov Appl: 9, 2024.
75. Xing M, Bian S, Li B, Yang Z and Li J: Functional peptide hydrogel for the synergistic treatment of atherosclerosis based on macrophage autophagy induction and Anti-inflammation. ACS Materials Lett 6: 384-399, 2024.
76. Firoozi S, Pahlavan S, Ghanian MH, Rabbani S, Tavakol S, Barekat M, Yakhkeshi S, Mahmoudi E, Soleymani M and Baharvand H: A cell-free SDKP-conjugated Self-assembling peptide hydrogel sufficient for improvement of myocardial infarction. Biomolecules 10: 205, 2020.
77. Purcell BP, Barlow SC, Perreault PE, Freeburg L, Doviak H, Jacobs J, Hoenes A, Zellars KN, Khakoo AY, Lee T, *et al*: Delivery of a matrix metalloproteinase-responsive hydrogel releasing TIMP-3 after myocardial infarction: Effects on left ventricular remodeling. Am J Physiol Heart Circ Physiol 315: H814-H825, 2018.
78. Paul A, Hasan A, Kindi HA, Gaharwar AK, Rao VT, Nikkhah M, Shin SR, Krafft D, Dokmeci MR, Shum-Tim D and Khademhosseini A: Injectable graphene oxide/hydrogel-based angiogenic gene delivery system for vasculogenesis and cardiac repair. ACS Nano 8: 8050-8062, 2014.
79. Davidson SM, Takov K and Yellon DM: Exosomes and cardiovascular protection. Cardiovasc Drugs Ther 31: 77-86, 2017.
80. Emanueli C, Shearn AI, Angelini GD and Sahoo S: Exosomes and exosomal miRNAs in cardiovascular protection and repair. Vascul Pharmacol 71: 24-30, 2015.
81. Zhang Y, Hu YW, Zheng L and Wang Q: Characteristics and roles of exosomes in cardiovascular disease. DNA Cell Biol 36: 202-211, 2017.

82. Chen CW, Wang LL, Zaman S, Gordon J, Arisi MF, Venkataraman CM, Chung JJ, Hung G, Gaffey AC, Spruce LA, *et al*: Sustained release of endothelial progenitor cell-derived extracellular vesicles from shear-thinning hydrogels improves angiogenesis and promotes function after myocardial infarction. Cardiovasc Res 114: 1029-1040, 2018.
83. Waters R, Alam P, Pacelli S, Chakravarti AR, Ahmed RPH and Paul A: Stem cell-inspired secretome-rich injectable hydrogel to repair injured cardiac tissue. Acta Biomater 69: 95-106, 2018.
84. Sharma V, Manhas A, Gupta S, Dikshit M, Jagavelu K and Verma RS: Fabrication, characterization and in vivo assessment of cardiogel loaded chitosan patch for myocardial regeneration. Int J Biol Macromol 222: 3045-3056, 2022.
85. Wang T, Jiang XJ, Tang QZ, Li XY, Lin T, Wu DQ, Zhang XZ and Okello E: Bone marrow stem cells implantation with alpha-cyclodextrin/MPEG-PCL-MPEG hydrogel improves cardiac function after myocardial infarction. Acta Biomater 5: 2939-2944, 2009.
86. Melchiorri AJ, Hibino N and Fisher JP: Strategies and techniques to enhance the in situ endothelialization of small-diameter biodegradable polymeric vascular grafts. Tissue Eng Part B Rev 19: 292-307, 2013.
87. Abbott WM, Callow A, Moore W, Rutherford R, Veith F and Weinberg S: Evaluation and performance standards for arterial prostheses. J Vasc Surg 17: 746-756, 1993.
88. Budd JS, Allen KE, Hartley G and Bell PR: The effect of preformed confluent endothelial cell monolayers on the patency and thrombogenicity of small calibre vascular grafts. Eur J Vasc Surg 5: 397-405, 1991.
89. Pasic M, Müller-Glauser W, von Segesser LK, Lachat M, Mihaljevic T and Turina MI: Superior late patency of small-diameter Dacron grafts seeded with omental microvascular cells: An experimental study. Ann Thorac Surg 58: 677-683, 1994.
