

Review

Therapeutic microneedles for myocardial repair

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Local myocardial delivery remains an unmet need in cardiovascular disease, as systemic therapies are hindered by cardiac motion, heterogeneous perfusion, and post-infarction extracellular matrix remodeling. Preclinical microneedle (MN) systems enable direct, localized, and sustained epicardial delivery of drugs, proteins, growth factors, and cells while minimizing systemic exposure. Recent studies have demonstrated tangible benefits: galunisertib-loaded MNs reduced fibrosis from ~14% to ~7%, and vascular endothelial growth factor (VEGF)-based MNs increased vascular density from ~0.2 to ~0.5 vessels per field. Mechanically adaptive and biodegradable MN platforms maintain stable contact with the beating heart and support programmable release profiles. This review synthesizes the current preclinical landscape of cardiac MN technologies and outlines the engineering and translational considerations that will guide their advancement toward future clinical applications.

Cardiovascular diseases: a global health challenge

Cardiovascular diseases (CVDs) account for the majority of deaths worldwide [1], including **myocardial infarction (MI)** (see [Glossary](#)), coronary artery occlusions, and heart failure [2]. According to reports from the World Health Organization (WHO) and the World Heart Federation (WHF), CVDs were responsible for 20.5 million deaths in 2021 alone, accounting for 33% of all deaths worldwide. Estimates suggest that cardiovascular-related deaths will reach 23.6 million by 2030 [3,4].

Among CVDs, MI is characterized by blockage of the coronary arteries, resulting in reduced blood flow and subsequent cardiomyocyte (CM) death [3]. Fibroblasts replace the dead cells, leading to the accumulation of fibrous tissue in the infarcted region. While this early **fibrosis** is essential for healing, its uncontrolled progression disrupts the structural integrity of the heart wall. As a result, the structurally weakened myocardium loses its contractile capacity, ultimately causing adverse ventricular remodeling—a major contributor to heart failure [1,5].

Currently, bypass surgery, stent placement, pharmacological therapy, or heart transplantation are used to restore blood flow or slow the progression of heart failure post-MI. However, these interventions cannot prevent excessive fibrosis, limit infarct expansion, or reverse adverse cardiac remodeling [6–8]. Conventional oral and intravenous administrations of therapeutics—including drugs, proteins, and cells—are largely ineffective due to their short half-lives and susceptibility to proteolytic degradation and rapid systemic clearance [8,9] ([Box 1](#)). As a result, only a minimal fraction (~1%) of the administered dose reaches the target tissue, requiring high systemic doses that often cause off-target toxicity. Moreover, intravenously delivered proteins or stem cells are rapidly cleared from circulation; for instance, intravenously administered VEGF has a half-life of ~30 min, exhibits minimal localization to the target, and cannot be retained for more than a day [14]. Even stem cell injection therapies, although considered a promising strategy, exhibit poor retention, with more than 90% of injected cells lost within the first 24 h [15,16].

Highlights

Systemic delivery remains insufficient for targeting myocardial tissue, creating a clinical need for localized epicardial therapeutics.

Microneedles (MNs) enable localized, sustained delivery of therapeutics directly into the myocardium.

MNs improve drug retention, enhance tissue adherence, and minimize off-target effects.

MNs can be tailored to mimic myocardial mechanics, conductivity, extracellular matrix architecture, and biological functionality.

Cardiac MN implantation is challenged by the heart's continuous motion and the weakened nature of the infarcted tissue.

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Box 1. Epicardial drug delivery challenges

Targeted drug delivery to the heart, especially the epicardial surface, faces numerous biological and mechanical challenges. The constantly moving myocardium has a moist, contractile surface that resists stable contact. In such a dynamic, compartmentalized, and highly vascularized environment, traditional delivery methods—whether oral, intravenous (IV), or catheter-mediated—often fail to achieve therapeutic concentrations at the target site.

One major drawback of systemic delivery pathways is their lack of spatial specificity. After MI, the injured heart undergoes region-specific remodeling, including inflammatory infiltration, fibrotic scarring, and altered extracellular matrix (ECM) stiffness. Systemically administered drugs may fail to reach the peri-infarct region or atrial myocardium in sufficient quantities, leading to subtherapeutic effects or off-target toxicity. Catheter-based delivery is another option but is invasive, requires real-time imaging, and is unsuitable for rapid or repeated administration. In contrast, MN technology offers a mechanically stable and minimally invasive platform for epicardial drug delivery, overcoming these limitations. When properly engineered, MNs can adhere to the superficial myocardium and penetrate the epicardium without breaching deeper cardiac layers [10]. By significantly increasing pull-out resistance (e.g., 0.34 N vs. 0.009 N for smooth MNs), bioinspired designs such as barbed or spiral-angled MNs modeled after honeybee stingers allow stable insertion into the beating heart without the need for sutures or adhesives [11]. This self-locking feature reduces shear-induced dislodgment, a common issue with traditional patches.

MNs provide mechanical stability while enabling controlled drug release at the right location and time. Biphasic designs achieve this by combining rapid surface-layer elution with deeper reservoir-mediated kinetics, whereas hydrogel-based MNs swell *in situ* to sustain therapeutic release [12]. These properties allow tailoring of pharmacokinetics to align with biological repair stages, such as delivering amiodarone to prevent postoperative atrial fibrillation or inhibiting TGF- β signaling to reduce fibrosis [13]. Moreover, by minimizing exposure to off-target organs such as the liver and kidneys, epicardial MN administration preserves systemic homeostasis and ensures localized drug utilization. Owing to their mechanical compatibility, biocompatibility, and tunable drug kinetics, MNs represent one of the most promising strategies to overcome long-standing challenges in epicardial drug delivery for cardiovascular therapies.

