Injectable Hydrogels to Treat Myocardial Infarction

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Introduction

Each year, over 700,000 Americans experience myocardial infarction (MI), which remains the leading cause for heart failure worldwide [1]. MI, commonly known as heart attack, is defined by an ischemic event that results in the sudden death of myocardial tissue due to partial or full occlusion of the coronary arteries [2]. As the tissue experiences a sudden reduction of oxygen and nutrient supply, massive death of cardiomyocytes occurs. Within minutes of the onset of ischemic injury, inflammatory cells, such as neutrophils and then macrophages, infiltrate into the infarct. These cells degrade the surrounding extracellular matrix (ECM) as well as trigger the upregulation of apoptotic signals, proteases, and matrix metalloproteinases (MMPs) [2–5]. The infarct consists of a core of necrotic myocardial tissue surrounded by a border zone that contains the tissue at risk. For days to months after MI, further cardiomyocyte death and ECM degradation in the border zone can expand the necrotic core, a process referred to as infarct expansion [5].

Due to the extremely limited capability of adult myocardial tissue to regenerate, fibroblasts will infiltrate the infarct to deposit a stiff fibrous scar, composed primarily of collagen, in the left ventricle (LV) wall. This scar is a dynamic environment that changes for years post-MI with continued collagen turnover and active myofibroblasts [6]. Mostly acellular scar tissue increases the collagen content of the ECM up to 20-fold higher than that in the healthy myocardial ECM, and its tensile strength serves to balance the distending forces of the heart wall as it beats [4, 7]. However, because the fibrotic scar lacks cardiac muscle, the LV begins to dilate in order to maintain stroke volume via the Frank-Starling law [4]. Simultaneously, the LV wall will become thinner as the chamber expands and the remaining bundles of muscle fibers around the

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V. Serpooshan, S. M. Wu (eds.), *Cardiovascular Regenerative Medicine*,
https://doi.org/10.1007/978-3-030-20047-3_10

infarct slide past each other, otherwise known as myocyte slippage [5]. This dilation further increases the LV wall stresses. Myocyte hypertrophy is initiated in an ultimately insufficient attempt to offset these additional wall stresses, which only triggers a cycle of additional dilation. While dilation initially serves as a compensatory method to maintain cardiac function, continued dilation and thinning leads to heart failure as these effects become deleterious [5]. Ejection fraction (EF), a common functional measurement of the percentage of blood that is pumped from the LV, greatly reduces after MI as the patient progresses toward heart failure as a direct result of LV remodeling. Fibrosis, LV dilation, wall thinning, increased wall stresses, and reduced functional output are all major consequences of negative LV remodeling. This is a therapeutic opportunity for injectable hydrogels. To prevent or reverse negative LV remodeling, injectable hydrogels often target the border zone of the infarct where cell death can still be prevented, and infarct expansion may be reduced. If bioactive, these hydrogels may also serve as scaffolds to positively remodel the infarct.

To investigate the efficacy of these injectable hydrogel therapeutics to treat MI, small animal models using murine species are powerful tools for a primary investigation to show proof of concept. More extensive reviews on these small animal models can be found in the literature [8–10]. However, large animals such as porcine or ovine models are required for preclinical studies of MI treatment, before moving into human patients, since the cardiovascular system of these animals is more mimetic of human systems. In both porcine and ovine models, predictable coronary anatomy and the lack of many pre-existing collateral vessels allow for the generation of infarcts that are easily reproducible in size and location [11]. This can occur through either total occlusion of a coronary artery, typically via surgery, or ischemia-reperfusion, typically achieved with a balloon catheter. Generally, pigs have similar cardiac to body mass ratios, hemodynamics, and development of cardiac injury post-MI to those in humans (both spatially and temporally) [12]. Therefore, to emphasize clinical relevance, this chapter presents a concise review of large animal studies (summarized in Table 10.1) and any subsequent clinical trials (summarized in Table 10.2) involving injectable hydrogel therapeutics for treating MI, with a focus on how design principles may impact efficacy of the material.

Properties of an Injectable Hydrogel

A hydrogel is defined as a hydrophilic polymeric network capable of absorbing water, resulting in a swollen, flexible, and porous material that can closely resemble the physical properties of many soft tissues [13]. A physical hydrogel is one in which the cross-links between polymers are due to ionic interactions, hydrogen bonding, and other non-covalent bonding. These hydrogels are easily influenced by their environment, and their degree of cross-linking may be reversed depending on pH, temperature, or ionic strength. Conversely, chemically cross-linked hydrogels rely on covalent bonding, and gelation is often permanent. However, both physical and chemical hydrogels may be degraded by enzymatic or hydrolytic reactions, depending on the chemical structure of the polymeric backbone.

Table 10.1 Tabulated comparison of large animal preclinical studies evaluating the efficacy of injectable hydrogels to treat myocardial infarction

Material	Delivery	Time of delivery post-MI	Echo/ MRI	Functional efficacy	Model	Biologics/cells delivered	Modifications	Refs #
Fibrin/ Alginate	Thoracotomy microinjections	7 days	Echo	No significance	Porcine	N/A	N/A	[19]
Alginate	Intracoronary infusion	4 days	Echo	Reduced LV areas	Porcine	N/A	Calcium cross-linked	[20]
Alginate	Open-chest microinjections	Immediate	Echo	N/A	Porcine	MSCs	RGD	[46]
Algisyl-LVR	Open-chest microinjections	Micro-embolization model	Echo	Trends for decreased LV volumes	Canine	N/A	N/A	[24]
Algisyl-LVR	Open-chest microinjections	8 weeks	Echo	No significant differences in LV volumes	Porcine	N/A	N/A	[25]
PEG	Transendocardial catheterization	4 weeks	N/A	N/A	Porcine	HGF/IGF-1	UPy coupled via alkyl spacers	[42]
HA	Thoracotomy microinjections	Immediate	MRI & echo	Reduced LV volumes	Porcine	rTIMP-3	Methacrylated	[40]
HA	Thoracotomy microinjections	Immediate	Echo	Attenuated LVEDV dilation	Porcine	rTIMP-3	Aldehyde, hydrazide functionalization of HA and dextran sulfate; MMP cleavable peptide	[41]
HA	Thoracotomy microinjections	30 minutes	Echo	No significance	Ovine	N/A	Methacrylate	[35]
HA	Thoracotomy microinjections	30 minutes	MRI	Maintained LVEDV compared to saline	Ovine	N/A	Hydroxyethyl methacrylate	[36]
HA	Open-chest microinjections	Immediate	Echo	Reduced LVEDV	Porcine	MNCs	N/A	[45]