90. Demiri EC, Iordanidis SL and Mantinaos CF: Experimental use of prosthetic grafts in microvascular surgery. Handchir Mikrochir Plast Chir 31: 102-106, 1999.
91. Ciolacu DE, Nicu R and Ciolacu F: Natural polymers in heart valve tissue engineering: Strategies, advances and challenges. Biomedicines 10: 1095, 2022.
92. Coenen AMJ, Bernaerts KV, Harings JAW, Jockenhoevel S and Ghazanfari S: Elastic materials for tissue engineering applications: Natural, synthetic, and hybrid polymers. Acta Biomater 79: 60-82, 2018.
93. Taghizadeh B, Ghavami L, Derakhshankhah H, Zangene E, Razmi M, Jaymand M, Zarrintaj P, Zarghami N, Jaafari MR, Moallem Shahri M, *et al*: Biomaterials in valvular heart diseases. Front Bioeng Biotechnol 8: 529244, 2020.
94. Lee JM, Courtman DW and Boughner DR: The glutaraldehyde-stabilized porcine aortic valve xenograft. I. Tensile viscoelastic properties of the fresh leaflet material. J Biomed Mater Res 18: 61-77, 1984.
95. Spina M, Ortolani F, El Messlemani A, Gandaglia A, Bujan J, Garcia-Honduvilla N, Vesely I, Gerosa G, Casarotto D, Petrelli L, *et al*: Isolation of intact aortic valve scaffolds for heart-valve bioprostheses: Extracellular matrix structure, prevention from calcification, and cell repopulation features. J Biomed Mater Res A 67: 1338-1350, 2003.
96. Steinhoff G, Stock U, Karim N, Mertsching H, Timke A, Meliss RR, Pethig K, Haverich A and Bader A: Tissue engineering of pulmonary heart valves on allogenic acellular matrix conduits: In vivo restoration of valve tissue. Circulation 102: III50-III55, 2000.
97. Kniebs C, Kreimendahl F, Köpf M, Fischer H, Jockenhoevel S and Thiebes AL: Influence of different cell types and sources on Pre-Vascularisation in fibrin and Agarose-collagen gels. Organogenesis 16: 14-26, 2020.
98. Shah DN, Recktenwall-Work SM and Anseth KS: The effect of bioactive hydrogels on the secretion of extracellular matrix molecules by valvular interstitial cells. Biomaterials 29: 2060-2072, 2008.
99. Ku CH, Johnson PH, Batten P, Sarathchandra P, Chambers RC, Taylor PM, Yacoub MH and Chester AH: Collagen synthesis by mesenchymal stem cells and aortic valve interstitial cells in response to mechanical stretch. Cardiovasc Res 71: 548-556, 2006.
100. Sales VL, Mettler BA, Engelmayr GC Jr, Aikawa E, Bischoff J, Martin DP, Exarhopoulos A, Moses MA, Schoen FJ, Sacks MS and Mayer JE Jr: Endothelial progenitor cells as a sole source for ex vivo seeding of tissue-engineered heart valves. Tissue Eng Part A 16: 257-267, 2010.
101. Cebotari S, Lichtenberg A, Tudorache I, Hilfiker A, Mertsching H, Leyh R, Breymann T, Kallenbach K, Maniuc L, Batrinac A, *et al*: Clinical application of tissue engineered human heart valves using autologous progenitor cells. Circulation 114 (1 Suppl): I132-I137, 2006.
102. Petsche Connell J, Camci-Unal G, Khademhosseini A and Jacot JG: Amniotic fluid-derived stem cells for cardiovascular tissue engineering applications. Tissue Eng Part B Rev 19: 368-379, 2013.
103. Choi A, Seo KD, Yoon H, Han SJ and Kim DS: Bulk poly(N-isopropylacrylamide) (PNIPAAm) thermoresponsive cell culture platform: Toward a new horizon in cell sheet engineering. Biomater Sci 7: 2277-2287, 2019.
104. Wen C, Zhang J, Li Y, Zheng W, Liu M, Zhu Y, Sui X, Zhang X, Han Q, Lin Y, *et al*: A zwitterionic hydrogel coated titanium surface with high-efficiency endothelial cell selectivity for rapid re-endothelialization. Biomater Sci 8: 5441-5451, 2020.