Beyond systemic delivery, cells, small molecules, proteins, genes, and drugs have also been injected directly into the damaged myocardium to stimulate **angiogenesis**, activate cellular pathways, or modulate fibrosis and promote ventricular remodeling [16–18]. However, direct intramyocardial injection similarly fails to achieve effective regeneration because of low retention, short half-lives, and instability of biomolecules in the ischemic environment [15,19]. These limitations can be partially mitigated through the incorporation of therapeutics into scaffold-based matrices or **nanoparticles (NPs)** [14,20]. Nevertheless, conventional cardiac patches, including hydrogels, fibrous films, elastomers, and cell sheets, largely depend on passive diffusion following placement on the myocardial surface. This delivery mechanism often results in insufficient tissue penetration and limited therapeutic retention within the myocardium [1,15,21]. As a result, there is growing interest in strategies capable of achieving localized, sustained, and spatially controlled delivery directly within cardiac tissues. In this regard, **microneedles (MNs)** are emerging as a compelling alternative, offering the potential for direct intramyocardial administration with enhanced retention, improved dosing precision, and greater control over therapeutic distribution [15,22]. Herein, the authors review MN platforms that deliver diverse therapeutics and highlight their roles in cardiac repair, alongside recent adhesive, barbed, and stimuli-responsive designs that improve retention and targeting.

MN technology: a minimally invasive revolution

MN technology offers a minimally invasive strategy for precise, localized myocardial delivery of therapeutic agents [23–26]. Initially used for transdermal applications, MNs have been adapted for cardiac applications, including MI, arrhythmias, transplant rejection, and hypertensive crises (Figure 1). By penetrating the epicardium without damaging the deeper myocardium, MNs bypass systemic circulation, improve local bioavailability, and access the post-injury microenvironment [27]. This site-specific delivery enables effective administration of antifibrotic, immunosuppressive, and antiarrhythmic agents to the peri-infarct or atrial regions [28].

Cardiac MNs are typically fabricated using micromolding, lithography-derived templates, and high-resolution 3D printing techniques such as stereolithography (SLA) and digital light

Glossary

Angiogenesis: the formation of new blood vessels from pre-existing ones, essential for tissue regeneration and healing after myocardial infarction.

Cardiac stromal cells (CSCs): supportive cells in the heart that contribute to extracellular matrix remodeling, paracrine signaling, and cardiac repair.

Ejection fraction (EF): a clinical parameter that measures the percentage of blood ejected from the left ventricle with each contraction, serving as a key indicator of cardiac function.

Extracellular matrix (ECM): the structural network surrounding cells in tissues, critical for biomechanical support and cellular signaling.

Exosomes: small extracellular vesicles released by cells that carry proteins, lipids, and RNAs; they facilitate intercellular communication and contribute to cardiac repair.

Fractional shortening (FS): a percentage measurement that quantifies the reduction in ventricular diameter from diastole to systole, reflecting contractile function.

Fibrosis: the excessive deposition of ECM components, leading to stiffening of cardiac tissue and impaired function following injury.

Induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs): cardiomyocytes derived by differentiating induced pluripotent stem cells; widely used in disease modeling, drug screening, and regenerative medicine.

Mesenchymal stromal cell-derived biological factors (MSCFs): molecules secreted by MSCs, including cytokines, growth factors, and exosomes, that contribute to cardiac repair.

Microneedles (MNs): a minimally invasive delivery device composed of microscale projections designed to penetrate tissues and enable localized therapeutic release.

Myocardial infarction (MI): a condition caused by obstruction of blood flow to heart tissue, resulting in ischemic injury and potential progression to heart failure.

Nanoparticles (NPs): ultrafine particles used in the biomedical field for targeted drug delivery, imaging, and diagnostics.

Postoperative atrial fibrillation (POAF): a common arrhythmia

processing (DLP), which enable micron-scale features with tip diameters of ~ 10 – $50\ \mu\text{m}$ and heights of 200 – $1000\ \mu\text{m}$ for cardiac applications [29]. These dimensions are commonly used in rodent and porcine models [30]. Collectively, these scalable fabrication platforms facilitate precise control over MN geometry to match the required tissue penetration depth and accommodate the physicochemical characteristics of the delivered therapeutics.

Cardiac MNs are fabricated using biocompatible materials such as gelatin, hyaluronic acid (HA), and synthetic polymers including poly(lactic-co-glycolic acid) (PLGA) [10,13,31]. These materials enable controlled drug release via swelling or polymer degradation, which can be tailored for prolonged action (e.g., antifibrosis) or rapid release (e.g., antiarrhythmia). The bioresorbable design of MNs minimizes inflammation and eliminates removal procedures. However, stable adhesion to the moving myocardium remains a key design challenge (Box 2). Inspired by natural systems such as bee stingers, barbed MNs have been developed to enhance tissue retention without sutures or adhesives [11]. Quantitative comparisons highlight their efficacy: barbed MNs exhibit approximately 18-fold higher pull-out resistance compared with smooth MNs [30], and swellable mussel adhesive protein (MAP)-based roots can increase adhesion forces by approximately two-fold [32].