(continued)

Table 10.1 (continued)

Material	Delivery	Time of delivery post-MI	Echo/ MRI	Functional efficacy	Model	Biologics/cells delivered	Modifications	Refs #
HA (Extracel-HP)	Thoracotomy injection	Immediate	Echo	Decreased LV volumes for multiple treatment groups	Porcine	PRP, AA, ibuprofen, and allopurinol	N/A	[43]
Myocardial matrix	Transendocardial catheterization	2 weeks	Echo	Reduced LV volumes	Porcine	N/A	N/A	[32]
Peptide NFs	Open-chest microinjections	Immediate	Echo	Improved fractional shortening	Porcine	VEGF	N/A	[39]
Peptide NFs	Open-chest microinjections	Immediate	Echo	Reduced LV volumes	Porcine	MNCs	N/A	[47]

Echo echocardiography, *MRI* magnetic resonance imaging

Table 10.2 Tabulated comparison of clinical trials evaluating the safety, feasibility, and efficacy of injectable hydrogels to treat myocardial infarction

Therapeutic	Trial name	Delivery	Time of delivery post-MI	Echo/ MRI	Functional efficacy	Phase	Identifier	Refs (#)
BL-1040 / IK_5001	N/A	Intracoronary infusion	2–5 days	Echo	LV volume preservation up to 6 months postinjection	I/II	NCT00557531	[22]
	PRESERVATION-I	Intracoronary infusion	2–5 days	Echo	No significance in LV volume differences between groups	II	NCT01226563	[23]
Algisyl-LVR	N/A	Open-chest injection during CABG	Symptomatic heart failure	MRI	Trends for decreasing LV volumes at 6 months postinjection (only 3 patients)	II	NCT00847964	[27]
	AUGMENT-HF	Thoracotomy injection	Symptomatic heart failure	Echo	No significance in LV volume differences between groups	II/III	NCT01311791	[26]
VentriGel	N/A	Transendocardial	60 days–3 years	MRI	Study not yet published	I	NCT02305602	N/A

Echo echocardiography, *MRI* magnetic resonance imaging

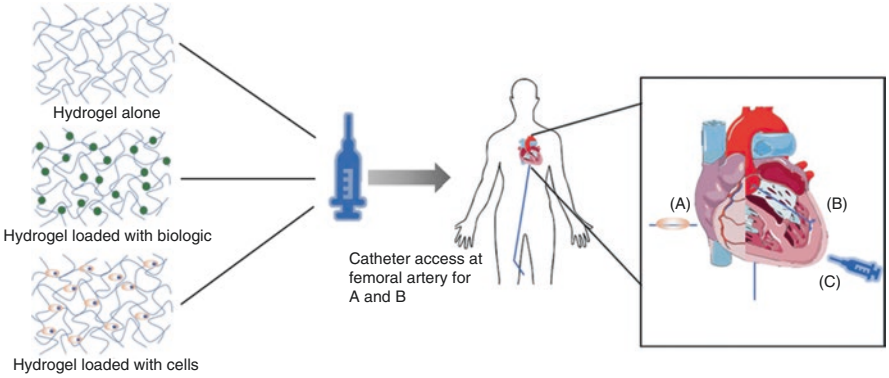

Fig. 10.1 Injectable hydrogel therapeutics can be delivered alone or may be loaded with a biologic payload or stem cells to improve localized retention, as well as prolong the therapeutic delivery. Injectable hydrogels may be delivered minimally invasively through catheter approaches of intracoronary infusion (A) or transendocardial delivery (B). However, the more invasive approach of surgical-based injection is required for some materials (C)

It is critical to keep in mind the changes occurring in the myocardial tissue after MI when designing a biomaterial therapeutic. Injectable hydrogels provide a unique opportunity to recapitulate soft tissue through the tunability of their mechanical properties, porosity, ability to absorb water, and ability to be created by many different polymers, both natural and synthetic [10]. While biomaterial design plays a key role in therapeutic efficacy, it also plays a role in delivery. Catheter delivery of a hydrogel therapeutic is a favorable method versus those that require direct surgical access to the heart. To accomplish this, though, the hydrogel must be injectable not only through a syringe and needle, but also a long narrow catheter. Therefore, the materials would need to have the appropriate viscosity, often accomplished by using shear thinning materials. Further, after injection into the heart wall, the material should gel in situ at physiological temperature (37 °C), pH (7.4), and salt conditions [14]. This gelation time must also be relatively short (less than ~30 s) to minimize loss of material to the surrounding vasculature due to the beating of the heart [14]. These injectable hydrogels can be delivered alone or loaded with a drug, biological reagent, or therapeutic cells (Fig. 10.1) that are continuously released to the infarct region over time as the hydrogel is degraded.

Biomaterials Alone

Natural or synthetic biomaterials can be used to provide biochemical cues or alter the local tissue environment to prevent negative LV remodeling and attenuate cardiomyocyte death. Initially, the hypothesis for the mechanism of action of these materials hinged on the mechanical support they could provide to the LV wall. However, later studies suggested bioactivity and cellular interaction play a more dominant role in affecting cardiac function [15, 16], although changes in polymer

mechanical properties are also likely to influence the local cell and tissue response. Natural biomaterials include those derived from polymers found in nature such as alginate, fibrin, and collagen or from decellularization of ECMs. Because these materials are naturally derived, they are also most easily degraded by the body with no toxic byproducts. Protein-based materials contain native peptide sequences that facilitate cell adhesion and infiltration. Synthetic biomaterials are made from polymers not found in nature, such as polyethylene glycol (PEG), or naturally derived polymers that are modified using synthetic compounds to improve their degradation rate or physical strength, such as hyaluronic acid (HA). Hydrogels from these materials can often have much stronger mechanical properties due to the ease of tunability during polymerization and processing [17]. However, they have limited bioactivity. Commonly, synthetic polymers are used to enhance mechanical properties of naturally derived materials or to deliver biologics or cells, as will be discussed in the following sections.

Alginate

Alginate is a polysaccharide that is naturally produced by brown algae and can easily be turned into a hydrogel by using calcium as an ionic cross-linking agent [18]. Although alginate is not naturally produced in humans, it still contains biocompatible structures which can be easily modified with other functional molecules such as RGD peptides to promote cell adhesion. Humans, however, do not have the native enzymes capable of breaking down alginate, and instead, their degradation must be regulated by the design of the cross-linking conditions. Properties such as cross-linking may be altered depending on how long the specific clinical application requires the therapeutic to remain at the site of injury [18].