105. Chen Y, Gao P, Huang L, Tan X, Zhou N, Yang T, Qiu H, Dai X, Michael S, Tu Q, *et al*: A tough nitric oxide-eluting hydrogel coating suppresses neointimal hyperplasia on vascular stent. Nat Commun 12: 7079, 2021.
106. Peng X, Wang X, Cheng C, Zhou X, Gu Z, Li L, Liu J and Yu X: Bioinspired, artificial, small-diameter vascular grafts with selective and rapid endothelialization based on an amniotic Membrane-derived hydrogel. ACS Biomater Sci Eng 6: 1603-1613, 2020.
107. Kang MK, Heo SH and Yoon JK: In-Stent Re-Endothelialization Strategies: Cells, extracellular matrix, and extracellular vesicles. Tissue Eng Part B Rev 31: 317-330, 2025.
108. Tong Q, Sun A, Wang Z, Li T, He X, Qian Y and Qian Z: Hybrid heart valves with VEGF-loaded zwitterionic hydrogel coating for improved anti-calcification and re-endothelialization. Mater Today Bio 17: 100459, 2022.
109. Wang L, Xu R, Meng L, Zhang Q, Qian Z, Chen J and Pan C: A fucoidan-loaded hydrogel coating for enhancing corrosion resistance, hemocompatibility and endothelial cell growth of magnesium alloy for cardiovascular stents. Biomater Adv 163: 213960, 2024.
110. Yi S, Karabin NB, Zhu J, Bobbala S, Lyu H, Li S, Liu Y, Frey M, Vincent M and Scott EA: An Injectable hydrogel platform for sustained delivery of Anti-inflammatory nanocarriers and induction of regulatory T cells in atherosclerosis. Front Bioeng Biotechnol 8: 542, 2020.
111. Sayegh MN, Cooney KA, Han WM, Wang L, Strobel F, Hansen LM, García AJ and Levit RD: A hydrogel strategy to augment tissue adenosine to improve hindlimb perfusion. Arterioscler Thromb Vasc Biol 41: e314-e324, 2021.
112. Zhang Y, Xiong TY and Feng Y: Current status and challenges of valvular heart disease interventional therapy. Cardiol Discovery 2: 97-113, 2022.
113. Cannegieter SC, Rosendaal FR and Briët E: Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 89: 635-641, 1994.
114. Fann JI, Miller DC, Moore KA, Mitchell RS, Oyer PE, Stinson EB, Robbins RC, Reitz BA and Shumway NE: Twenty-year clinical experience with porcine bioprostheses. Ann Thorac Surg 62: 1301-1311, 1996.
115. Schoen FJ and Levy RJ: Tissue heart valves: Current challenges and future research perspectives. J Biomed Mater Res 47: 439-465, 1999.
116. Siddiqui RF, Abraham JR and Butany J: Bioprosthetic heart valves: Modes of failure. Histopathology 55: 135-144, 2009.
117. Yacoub MH and Takkenberg JJ: Will heart valve tissue engineering change the world? Nat Clin Pract Cardiovasc Med 2: 60-61, 2005.
118. Masoumi N, Johnson KL, Howell MC and Engelmayr GC Jr: Valvular interstitial cell seeded poly(glycerol sebacate) scaffolds: Toward a biomimetic in vitro model for heart valve tissue engineering. Acta Biomater 9: 5974-5988, 2013.
119. Neuenschwander S and Hoerstrup SP: Heart valve tissue engineering. Transpl Immunol 12: 359-365, 2004.
120. Vesely I: Heart valve tissue engineering. Circ Res 97: 743-755, 2005.
121. Flanagan TC, Cornelissen C, Koch S, Tschoeke B, Sachweh JS, Schmitz-Rode T and Jockenhoevel S: The in vitro development of autologous fibrin-based tissue-engineered heart valves through optimised dynamic conditioning. Biomaterials 28: 3388-3397, 2007.
122. Green JJ and Elisseeff JH: Mimicking biological functionality with polymers for biomedical applications. Nature 540: 386-394, 2016.