The aforementioned designs improve operative practicality and reduce device detachment under shear stress. Additionally, MNs can provide mechanical support post-MI. By reinforcing the thinning ventricular wall, they help maintain shape and reduce remodeling. Mechanical integration with the beating heart requires tolerance to physiological epicardial deformation, which typically reaches ~ 10 – 15% circumferential strain—benchmarks that have been used in recent MN

occurring after cardiac surgery, increasing the risk of stroke and other complications.

Reactive oxygen species (ROS): highly reactive molecules that induce oxidative stress, contributing to cardiac injury, inflammation, and remodeling.

Vascular endothelial growth factor (VEGF): a central signaling protein that regulates blood vessel formation and repair, playing a critical role in ischemic tissue recovery.

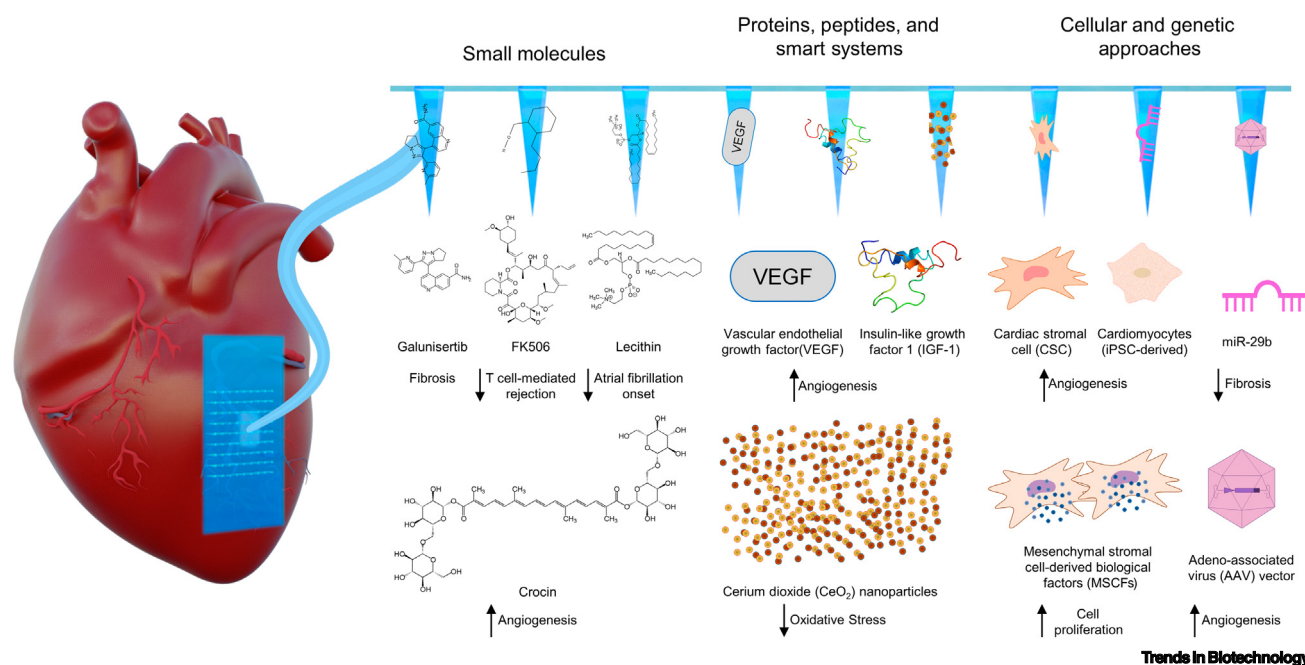


Figure 1. Schematic overview of microneedle applications in MI therapy. The illustration shows an epicardially applied MN loaded with representative therapeutic cargoes, including small molecules, proteins, cells, and genetic materials, each depicted with corresponding molecular or structural icons. These therapies target key pathways involved in cardiac repair, such as angiogenesis, fibrosis reduction, inflammation modulation, and tissue regeneration. (AAV: adeno-associated virus; CSC: cardiac stromal cell; IGF-1: insulin-like growth factor-1; iPSC: induced pluripotent stem cell; MI: myocardial infarction; MN: microneedle; miR-29b: microRNA-29b; MSCFs: mesenchymal stromal cell-derived biological factors; VEGF: vascular endothelial growth factor).

Box 2. Mechanical design strategies for cardiac MNs

Applying MNs to the heart requires careful mechanical considerations, as the epicardial surface is curved, moist, and in constant motion. Achieving secure integration with such a biomechanically active organ demands a delicate balance between structural stability, conformal apposition, and tissue biocompatibility.

One bioinspired strategy to enhance mechanical interlocking involves mimicking nature. Barbed MNs modeled after honeybee stingers have been engineered to anchor into the epicardium without the need for sutures or adhesives. These spiral-barbed PP MNs (~3 mm in length) demonstrate pull-out resistance 30–40 times greater than that of smooth MNs (0.34 N vs. 0.009 N), allowing stable fixation during continuous cardiac motion. This robust mechanical interface ensures therapeutic retention at the target site while minimizing the risk of detachment or misalignment. Geometry also plays a critical role. MN arrays can be molded to match the heart's curvature, ensuring tight and uniform tissue contact. In some designs, controlled coagulative bonding induced by minimal bleeding is leveraged to improve adhesion to the moist epicardial surface [11]. Such strategies are particularly valuable when surgical suturing is impractical, such as during emergency or intraoperative procedures.