In an early investigation into the therapeutic potential of alginate, done by Mukherjee et al., alginate was combined with fibrin to form an injectable hydrogel composite material (Fib-Alg) [19]. Fibrin is the body's native wound healing scaffold formed by thrombin cleaving fibrinogen to form a clot. It is commercially used as a sealant and surgical adhesive and often experimentally used as a tissue engineering scaffold. For this study, an invasive delivery option was chosen by reopening the initial thoracotomy site 7 days post-MI, likely because of the quick gelling and dual component nature of the Fib-Alg material, which would make catheter delivery more difficult. Using an injection grid, the composite material was injected using a double barrel syringe, resulting in rapid gelation upon mixing of the fibrin and alginate solutions [19]. The Fib-Alg group showed similar capillary density to the control healthy animals 28 days after MI, while the saline control was significantly reduced compared to the Fib-Alg and healthy controls. This study only provided proof of concept and no statistical significance was achieved on functional echocardiographic measurements.

In a study done by Leor et al., a calcium cross-linked alginate solution was delivered at day 4 post-MI via intracoronary infusion instead of using needle-based injection like most hydrogels (Fig. 10.2) [20]. After MI, inflammatory cytokines

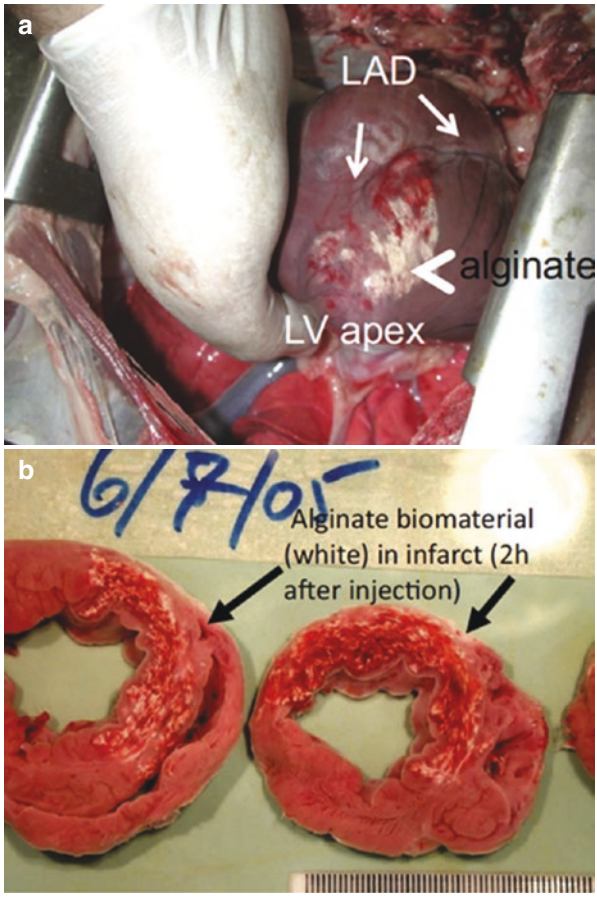

Fig. 10.2 (**a**) and (**b**): calcium cross-linked alginate hydrogel. Intracoronary infusion of alginate solution is visible in the porcine heart 2 hours after injection. (Reprinted with permission from Ref. [20])

increase the permeability of the microvasculature of the heart resulting in an increased ability for larger molecules to extravasate through the endothelial cell layer in blood vessels to reach surrounding tissue. This is commonly referred to as "leaky vasculature" [21]. As the alginate solution was infused through a balloon catheter, the material that entered the infarct region gelled because of the high concentration of calcium in the infarct, while the material remaining in the blood stream was likely excreted by the kidneys [20]. This study showed that the calcium cross-linked alginate solution is capable of reversing enlargement of LV end-diastolic and end-systolic area, as measured by echocardiography, and increasing scar thickness up to 2 months after MI in a porcine model. The initial hypothesis of the mechanism of action for the material was that it would act as an LV mechanical wall support. However, staining with α-smooth muscle actin (αSMA) showed increased presence of myofibroblasts in the infarct compared to the control group, which could have accounted for its observed efficacy.

A Phase I/II study using the alginate material (Identifier: NCT00557531), called BL-1040 or IK-5001, showed proof of concept for safe and feasible delivery at least 2 days after successful percutaneous coronary intervention (PCI) and up to 1 week after MI. This study was not a randomized controlled trial, but echocardiographic measurements showed preservation of LV volumes up to 6 months postdelivery [22]. A 303-patient, multicenter, randomized, double-blind, placebo-controlled clinical trial, PRESERVATION-I, was subsequently completed in 2015 (Identifier: NCT01226563). PRESERVATION-I delivered the IK-5001 2–5 days after successful PCI in patients that previously experienced large ST-elevation myocardial infarction (STEMI), as defined by their inclusion criteria. LV dimensions were measured using 3D echocardiography by an independent, blinded echocardiographic core laboratory. The results yielded no significant differences in LV end-diastolic volume index (LVEDVI) changes over 6 months between the saline control and IK-5001-treated groups, indicating the material may not have the ability to prevent negative LV remodeling [23]. The trial publication suggests that the patient cohort chosen for this study may have had infarcts too large for the volume of material they were delivering to have any therapeutic effect. Additionally, the authors recognized that faster delivery of the material, for instance, in the initial PCI during MI, might be more effective since microvascular obstruction several days post-MI may prevent material delivery. In terms of safety, the assessment of IK-5001 concluded that there were increased events of stent thrombosis in IK-5001 treated patients compare to saline treated. Failed primary endpoints halted further evaluation of this material.

An initial investigation into another formulation of alginate, Algisyl-LVR, was done in a canine model of chronic heart failure (CHF) with delivery of material via open-chest direct injection. This study, done by Sabbah et al., showed trends for decreasing LV end-systolic volume (ESV) and end-diastolic volume (EDV), as well as significantly increased LV wall thickness in the alginate-treated groups compared to the saline controls up to 17 weeks postinjection [24]. A subsequent study done by Choy et al. demonstrated efficacy of Algisyl-LVR to act as a permanent scaffold to increase EF in a porcine model of CHF (Fig. 10.3) [25]. In this CHF model, Algisyl-LVR or saline control was delivered via sternotomy 8 weeks after MI. Injections were performed at the mid-ventricular level, with a total of 10–19 intramyocardial injections equally spaced circumferentially around the beating heart (Fig. 10.3a). Because the scaffold is permanent, the inflammatory response for this type of biomaterial resolves with the body forming a fibrous capsule around the material to essentially wall it off from surrounding tissue (Fig. 10.3b). Echocardiographic (2D and 3D) measurements yielded no statistical differences in LV EDV/ESV between treatment groups, while a significant increase in EF was shown in the Algisyl-LVR group compared to the saline control group. The Algisyl-LVR treated animals also exhibited increased LV wall thickness and reduced myofiber stress, indicating some recovery or rescue of function due to treatment [25]. Additionally, 8 weeks after therapeutic delivery, animals that received Algisyl-LVR showed reduced expression of miRNA-195, 21, and 210, which are commonly associated with cardiac stress.