123. Burdick JA and Murphy WL: Moving from static to dynamic complexity in hydrogel design. Nat Commun 3: 1269, 2012.
124. Seliktar D: Designing cell-compatible hydrogels for biomedical applications. Science 336: 1124-1128, 2012.
125. Li J, Qiao W, Liu Y, Lei H, Wang S, Xu Y, Zhou Y, Wen S, Yang Z, Wan W, *et al*: Facile engineering of interactive double network hydrogels for heart valve regeneration. Nat Commun 15: 7462, 2024.
126. He L, Wang W, Li Q, Jiang Y, Xia Z, Xia Z, Li J and Dong Q: VEGF-loaded HANB/F127DA photosensitive hydrogel in combination with exercise training: For improving post-myocardial infarction myocardial remodeling. Biomater Adv 183: 214767, 2026.
127. Huangfu Y, Zhang Y, Zhang Y, Wang S, Ding S, Gao R, Li H, Ju W, Zhang C, Huang P, *et al*: Spatially heterogeneous microgel-annealed PRP-derived fibrin hydrogel promotes coordinated vasculogenesis and angiogenesis after myocardial infarction. Acta Biomater 213: 182-199, 2026.
128. Jia Y, Yin T, Wang Z, Chen L, Fan H, Wu J, Yu Q, Zhang Y and Shen Z: Injectable alginate composite hydrogel with spatiotemporal codelivery of pro-angiogenic and anti-fibrotic agents for synergistic myocardial repair. Mater Today Bio 37: 102854, 2026.
129. Tong J, Sun D, Sun J, Zhang J, Chen M, Liu X, Zhang R, Zhang F, Zheng C, Wei Y, *et al*: Intelligent responsive PVA hydrogel loaded with composite MXene nanozyme enables efficient myocardial infarction repair by disrupting the oxidative stress-inflammation cascade. Mater Today Bio 35: 102556, 2025.
130. Fan P, Liu Y, Qian X, Li J, Xu Y, Qiu X, Tong L, Tong F, Fan Z, Zheng Y, *et al*: An intelligent nanoreservoir system promotes heart valve regeneration via ROS scavenging and immunomodulation. Bioact Mater 55: 205-223, 2026.
131. Wang W, He L, Li X, Zhou Z, Xia Z, Xia Z, Dong Q and Li J: Gelatin-based hydrogel patch by promoting M2 macrophage polarization to reduce inflammation and fibrosis alleviate post-myocardial infarction ventricular remodeling. Int J Biol Macromol 322: 146652, 2025.
132. Chen W, Wang C, Liu W, Zhao B, Zeng Z, Long F, Wang C, Li S, Lin N and Zhou J: A Matrix-Metalloproteinase-Responsive hydrogel system for modulating the immune microenvironment in myocardial infarction. Adv Mater 35: e2209041, 2023.
133. Wang D, Xu A, Su H, Zhang Y, Jiang L, Wang Y, Liang G and Zhang Y: Sustained release of dual p38 inhibitors via supramolecular hydrogels to enhance cardiac repair after MI/R injury. Biomaterials 326: 123670, 2026.
134. Zhou W, Tang Q, Wang S, Ding L, Chen M, Liu H, Wu Y, Xiong X, Shen Z and Chen W: Local thiamet-G delivery by a thermosensitive hydrogel confers ischemic cardiac repair via myeloid M2-like activation in a STAT6 O-GlcNAcylation-dependent manner. Int Immunopharmacol 131: 111883, 2024.
135. Zhang L, Shao L, Li J, Zhang Y and Shen Z: Annexin A1-Loaded alginate hydrogel promotes cardiac repair via modulation of macrophage phenotypes after myocardial infarction. ACS Biomater Sci Eng 10: 3232-3241, 2024.
136. Yuan L, Hu Z, Peng S, Li N, Wu H and Wang Y: Molecular mechanisms of myocardial repair and cardiac function improvement with Hydrogel-mediated Macrophage-derived exosome delivery. FASEB J 39: e70977, 2025.