The mechanical performance of MNs must also be tailored to penetration depth requirements. Cardiac-targeted MNs are typically designed with heights ranging from several hundred microns to a few millimeters, sufficient to pierce the epicardium while avoiding perforation into deeper myocardial or endocardial layers [1]. This dimensional precision enables localized therapy while preserving the structural integrity of the heart. Some MNs are engineered to provide both drug delivery and mechanical reinforcement [31]. Following MI, ventricular wall thinning increases wall stress and impairs cardiac function. In this context, MNs can act as bioactive meshes, simultaneously reducing wall tension and administering therapeutic agents. In preclinical MI models, such dual-functional MN systems preserved ejection fraction and limited infarct expansion, demonstrating combined structural and pharmacological benefits.

Ultimately, cardiac MNs must be rationally designed to balance toughness for stable adhesion with safety for tissue preservation, as well as stiffness for penetration with flexibility for conformal contact. These mechanical strategies open new therapeutic avenues in cardiovascular therapies by enabling MN platforms to integrate seamlessly with the continuously beating heart.

mechanical testing studies [33]. This dual functionality, i.e., mechanical and therapeutic roles, can improve long-term outcomes by limiting infarct expansion.

MNs provide a modular platform for delivering small molecules, proteins, peptides, gene products, and stem cells with minimal tissue trauma [13,28,34]. Deployment induces only mild, localized fibrosis, substantially lower than that associated with metal implants or long-term catheters [11]. Their capacity to modulate release kinetics and target specific myocardial layers enables precise therapy. For instance, localized galunisertib delivery reduces off-target effects and supports post-MI remodeling [13]. Overall, MNs integrate engineering innovation with regenerative biology to offer sustained, site-specific treatment for cardiac pathologies (Box 3).

Box 3. Technical innovations shaping future MN therapies

Hydrogel-laden MNs offer softer mechanics and high water content, protecting biomolecules and living cells while enabling stimuli-responsive or sustained therapeutic release. For example, hydrogel matrices have already supported stem cell viability in regenerative applications [35] and similar engineered approaches could be tailored for myocardial repair and tissue integration.

Oxygen-generating MNs incorporate components such as calcium peroxide (CaO_2), gradually releasing oxygen to relieve hypoxia, a key biological barrier to graft survival and functional regeneration. In ischemic models, these innovative systems enhanced angiogenesis, facilitated metabolic recovery, and improved tissue viability [36–39], suggesting clear translational potential for post-MI applications.

Immune-instructive MNs represent another exciting frontier. Rather than providing indiscriminate immunosuppression, MNs could be rationally engineered to direct host responses toward pro-regenerative phenotypes, such as M2 macrophages or regulatory T cells. Comparable bioinspired approaches in wound healing [40] illustrate both the promise and feasibility of this emerging strategy.

Together, these advances underscore how MNs may progressively evolve from passive drug carriers into active therapeutic tools, combining biochemical, metabolic, and immunological functions within a single sophisticated, minimally invasive platform for cardiac care.

Therapeutic approaches using MN-integrated cardiac patches

Across cardiac MN studies, two consistent themes emerge: drug-release behavior and biological mechanisms of action. Release kinetics depend on MN material composition and structural architecture. Fast-dissolving matrices or surface-loaded tips generate rapid burst release, whereas hydrogel-based or crosslinked PLGA MNs provide sustained, near-linear delivery over days to weeks, supporting modulation of pathways such as transforming growth factor beta (TGF- β)/Smad signaling, macrophage polarization, or matrix remodeling. Multilayer MNs enable bi-/multi-phasic profiles, pairing early high-dose exposure with long-term maintenance delivery, while cell-laden MNs function as self-regulated paracrine reservoirs rather than classical diffusion systems.

Despite diverse cargoes, including small molecules, proteins, growth factors, nucleic acids, and living cells, their therapeutic actions ultimately converge on core myocardial repair processes. Antifibrotics limit maladaptive **extracellular matrix (ECM)** deposition, pro-angiogenic factors restore microvascular perfusion, immunomodulators shift inflammatory responses toward reparative phenotypes, antiarrhythmic agents stabilize conduction, and cell- or gene-based therapies enhance structural and electrical integration. Critically, the localized and high-retention delivery provided by MNs allows these mechanisms to act directly within the dynamic peri-infarct niche, reducing systemic toxicity while aligning drug kinetics with biological demand. Together, these features illustrate how release-profile engineering and mechanistic targeting collectively define the therapeutic logic of cardiac MN platforms.

Small molecules and drug delivery

Recent studies have demonstrated that MN-based patches, each uniquely designed to achieve distinct therapeutic objectives, are redefining treatment paradigms for CVDs, particularly MI (Table 1). A prime example is the implementation of galunisertib-loaded gelatin methacryloyl (GelMA) MNs (~570 μm height, 260 μm base) to inhibit TGF- β /Smad2 signaling and reduce post-MI fibrosis, achieving a release time of over 15 days [13]. In a rat MI model, these MNs not only reduced mortality (80% survival vs. 50% in controls), but also significantly improved cardiac function, as evidenced by increased **ejection fraction (EF)** and **fractional shortening (FS)**, along with decreases in pathological markers such as plasma brain natriuretic peptide (BNP) and CM hypertrophy. Importantly, the MNs achieved these antifibrotic effects without disrupting angiogenesis or inducing systemic inflammation, highlighting their biological specificity and biocompatibility.