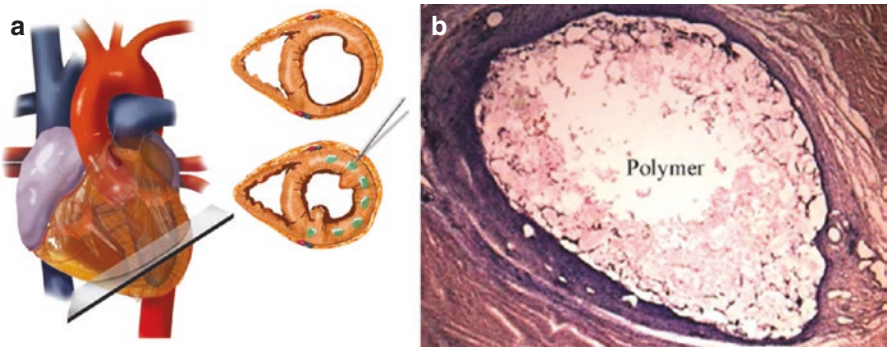

Fig. 10.3 (**a**) Algisyl-LVR implantation, demonstrating equally spaced injections at mid-ventricular level. (**b**) H&E stained histological section of treated group myocardium, showing implanted Algisyl-LVR polymer at 100×. (Reprinted with permission from Refs. [25, 26])

A first-in-man trial looked into the safety and feasibility of delivering Algisyl-LVR in 11 patients who developed HF from ischemic and non-ischemic dilated cardiomyopathy (DCM) in combination with coronary artery bypass grafting (CABG) via sternotomy (Identifier: NCT00847964). While HF from DCM has some differences in progression from MI, negative LV remodeling still remains a therapeutic target. Publication of the trial results by Lee et al. has shown safety of the material. However, only 3 out of the 11 patients could safely undergo MRI, and consequently, the sample size of functional data is small ($n = 3$) [27]. Although there were no statistically significant differences, the LV wall thickness, EDV, ESV, and myofiber stress showed decreasing trends for up to 6 months postinjection. Due to the success in showing safety and feasibility, Algisyl-LVR has also completed a multicenter, randomized, and controlled Phase II/III clinical trial (AUGMENT-HF), investigating the safety and efficacy of Algisyl-LVR alone to treat advanced heart failure (Identifier: NCT01311791) [26]. Since this material requires thoracotomy to perform direct injection delivery of the material, it was considered unethical to have a control group with saline injection, and instead, the control group consisted of patients who received standard medical care only. The experimental group received standard medical care as well as Algisyl-LVR injections. The primary efficacy endpoint of AUGMENT-HF was changed in peak VO_2 from baseline to 6 months after material injection. Peak VO_2 is a measurement of volume of oxygen delivered to the body during exercise. Increased peak VO_2 has been previously shown to be closely related to a better prognosis for chronic heart failure patients [28]. AUGMENT-HF yielded significant increases in patients treated with Algisyl-LVR compared to saline controls, as well as increased quality of life based on patient surveys standardized by the New York Heart Association (NYHA). However, similar to the preclinical trial of this material, no statistical differences were seen in any echocardiographic measurements of LV dimensions at 3 and 6 months postdelivery. Although not statistically significant, some adverse events were seen in the Algisyl-LVR group with a 30-day absolute mortality rate of 8.75% and surgical complication rate of 25%, compared to no mortality in the control group.

Comparing clinical trials PRESERVATION-I and AUGMENT-HF, it is worth noting some differences and similarities in material design and therapeutic targets. Algisyl-LVR does not degrade and is intended for permanent implantation via surgical-based injection into the heart wall. IK-5001, however, is delivered by intracoronary infusion, which heavily depends on the presence of leaky vasculature immediately following MI. IK-5001 material will eventually degrade over 3–6 months. For this reason, Algisyl-LVR is better suited to treat chronic heart failure patients, while IK-5001 would only be suitable for acute MIs. Both trials indicated increased exercise capacity of patients treated with Algisyl-LVR and IK-5001 compared to the saline controls using a 6-minute walk test. Since PRESERVATION-I failed to produce significant data for the defined primary outcome, a study redesign is required to continue clinical trials for the treatment of MI using the IK-5001 material. It is also important to point out that both trials failed to produce significant improvements in LV volumes or dimensions when compared to their respective control groups, which is a critical determinant of efficacy in treating MI and preventing the development of heart failure. Both materials were hypothesized to act as mechanical supports to prevent negative LV remodeling, but the results of these studies may point to the requirement of additional biochemical activity for effective treatment.

Tissue-Derived ECM

Decellularized ECM hydrogels can be derived from various tissue types, such as heart, pancreas, skeletal muscle, and brain. Since each tissue type has a specific biochemical composition, some studies have shown improved efficacy using a tissue-specific source, possibly related to which germ layer the tissue arose from [29–31]. To create an injectable hydrogel, the tissue undergoes decellularization and enzymatic digestion, which changes the microstructure of the ECM. However, the hydrogel maintains the biochemical complexity of the tissue from which it was derived, and for the most part, the nanostructure of the ECM. This can provide a therapeutic that is highly mimetic of native myocardial ECM. A preclinical porcine study investigated the efficacy of a porcine-derived, decellularized, LV myocardial ECM hydrogel, termed myocardial matrix, to prevent negative LV remodeling and improve cardiac function. The study showed that delivery of the myocardial matrix 2 weeks after MI increased EF and reduced LV volumes 3 months after treatment compared to untreated and saline control groups [32]. Additionally, analysis with Masson's trichrome staining showed a thicker muscle layer in the endocardium of the matrix injected heart (Fig. 10.4) as well as reduced infarct fibrosis. The myocardial matrix hydrogel fully degraded in vivo in approximately 3 weeks. However, the effects of repair were longer lasting [32]. To investigate the mechanism of action, a gene expression study was performed in rat model and showed that the material can adjust the inflammatory response toward pro-remodeling. It can also reduce fibrosis, promote cardiomyocyte survival in the infarct, and modulate cardiomyocyte metabolism [33].