137. Niu H, Liu Z, Guan Y, Wen J, Dang Y and Guan J: Harnessing synergistic effects of MMP-2 Inhibition and bFGF to simultaneously preserve and vascularize cardiac extracellular matrix after myocardial infarction. Acta Biomater 191: 189-204, 2025.
138. You T, Zhang Y, Su H, Wang N, Zhang X, Anwaier S, Long X, Han L, Wu Y, Liang J, *et al*: Ameliorating post-infarction myocardial fibrosis and cardiac function via ROS-responsive hydrogel-mediated IL-11 antibody delivery. Bioact Mater 60: 527-538, 2026.
139. Luo Q, Cheng N, Yang Y, Shao N, Nie T, Chen J, Huang C, Zhang S, Huang Y, Ieong CM, *et al*: Multi-stage cooperative ROS-responsive hydrogel platform for drug delivery in myocardial ischemia-reperfusion injury repair. Mater Today Bio 32: 101854, 2025.
140. Zhang Y, Xu Y, Wu C, Chen S, Chen Z, Qin F, Hu X, Zhang J and Wang Y: Injectable conductive hydrogel patch with spatiotemporally tailored asymmetric adhesion for myocardial infarction repair. Adv Mater 38: e10824, 2026.
141. Cui Z, Ni NC, Wu J, Du GQ, He S, Yau TM, Weisel RD, Sung HW and Li RK: Polypyrrole-chitosan conductive biomaterial synchronizes cardiomyocyte contraction and improves myocardial electrical impulse propagation. Theranostics 8: 2752-2764, 2018.
142. Xu Z, Li X, Mi X and Lin Y: Exosomes loaded stimuli responsive conductive hydrogel restores cardiac function post-myocardial infarction via SIRT1/p53-mediated anti-inflammatory mechanism: Mechanistic insights into cardioprotection. Biomater Adv 180: 214610, 2026.
143. Wang S, Zhao X, Zhan Y, Liang J, Shi J, Gu J and Wang H: A ROS-Scavenging and Conductive Hydrogel-based cardiac patch with controlled release of edaravone for myocardial infarction treatment assisted by electrical stimulation. Biomacromolecules 26: 7930-7943, 2025.
144. Tran DL, Phan HN, Nguyen HTA, Nguyen HT, Nguyen LM, Phung VT and Nguyen DH: An injectable conductive hydrogel enabling sustained nitric oxide generation for cardiac tissue regeneration. J Mater Chem B 14: 4330-4345, 2026.
145. Luque GC, Picchio ML, Daou B, Lasa-Fernandez H, Criado-Gonzalez M, Querejeta R, Filgueiras-Ramas D, Prato M, Mecerreyes D, Ruiz-Cabello J, *et al*: Printable Poly(3,4-ethylen edioxythiophene)-based conductive patches for cardiac tissue remodeling. ACS Appl Mater Interfaces 16: 34467-34479, 2024.
146. Xu Z, Chen J, Shu L, Hong W, Mo Y, Wang J, Liu Y, Wong WT, Tsang SY, Tan N, *et al*: Fabrication of a conductive, ionic liquid functionalized, oxygen-generating hydrogel loaded with ADSC-derived exosomes to enhance angiogenesis and cardiac repair after acute myocardial infarction. Theranostics 16: 1997-2018, 2026.
147. Yu R, Zhao R, Guo D, Shi M, Wen H, Niu X, Ni P, Liu M, Luo H, Qi B, *et al*: Supramolecular antioxidant conductive injectable hydrogel encapsulating L-arginine for synergistic modulation of myocardial infarction. J Control Release 390: 114552, 2026.
148. Abdollahiyan P, Baradaran B, de la Guardia M, Oroojalian F and Mokhtarzadeh A: Cutting-edge progress and challenges in stimuli responsive hydrogel microenvironment for success in tissue engineering today. J Control Release 328: 514-531, 2020.
149. Sood N, Bhardwaj A, Mehta S and Mehta A: Stimuli-responsive hydrogels in drug delivery and tissue engineering. Drug Deliv 23: 758-780, 2016.
150. Xue K, Wang X, Yong PW, Young DJ, Wu YL, Li Z and Loh XJ: Hydrogels as emerging materials for translational biomedicine. Adv Therap 2: 1800088, 2019.