For antiarrhythmic prophylaxis, Langmuir–Blodgett (LB)-coated MNs delivered amiodarone in a dual-phase fashion to prevent **postoperative atrial fibrillation (POAF)** [31]. These MNs combined a PLGA reservoir for sustained 30-day release with a lecithin-based LB surface coating, enabling rapid drug delivery on day 1. In atrial tissue, drug accumulation from LB-MNs reached 3.72 $\mu\text{g}/\text{mg}$ on day 1, far exceeding levels achieved via oral administration or uncoated MNs. Electrocardiographic analysis showed that LB-MN treatment delayed the onset of atrial fibrillation (AF) and shortened its duration, maintaining rhythm profiles comparable to healthy controls for up to 30 days. Histological examination revealed preserved atrial collagen architecture, balanced type I/III collagen ratios, and prevention of fibrosis. No systemic toxicity or organ damage was observed, and the PLGA MNs biodegraded naturally, eliminating the need for removal and highlighting their clinical practicality.

Antioxidant therapy using MNs was explored with crocin (CRO)-loaded HA/polyvinylpyrrolidone (PVP) dissolving MNs (CRO-DMNs) to overcome CRO's poor oral bioavailability [10]. HA/PVP MNs (550 μm in height) delivered CRO transdermally into the dermis within 30 min, with full skin recovery achieved in under 90 min. In MI models, CRO-DMNs significantly reduced infarct

Table 1. Summary of cardiac MN studies (MN: microneedle; MI: myocardial infarction; BNP: brain natriuretic peptide; GelMA: gelatin methacryloyl; EF: ejection fraction; FS: fractional shortening; AF: atrial fibrillation; VWF: von Willebrand factor; α -SMA: alpha-smooth muscle actin; CD31: cluster of differentiation 31; IFN- γ : interferon-gamma; LV: left ventricular; GO: graphene oxide; NIR: near-infrared; NPs: nanoparticles; ROS: reactive oxygen species; CeNPs: cerium nanoparticles; US: ultrasound stimulation; POAF: postoperative atrial fibrillation; PLGA: poly(lactic-co-glycolic acid); LB: Langmuir-Blodgett; CRO: crocin; HA: hyaluronic acid; PVP: polyvinylpyrrolidone; PP: polypropylene; FK506: tacrolimus; PS: polystyrene; VEGF: vascular endothelial growth factor; MAP: mussel adhesive protein; PVA: polyvinyl alcohol; NO: nitric oxide; CSCs: cardiac stromal cells; MSCFs: mesenchymal stromal cell-derived biological factors; iPSC-derived CMs: induced pluripotent stem cell-derived cardiomyocytes; IL-10: interleukin-10; CNT: carbon nanotubes; HAMA: hyaluronic acid methacryloyl; ZIF-8: zeolitic imidazolate framework-8; ZIF-90: zeolitic imidazolate framework-90; CM(s): cardiomyocyte(s); METTL3/14: N6-adenosine-methyltransferase-3/14; SAH: S-adenosylhomocysteine; m6A: N6-methyladenosine; AAV: adeno-associated virus).

Application focus	Therapeutic	Type of therapeutic	MN	Advantage	Disadvantage	Findings	Refs
Cardiac fibrosis post-MI	Galunisertib	Small molecule	GelMA hydrogel	Sustained release, myocardial penetration, and high mechanical strength	Requires open-chest epicardial implantation, targets fibrosis only; limited pathway coverage; and long-term GelMA degradation effects remain untested	80% survival vs. 50% in control Decreased BNP Decreased fibrosis (~14% to ~7%) Improved cardiac function (increased EF and FS) Decreased CM hypertrophy	[13]
POAF	Amiodarone	Small molecule	LB coated PLGA	Dual-phase release, high local concentration, and minimal systemic exposure	Requires direct atrial access and surgical exposure for implantation, and LB coating may limit procedural standardization	3.72 μ g/mg of drug accumulated in atrial tissue on day 1 Delayed onset of AF and shortened its duration (rhythm profiles maintained comparable to healthy controls for up to 30 days) Preserved atrial collagen (balanced type I/III ratio) No systemic toxicity	[31]
MI with antioxidant support	CRO	Small molecule	HA/PVP dissolvable	Transdermal delivery, fast skin recovery, and enhanced antioxidant efficacy	Rapid dissolution may not support prolonged dosing required in MI therapy	Decreased infarct size (~45% to ~20%) CD31 ⁺ / α -SMA ⁺ expressions (~25 to ~45 vessels/mm ² for CD31 ⁺ and ~18 to ~40 vessels/mm ² for α -SMA ⁺) Decreased fibrosis and inflammation, restored mitochondrial structure	[10]
Mechanical support in MI	None (mechanical support)	Polymer alone	Barbed PP	Tissue interlocking, no sutures needed, and stable epicardial fixation	Large needle height (~3 mm) increases risk of myocardial irritation or conduction interference	Improved cardiac function (EF from 48% in controls to 71%) Decreased wall stress (0.24 N to 0.12 N) Decreased pathological fibrosis gene expression (e.g., <i>Tgfb3</i> and <i>Col3a1</i>) by RNA-seq Increased metabolic pathway gene expression	[11]
Acute cardiac allograft rejection	FK506	Small molecule	PVA-sucrose/PS biphasic	Sustained release, directional delivery, and avoids systemic toxicity	Non-biodegradable PS backing may pose long-term biocompatibility or regulatory challenges	Prolonged growth survival (12.3 vs. 7.2 days), CD3 ⁺ CD4 ⁺ T cells: 23.8% (oral FK506 group) vs. 16.2% (high-dose BMN-FK506 group)	[12]