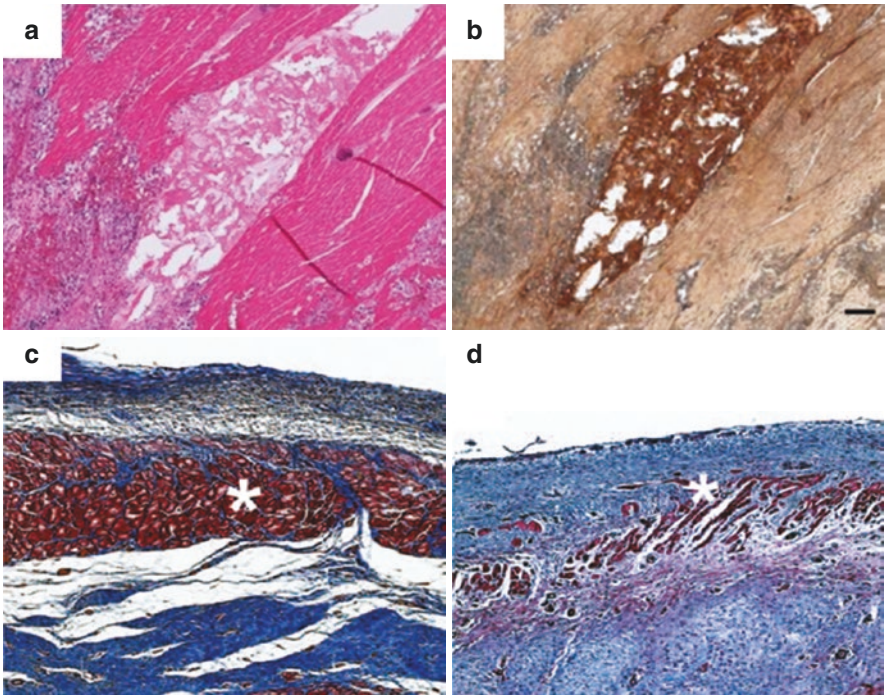

Fig. 10.4 Myocardial matrix hydrogel derived from decellularized porcine myocardial ECM. Myocardial matrix hydrogel mitigated negative LV remodeling in the infarct. H&E (**a**) and diaminobenzene (**b**) staining of biotin labeled hydrogel showed the presence of myocardial matrix in the infarct 24 hours after injection. Masson's trichrome staining images of infarcted pig heart with myocardial matrix hydrogel-treated (**c**) and saline-injected groups (**d**) showed distinct and thicker muscle layer in matrix-treated hearts. (Reprinted with permission from Refs. [32, 34])

There is a recently completed, Phase I, open-label clinical trial determining the safety and feasibility of the myocardial matrix hydrogel, commercially produced as VentriGel, to treat MI up to 3 years after the initial PCI (Identifier: NCT02305602). VentriGel is delivered minimally invasively via transendocardial injections using the Myostar catheter after 3D NOGA™ mapping to determine injection points based on electrical activity. Results are not yet published, but secondary endpoints will be used as a first investigation into the efficacy of the material from magnetic resonance imaging (MRI) data such as ESV, EDV, and EF. Compared to the alginate products examined in AUGMENT-HF and PRESERVATION-I, VentriGel is being regulated as a biologic in the United States as opposed to a device. This is due to the presence of biochemically active compounds and other proteins found in native ECM. Although this makes the FDA approval process for VentriGel more rigorous, it may provide an advantage in efficacy for preventing negative LV remodeling compared to biomaterials that lack biochemically active compounds.

Hyaluronic Acid

Hyaluronic acid (HA) is a highly abundant, anionic, non-sulfated glycosaminoglycan (GAG) natively found in the ECM of many connective and soft tissues. HA serves as an important signaling molecule for cell migration and proliferation. In order to induce gelation, HA macromers can be chemically modified by attaching groups capable of covalent or non-covalent cross-linking. A common substitution is the introduction of methacrylate. Methacrylate substitution can be controlled with a high degree of accuracy, allowing for increased tunability of the material's physical properties. This allows the gel to better mimic the mechanical properties of the tissue that is targeted for therapy.

Ifkovits et al. designed a study using an left anterior decsending (LAD) coronary artery ligation ovine model of acute MI to investigate the efficacies of hydrogels with compressive moduli comparable to that of the cardiac tissue (MeHA low) and approximately 10 times greater than that of healthy myocardium (MeHA high) [35]. Both high and low MeHA had a similar degradation profile that spanned over 8 weeks in vivo, allowing for prolonged presence of the material. The key differences between the two materials were their mechanical properties. MeHA high and low, as well as saline control microinjections directly into the infarct region, were performed 30 minutes following MI through the thoracotomy opening. This study showed that 8 weeks after delivery, the high and low MeHA significantly reduced wall thinning compared to the saline control group. Further, MeHA high significantly reduced infarct length compared to MeHA low and saline control groups. Echocardiographic 3D functional measurements of normalized EF, EDV, and ESV were however not statistically significant. While mechanical properties play a role in repair, the lack of difference between the low and high MeHA groups may suggest that additional biochemical cues can provide a synergistic effect.

In a study done by Dorsey et al., hydroxyethyl methacrylate HA (HeMA HA) was investigated in an acute porcine model with delivery of the biomaterial only 30 minutes after MI, while the thoracotomy site was still open. Infarct was induced via ligation of the LCX coronary artery [36]. This quick delivery time was chosen to minimize the number of procedures the animal had to undergo. However, this limits the clinical relevance of the study, as the average time for cardiac balloon-angioplasty intervention in human patients experiencing MI is more than an hour, and injectable materials via needle-based injection are unlikely to be administered until several days to weeks after MI. The HeMA HA material degraded well before 12 weeks in vivo. However, positive effects of the material were still observed up to 12 weeks after MI, implying lasting effects of the material after degradation. Cine MRI and spatial modulation of magnetization (SPAMM) were used to analyze cardiac dimensions and finite element (FE) measurements of wall stresses. Significant increases in EF for HeMA HA-treated animals were seen starting at 8 weeks, and LV EDV was maintained up to 12 weeks, while in the saline control group, EDV became significantly larger than baseline at 1 week post-MI. Significantly increased