151. Zhao XY, Li PC, Chen YM, Cao K, Wei W, Aziz Y and Zrínyi M: Adipose tissue engineering biomaterials: Smart scaffolds, vascularization, and clinical frontiers. Biomolecules 16: 362, 2026.
152. Tong S, Chen J, Li Y and Zhao W: Emerging gel technologies for atherosclerosis research and intervention. Gels 12: 80, 2026.
153. Felisbino MB, Rubino M, Travers JG, Schuetze KB, Lemieux ME, Anseth KS, Aguado BA and McKinsey TA: Substrate stiffness modulates cardiac fibroblast activation, senescence, and proinflammatory secretory phenotype. Am J Physiol Heart Circ Physiol 326: H61-H73, 2024.
154. Shayan M, Huang MS, Navarro R, Chiang G, Hu C, Oropeza BP, Johansson PK, Suhar RA, Foster AA, LeSavage BL, *et al*: Elastin-like protein hydrogels with controllable stress relaxation rate and stiffness modulate endothelial cell function. J Biomed Mater Res A 111: 896-909, 2023.
155. Krebs C, Macara LM, Leiser R, Bowman AW, Greer IA and Kingdom JC: Intrauterine growth restriction with absent end-diastolic flow velocity in the umbilical artery is associated with maldevelopment of the placental terminal villous tree. Am J Obstet Gynecol 175: 1534-1542, 1996.
156. Page G, Ratchada P, Miron Y, Steiner G, Ghetti A, Miller PE, Reynolds JA, Wang K, Greiter-Wilke A, Polonchuk L, *et al*: Human ex-vivo action potential model for pro-arrhythmia risk assessment. J Pharmacol Toxicol Methods 81: 183-195, 2016.
157. Nash KM, Boe BA, Carrillo SA, Harrison A, Iwaki R, Kelly J, Kirkton RD, Krishnamurthy R, Lawson JH, Matsuzaki Y, *et al*: Evaluation of tissue-engineered human acellular vessels as a Blalock-Taussig-Thomas shunt in a juvenile primate model. JTCVS Open 15: 433-445, 2023.
158. Kelsey LJ, Fry DM and VanderKolk WE: Thrombosis risk in the trauma patient. Prevention and treatment. Hematol Oncol Clin North Am 14: 417-430, 2000.
159. Cutiongco MF, Anderson DE, Hinds MT and Yim EK: In vitro and ex vivo hemocompatibility of off-the-shelf modified poly(vinyl alcohol) vascular grafts. Acta Biomater 25: 97-108, 2015.
160. Ren H, Pan Z, Yuan J and Liu J: Zwitterionic hydrogel coatings enhance anti-fouling and anti-thrombogenicity of decellularized swim bladder for bioprosthetic heart valves. Colloids Surf B Biointerfaces 260: 115349, 2026.

161. Liu Y, Zhang J, Zhang Y, Yoon HY, Jia X, Roman M and Johnson BN: Accelerated engineering of optimized functional composite hydrogels via High-throughput experimentation. ACS Appl Mater Interfaces 15: 52908-52920, 2023.
162. Pleshakov PS, Shmakov SV, Filatov NA and Bukatin AS: Negative pressure actuated microfluidic droplet generation enables High-throughput and robust synthesis of cell-laden alginate microgels. ACS Biomater Sci Eng 12: 180-189, 2026.
163. Zheng F, Tian R, Lu H, Liang X, Shafiq M, Uchida S, Chen H and Ma M: Droplet microfluidics powered hydrogel microparticles for stem Cell-mediated biomedical applications. Small 20: e2401400, 2024.
164. S A Bento C, Gaspar MC, Coimbra P, de Sousa HC and E M Braga M: A review of conventional and emerging technologies for hydrogels sterilization. Int J Pharm 634: 122671, 2023.
165. Gil-Cabrerizo P, Simon-Yarza T, Garbayo E and Blanco-Prieto MJ: Navigating the landscape of RNA delivery systems in cardiovascular disease therapeutics. Adv Drug Deliv Rev 208: 115302, 2024.