						Decreased cytokines (~160 to ~60 pg/ml for IFN- γ)	
Adhesive MN-MI	VEGF and fibronectin-derived peptides	Peptide	Silk fibroin-MAP	Superior tissue adhesiveness, direct therapeutic delivery, and mechanical fixation, swellable MN	Potential immunogenicity of engineered MAP-peptide fusions, uncertain long-term degradation of MAP-based MNs, and challenges in scalable manufacturing and sterilization of multilayer MNs	Decreased infarct size (from 31.30% to 19.80%) Increased wall thickness ~twofold Delayed left ventricular (LV) remodeling	[32]
MI-microcapped MN	Methylprednisolone, interleukin-10, and VEGF	Drug and protein	Chitosan/PVA and PLGA	Multidrug release for both initial and longer stages of MI	Difficulties of multidrug loading and precise timing control and limited penetration depth of microcapped MNs	Increased angiogenesis (~0.2 to ~0.5 vessels per field) Decreased infarct size (from ~26% to ~15%) Decreased CM apoptosis (from ~34% to ~14%)	[34]
MI-minimally invasive application	VEGF	Protein	GO/PVA (NIR-responsive, shape-memory)	NIR-triggered self-unfolding (~10 s reshaping) enables 4-mm-incision implantation, photothermal GO controls VEGF release, and low fabrication cost	Limited NIR penetration, uncertain long-term biocompatibility of GO, and difficulties of minimally invasive surgery	Increased angiogenesis (expression of VWF and α -SMA markers), Improved cardiac function (EF ~70%; FS ~42%)	[41]
Oxidative stress and fibrotic remodeling post-MI	CeNPs	Nanoparticle	PVA	ROS-US sensitive, enhanced NO release, H ₂ O ₂ clearance, O ₂ generation, and reduction of free radicals	Potential long-term toxicity and biodistribution of CeNPs, risk of uncontrolled or excessive NO release, and limited applicability due to dependence on US stimulation	Decreased oxidative stress (~50% reduction in $\bullet$ OH, ~75% H ₂ O ₂ clearance) Improved cardiac function (EF from ~25% to ~65%; FS from ~7.5% to ~25%)	[42]
Cardiac repair-MI	L-Arginine/ZIF-90 NPs	Amino acid	GelMA/PPY/PDA	Reconstruction of electrical conduction, localized specific NO administration, alleviation of oxidative stress	Potential long-term toxicity and biodistribution of ZIF-90 NPs and PPY and risk of uncontrolled or excessive NO production	Increased Cx43 expression Decreased oxidative stress and CM apoptosis	[43]
Cardiac repair-MI	CSCs	Cell	PVA	Sustained release, enhanced release of regenerative factors, and myocyte proliferation	Immunogenicity concern, cell-based approach complexity; challenges in manufacturing, storage, and transportation processes, making large-scale clinical translation challenging	Increased myocyte proliferation (from ~2.5 to ~10 cells/mm ²) Increased angiogenesis (from ~11 to ~22 n/HPF) Improved cardiac function (EF from ~38% to ~60%)	[28]

(continued on next page)

Table 1. (continued)

Application focus	Therapeutic	Type of therapeutic	MN	Advantage	Disadvantage	Findings	Refs
Cardiac repair-MI	MSCFs	Cell-derived factors	PLGA, polypeptide gel, and HA	No sutures needed, enhanced CM proliferation, and enhanced the penetration of particles	Potential heterogeneity in particle sizes and uncontrollable loading of factors into PLGA	Decreased infarct size (from 20% to ~10%) Enhanced particle penetration into the infarcted area Improved cardiac function (EF from ~50% to ~80%; FS from ~20% to ~40%)	[44]
Cardiac regeneration-MI	iPSC-derived CMs, VEGF, and IL-10	Stem cell, protein, and drug	GelMA/CNT	Pre-differentiated CMs, electrical integration, and enhanced cellular consistency	Potential long-term toxicity of CNTs, complex iPSC-derived CM preparation, and risk of residual undifferentiated iPSCs pose a safety concern for clinical translation	Increased wall thickness (from ~500 μ m to ~700 μ m) Improved cardiac function (EF from ~20% to ~50%)	[45]
Cardiac fibrosis post-MI	miR-29b mimic exosomes	Exosome	Gelatin	Enhanced miR-29b expression, regulated inflammatory response	Challenging isolation and purification of exosomes, risk that electroporation method could affect exosome integrity	Decreased infarct size (from ~22% to ~10%) Decreased total fibrosis area (%) (from ~4% to ~1%)	[46]
Cardiac fibrosis post-MI	miR-30d/ZIF-8 NPs	Gene and NPs	HAMA	Protecting CMs from apoptosis Bioactivity of miR-30d	Potential immune response, complexity, and heterogeneity in miR-30d loading into ZIF-8 NPs	Increased miR-30d transfection efficiency (~sixfold), Decreased fibrosis, Improved cardiac function (EF increased by $16.31 \pm 3.5\%$; FS increased by $9.85 \pm 2.06\%$)	[47]
Cardiac fibrosis post-MI	SAH	Gene and NPs	PLGA and HA	m6A mRNA modification, reduced mitochondrial fragmentation and CM death, multidrug release	Challenging multilayer fabrication steps, concerns for long-term toxicity and immune response, potential off-target effects and unclear impact on other RNA regulators	Improved cardiac function, Decreased infarct size (from ~70% to ~50%), mitigating mitochondrial damage and fibrotic progression	[48]
Ischemic myocardial disease	AAV vector and VEGF	Biological vector	PVA	Effective transfer, overcomes the limitations of intramyocardial injection, homogeneous distribution of AAV delivery	Concerns about potential safety risks and immune responses of the viral vector, production and application complexity, unknown long-term efficacy and safety	Increased angiogenesis (increasing capillary density ~fourfold), increased VEGF expression, Decreased infarct size (from ~70% to ~45%), Improved cardiac function (EF from ~22% to ~37%; FS from ~12% to ~17%)	[49]