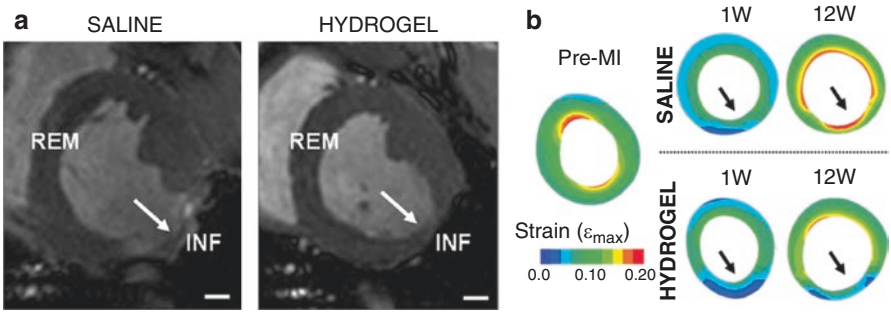

Fig. 10.5 (**a**) Representative magnetic resonance images showing increased wall thickness and smaller infarct size in hydrogel-treated animals. (**b**) Finite element simulation of diastolic principle strain maps of baseline and post hydrogel or saline injections, showing increased stiffness in the hydrogel-treated group compared to saline. (Reprinted with permission from Ref. [36])

wall thickness became evident at 12 weeks (Fig. 10.5a). Additionally, some trends indicated increased infarct thickness and stiffness in the direction of the cardiac muscle fibers, but the small sample size yielded no statistical significance (Fig. 10.5b).

Biologics Delivered

While biomaterials alone have the ability to promote repair and prevent negative LV remodeling, therapeutic efficacy may be potentially enhanced by introducing biologics into the material. Biomaterials have been used to deliver plasmids, RNA, or proteins that may act as growth factors, cytokines, or other regulators of cellular activity. Systemic delivery of the therapeutic often results in rapid dilution and degradation in the bloodstream and/or filtration out of the body. Consequently, a high dose is required to obtain the optimal concentration for treatment at the site of disease or injury with possible off target effects depending on localization efficiency. The benefit of delivering a biologic within a hydrogel is that the encapsulation may protect the biologic from degradation or excretion while also allowing a prolonged and localized delivery of the therapeutic [37, 38]. For MI treatment specifically, biomaterials provide an exciting opportunity to prevent the development of heart failure through the prolonged delivery of a therapeutic that targets the negative remodeling of the LV based on specific changes occurring in the infarcted environment.

Self-assembling peptide nanofibers (NFs) of a specific sequence can undergo gelation upon injection and have been investigated as a therapeutic delivery system for recombinant human vascular endothelial growth factor (VEGF) in a study by Lin et al. [39]. The NFs were designed to remain in the infarct for an extended period, with 70% of the material still at the injection site for up to 1 month. In this porcine model, MI was induced via permanent occlusion of the LAD coronary artery with immediate subsequent injection of PBS, NFs alone, VEGF alone, or the

combinatorial NF-VEGF therapy. LV volumes from 2D echocardiographic measurements showed that the EDV and ESV from both the VEGF alone and NF-VEGF groups were significantly lower compared to the saline control group. Additional cardiac functional data showed significant improvement at 28 days post-MI in the NF-VEGF group through improved LV fractional shortening (FS) compared to the other groups. VEGF alone and NF-VEGF injections both significantly improved angiogenesis in the border zone of the infarct, but only the combinatorial therapeutic of NF-VEGF significantly increased arteriogenesis at 28 days post-MI. While this study may not confidently show the efficacy of the combinatorial treatment compared to VEGF alone, it still points to the importance of biochemical cues to promote repair in the infarct.

As previously mentioned, MMPs play a role in LV remodeling after MI due to their ability to degrade ECM components, specifically collagen. Because of this, MMP inhibition may be of interest to prevent negative LV remodeling and promote infarct repair. One study by Eckhouse et al. in a porcine model investigated the immediate injection of recombinant tissue inhibitor of MMP-3 (rTIMP-3), encapsulated in HA hydroxyethyl methacrylate (HEMA) gels by binding rTIMP-3 to the HA backbone via ester-mediated hydrolysis [40]. The injections were administered through the thoracotomy site used for MI. Functional measurements showed reduced wall stresses and reduced LV volumes with echocardiographic and MR imaging. Immunoblotting analysis also showed reduced MMP levels, increased TIMP levels, and reduced macrophage presence in groups treated with the rTIMP-3 gel (Fig. 10.6). Although this implies the rTIMP-3 gel can modulate the inflammatory response, some macrophages have a pro-regenerative capability, so this effect is not clear as positive or negative. However, levels of fibrillar collagen mRNA were reduced in the rTIMP-3 gel without reduced collagen content, showing that this group had less collagen turnover with increased ECM stability.

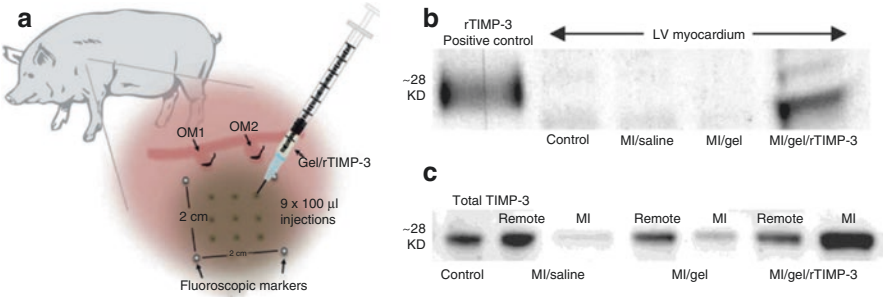

Fig. 10.6 Encapsulated recombinant tissue inhibitor of matrix metalloproteinase-3 (rTIMP-3) in hydroxyethyl methacrylate (HEMA) hydrogel. Immunoblotting of MI and remote regions of injection grid show presence of rTIMP-3 and native TIMP-3 in the infarcted pig hearts. Schematic of injection grid used for HEMA Gel/rTIMP-3 (**a**) and subsequent immunoblotting for His-tagged rTIMP-3 (**b**), as well as immunoblotting for rTIMP-3 and native TIMP-3 (**c**). (Reprinted with permission from Ref. [40])

A similar porcine study from the same research group has also shown the delivery of rTIMP-3 to the infarct via a more specialized hydrogel that is designed to degrade and release rTIMP-3 only in the presence of MMPs, in an attempt to reduce off target effects [41]. The hydrogel was composed of an HA backbone modified with aldehyde (ALD) and hydrazide (HYD) functional groups, as well as dextran sulfate (DS) backbones modified with ALD. MMP sensitivity was induced by the incorporation of an MMP cleavable cross-linking peptide sequence: GGRMSMPV. Direct injection of the material through thoracotomy access requires a double barrel syringe to ensure equal mixing of ALD and HYD groups and gelation in vivo. When the hydrogel was injected into non-infarcted hearts, the gel degraded very little, in comparison to injection into infarcted hearts, where there was minimal material left 14 days after MI. Echocardiography was used to assess functional benefits of the hydrogel and rTIMP-3 system. Significant increases in LV EF, attenuated LVEDV dilation, increased wall thickness, and improved pulmonary capillary wedge pressure (PCWP) compared to the saline and hydrogel alone controls all signify the ability of the hydrogel and rTIMP-3 system to mitigate negative LV remodeling up to 28 days post-MI. Normal levels of MMPs were also observed in the hydrogel and rTIMP-3 group compared to the saline and hydrogel alone controls without evidence of any increased levels of rTIMP-3 in the systemic circulation. Looking at gene expression, the hydrogel and rTIMP-3 group showed significant upregulation of myosin heavy chain isoform (MYH14) compared to the control groups, suggesting a more mature and contractile phenotype of myofibroblasts in this treatment group.

Bastings et al. investigated the therapeutic carrying ability of a modified PEG hydrogel that undergoes reversible gelation at physiological pH of 7.4 via cross-linking of ureido-pyrimidinone (UPy) units (Fig. 10.7a) [42]. This UPy hydrogel was loaded with human growth factor (HGF) and insulin-like growth factor-1 (IGF-1) and delivered via transendocardial injections with NOGA™-guided Myostar catheterization 4 weeks after MI in a porcine model. Comparing the GF-loaded UPy-gels with GFs in saline or saline alone controls, favorable remodeling was seen in the loaded UPy-gel group through reduced collagen content and increased myocardial viability, measured via Picrosirius red staining for collagen content (Fig. 10.7f). However, this study had minimal cardiac functional data, which would be critical in determining therapeutic efficacy for moving toward clinical trials.

A permanent occlusion porcine model examined the HA-based commercially available Extracel-HP gel as a delivery vehicle for a cocktail of ascorbic acid, ibuprofen, and allopurinol with platelet rich plasma (PRP) [43]. The ascorbic acid acts as a free radical scavenger to minimize reactive oxidant species (ROS) in the infarct, while the ibuprofen and allopurinol act as anti-inflammatory agents. The PRP contains natural stores of growth factors (GFs) and cytokines responsible for wound healing and angiogenesis. To attempt to control for all various components the treatment groups were as follows: HA hydrogel, PRP alone, cocktail group (ibuprofen, allopurinol, and ascorbic acid), full compound (HA hydrogel with cocktail and PRP), and saline. All injections were delivered through thoracotomy immediately following MI. This study showed the ability of the PRP control and full compound

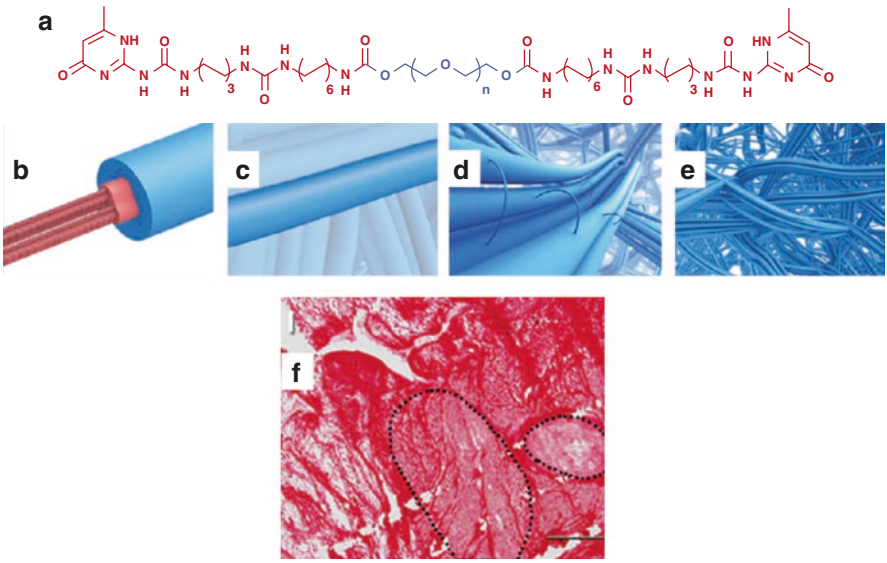

Fig. 10.7 Polyethylene glycol (PEG)-based hydrogel with ureido-pyrimidinone (UPy) cross-linking units to induce reversible gelation at physiological pH. (**a**) Chemical structure of UPy hydrogel polymer. (**b–e**) Schematic of hydrogel fibers with UPy-stacks in red, surrounded by hydrophilic PEG, which can then interact with neighboring fibers and ultimately form a hydrogel network. (**f**) Picrosirius red staining of cryosections of infarcted heart treated with UPy-gel + HGF/IGF shows surviving cardiomyocyte islands denoted by the dashed lines. (Reprinted with permission from Ref. [42])

to promote increased neovascularization in the infarct and border zone. Additionally, assessment of fibrosis with Masson's Trichrome staining showed significantly decreased collagen content in the PRP-only, cocktail, and full compound groups. However, all treatment groups showed significant decreases in LV volumes and increases in EF, compared to the saline control. This could indicate a need for more control groups to properly isolate the component of the full compound that is responsible for functional improvement. The efficacy of the PRP alone control group was associated with the bioactivity of compounds found in PRP that promote neovascularization, as well as the activation of platelets that may result in a fibrin network similar to a hydrogel itself.

Cells Delivered

Stem cell research has proven to be a promising subset of tissue engineering and regenerative medicine. Many preclinical studies have shown that stem or progenitor cells can have reparative properties in cardiac tissue via paracrine effects. However, there are still many problems associated with their implementation, such as identifying a good cell source and scaling up proliferation conditions for widespread

clinical application. Additionally, similar to delivering the biologics described earlier, cells are rapidly cleared from the region of delivery with very poor retention and survival and limited differentiation. Recent studies have shown improvement in cell retention, differentiation, and proliferation by delivering cells within an injectable hydrogel material that is able to serve as a localized scaffold for these cells upon injection [44]. Considering the extremely limited regenerative capacity of the native adult cardiac cells, stem cell delivery could promote MI repair via paracrine effects or, debatably, through direct differentiation.