size (from ~45% to ~20%), restored myocardial histology, and enhanced mitochondrial structure and vascular regeneration (CD31⁺ and α -SMA⁺ cells) more effectively than CRO injection. Transmission electron microscopy (TEM) revealed decreased vacuolization and preserved cristae in cardiomyocytes (CMs), while histological staining indicated reduced inflammation and fibrosis, demonstrating the synergistic effect of MN-mediated administration of natural compounds for cardiac repair.

To enhance adhesion to the myocardium, barbed polypropylene (PP) MNs (~3 mm) inspired by bee stingers were also engineered [11]. The spiral-barbed MNs exhibited 30–40 times greater pull-out resistance than smooth MNs (0.34 N vs. 0.009 N) and reduced wall stress while improving EF (71% vs. 48% in controls). They also decreased pathological gene expression associated with fibrosis (e.g., *Tgfb3* and *Col3a1*) and promoted the expression of metabolic pathway genes, as revealed by RNA-seq analysis. They were successfully applied via thoracoscopy, demonstrating translational feasibility.

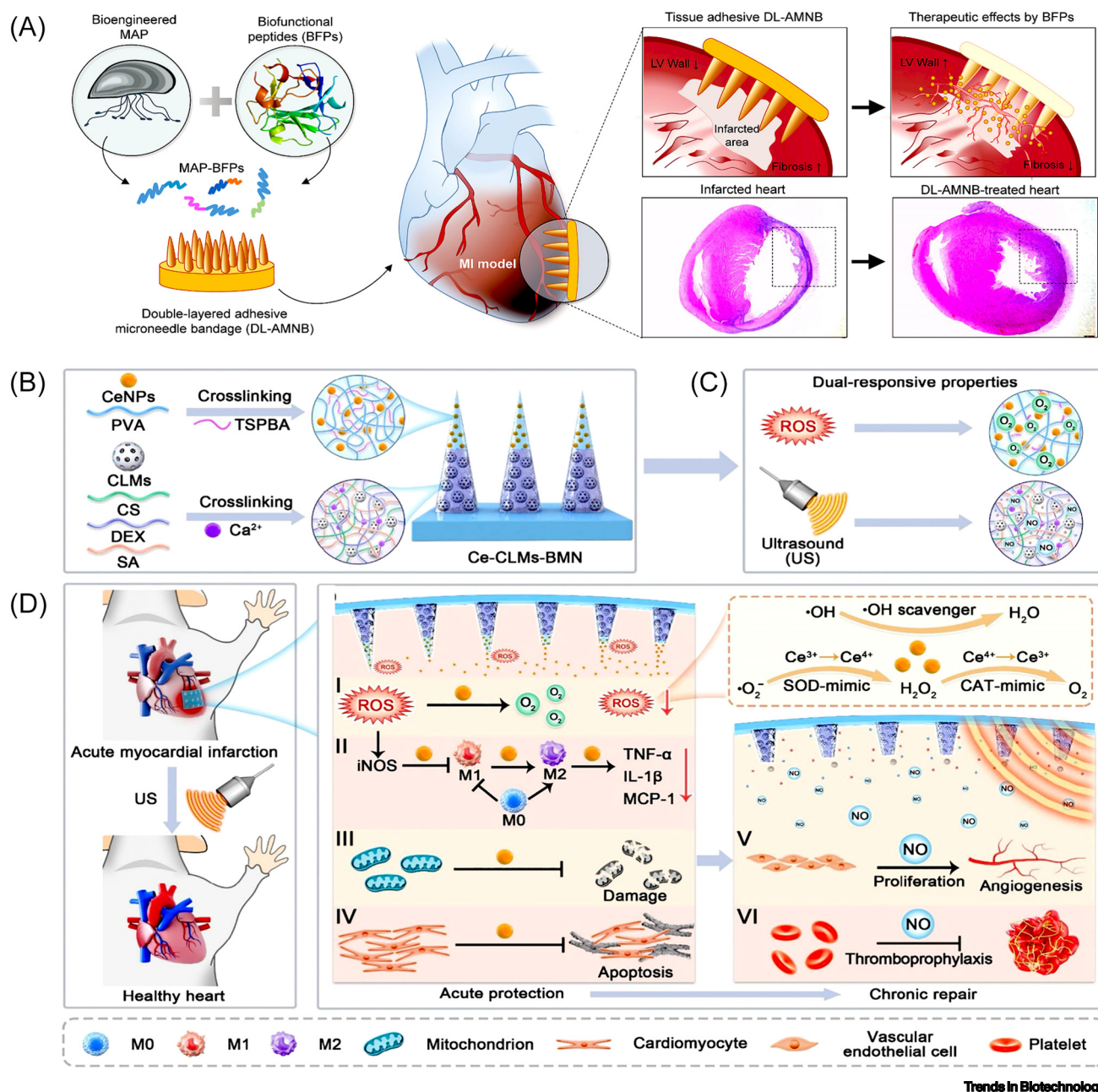
In the context of post-transplant immunomodulation, biphasic MNs (BMNs) were developed for transdermal delivery of tacrolimus (FK506), a critical immunosuppressant in heart transplantation [12]. The MNs, composed of polyvinyl alcohol (PVA)–sucrose dissolving tips and a polystyrene (PS) backing, achieved over 90% delivery efficiency and over 9 days of sustained release. BMN-treated animals exhibited prolonged graft survival and marked reductions in CD3⁺CD4⁺/CD8⁺ T cells, inflammatory cytokines (IL-2, IL-6, and IFN- γ), and myocardial immune infiltration compared with untreated and orally treated groups. For instance, CD3⁺CD4⁺ T cells were 23.8% in the oral FK506 group versus 16.2% in the high-dose BMN-FK506 group, reflecting enhanced immunosuppression and a lower risk of graft rejection. Additionally, the BMNs demonstrated excellent biosafety, with normal organ histology, preserved kidney and liver function, and rapid skin recovery within 5 h.