A study by Chen et al. investigated the open-chest injection of autologous DiI-labeled bone marrow mononuclear cells (MNCs) in a HA hydrogel in a preclinical porcine model of MI [45]. Autologous cells minimize any immune response from the patient. However, isolating and expanding these cells require additional procedures and time for proliferation. With delivery in the hydrogel, the MNCs had a statistically significant, twofold higher retention in the infarct as opposed to MNCs delivered in PBS. Interestingly, the HA+MNC treatment group also showed improved neovascularization. However, these vessels contained mainly unlabeled cells suggesting that the material had an ability to preserve endogenous vasculature, as opposed to direct differentiation into vessel formation. The HA + MNC groups also had improved EF and decreased LV EDV as measured with echocardiography, as well as reduced fibrosis and increased cardiomyocyte diameter. These may suggest a combinatorial effect between the HA and MNCs.

Another study by Panda et al. investigated the conductivity of tissue in the infarct region of a porcine MI model after open-chest injection into the infarct of mesenchymal stem cells (MSCs) in an RGD-modified alginate hydrogel [46]. This material was delivered 4 weeks after MI. This may explain the absence of differences seen in fibrosis between treatment groups, as there is inability to rescue many cardiomyocytes in the border zone at this time point. Echocardiography was performed, but data on LV dimensions or volumes were not reported in the study as a functional assessment. However, there was a high correlation between regions of improved conduction in the border zone and area of MSCs (Fig. 10.8). This suggested the MSCs were possibly able to bridge electrical signaling in cardiac tissues without directly differentiating into impulse generating cardiomyocytes [46].

In another study involving the previously discussed self-assembling peptide NFs, Lin et al. evaluated the efficacy of these fibers to encapsulate autologous MNCs to promote long-term pro-remodeling up to 3 months after MI [47]. In this porcine model, saline control, NFs alone, MNCs alone, or the combined therapeutic (MNCs and NFs) were injected into the infarct region immediately following MI while the chest was still open. The combined therapeutic showed that the NFs increased MNC retention in the infarct approximately 11.3-fold higher than injection of MNCs alone. They also significantly improved LV EF, EDV, and ESV, as measured by echocardiographic analysis at 3 months after MI. The MNC alone treatment, however, only provided functional benefits in the short term. About 30% of the NFs remained at the site of injection 3 months after MI, compared to the more rapidly degraded HA, which may be attributed to the differences in cell retention.

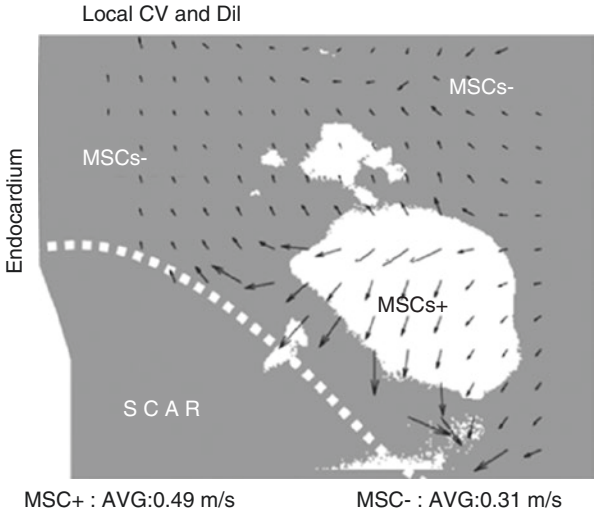

Fig. 10.8 Alginate-based hydrogel modified with cell adhesion peptide, RGD, to encapsulate mesenchymal stem cells (MSCs). Schematic of threshold of DiI fluorescently labeled cells overlaid with map of local conduction velocity vectors shows increased local conduction velocity in areas containing MSCs compared to areas lacking MSCs. (Reprinted with permission from Ref. [46])

The NF alone group still proved to be beneficial for function in the long term via pressure catheterization measurements. Additionally, both NF alone and the combined therapeutic significantly increased wall thickness and reduced collagen deposition compared to the saline and MNC alone controls. The combined therapeutic group, however, promoted neovascularization the most, with the highest capillary, artery, and arteriole density in the peri-infarct region among all groups. Positive staining for αSMA myofibroblasts also suggested the ability of the combined therapeutic to recruit these cells to the infarct. While the combined therapeutic showed the most beneficial long-term effects, evaluating the NF alone group suggested that the material not only provides a scaffold for cell retention but may play a role in preventing negative LV remodeling itself.

Conclusion and Future Outlook

Injectable hydrogels provide an exciting opportunity to treat MI, an ischemic injury that currently afflicts many patients, for which there is no existing therapeutic that can reverse or prevent further progression to HF. These minimally invasive therapeutics can be comprised of natural or synthetic polymers and may contain stem cells or biologics for combinatorial effects. While previous literature suggests that mechanical support to the infarct could prevent negative LV remodeling and promote regeneration, current opinions highlight that biochemical cues are the real key that promote repair through activating pro-regenerative pathways [48]. Encapsulating cells and biologic molecules within hydrogels has the potential to achieve these goals. However, cost remains a large factor with additive biologics in developing a therapeutic that is sustainable for clinical use. Therefore, the therapeutic efficacy of including additional factors must outweigh these costs when compared to delivering a hydrogel alone.

Translation of currently investigated injectable hydrogels also depends largely on their method of delivery. Algisyl-LVR is delivered via invasive surgical-based injection. However, minimally invasive catheter approaches, such as transendocardial delivery or intracoronary balloon infusion (used for the delivery of VentriGel and BL-1040/IK-5001, respectively), are favorable. Such methods reduce the risk for the patient when compared to delivery via injection during a surgery. However, some of these minimally invasive procedures, such as NOGA™ mapping, require a highly specialized cardiologist, which still may limit the translational feasibility. The future outlook for the field of injectable hydrogels to treat MI depends largely on the design of biomaterials to balance cost and translational feasibility, as well as minimize the invasiveness of delivery.

Acknowledgments The authors thank Raymond Wang, and Melissa Hernandez for providing feedback and edits on this chapter. This work was supported by the NIH NHLBI R01HL113468 (KLC) and T32HL105373 (MDD). Dr. Christman is a co-founder, board member, consultant, holds equity interest, and receives income from Ventrix, Inc.

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