Beyond small molecules, MNs are being adapted to deliver biological macromolecules (e.g., peptides and proteins) that more directly modulate myocardial healing through angiogenesis or apoptosis inhibition. Their modularity and responsiveness offer new opportunities for tailored and dynamic cardiac repair strategies.

Proteins, peptides, and smart systems

Therapeutic proteins, peptides, and growth factors are widely used to promote angiogenesis and decrease fibrosis in the infarcted myocardium (Table 1). In particular, platelet-derived growth factor and **VEGF** have been extensively studied in MI treatments [41,50,51]. Lim *et al.* produced double-layered adhesive MNs (750 μ m height, 250 μ m base) for cardiac regeneration, which contain a silk fibroin-based needle tip, a bioengineered MAP-based root, and four biofunctional peptides (Figure 2A). They incorporated VEGF-derived and fibronectin-derived Arg-Gly-Asp (RGD) peptides into MNs rather than full-length growth factors, which have short half-lives and are rapidly cleared. The MAP served as a protein glue with high adhesiveness (~100 kPa) and enabled direct peptide delivery at the adhered region. This approach achieved prolonged peptide retention, reduced scar size from 31.30% to 19.80%, and delayed left ventricular (LV) remodeling, resulting in a twofold increase in wall thickness [32].

Microcapped MNs were developed with three drug–polymer compartments: a chitosan/PVA microtip loaded with methylprednisolone (MP) to treat acute inflammation with an initial burst release (~50% by 3 h and ~100% by 72 h), a chitosan/PVA MN carrying interleukin-10 (IL-10) to decrease inflammation and cardiac remodeling with a mid-term release (~35% by day 3 and ~70% by day 25), and, for the later stages of MI, a slowly degrading chitosan/PVA/PLGA top



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Figure 2. Schematic overviews of a bioinspired adhesive MN system based on MAP and a dual-responsive MN platform for MI therapy. (A) Illustration of a DL-AMNB consisting of bioengineered MAP functionalized with BFPs for MI treatment. The right-hand panels schematically depict the adhesive and therapeutic effects of the bandage, showing increased LV wall thickness and reduced fibrosis compared with the infarcted heart, while the H&E-stained images highlight these effects within the dotted regions. Adapted, with permission, from [32], Copyright 2021 Elsevier. (B) Illustration of the fabrication process of the bilayer MN patch. The upper layer is formed by incorporating cerium dioxide nanoparticles (CeNPs) into a PVA matrix and crosslinking with a ROS-cleavable linker, N1-(4-boronobenzyl)-N3-(4-boronophenyl)-N1,N1,N3,N3-tetramethylpropane-1,3-diaminium (TSPBA), enabling ROS-responsive degradation. The lower layer is fabricated by embedding mesoporous silica NPs loaded with curcumin and L-arginine (L-Arg) (CLMs) into a calcium ion (Ca²⁺)-crosslinked chitosan (CS)/dextran (DEX)/sodium alginate (SA) matrix, providing a slowly degradable structure. (C) Conceptual depiction of the dual-responsive behavior of the MN patch. The upper layer responds to elevated ROS levels in the acute infarct microenvironment, triggering CeNPs release, while the lower layer enables US-triggered nitric oxide generation, allowing stage-specific therapeutic activation. (D) Schematic representation of the sequential therapeutic mechanisms of the MN patch applied to the infarcted myocardium. Following administration, the ROS-responsive upper layer rapidly counteracts the oxidative stress microenvironment during the acute phase by releasing CeNPs, which scavenge ROS and generate

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layer loaded with VEGF to stimulate angiogenesis within 15–25 days. These MNs enable sequential, time-controlled release of multiple agents from a single platform. In an MI model, they achieved improved therapeutic outcomes such as increased angiogenesis (~0.2 to ~0.5 vessels per field), reduced scar size (~26% to ~15%), and reduced CM apoptosis (~34% to ~14%) [34].

Recently, researchers have focused on developing smart MNs capable of providing controlled, localized, and sustained release of therapeutic molecules (Table 1). Fan *et al.* developed VEGF-loaded graphene oxide (GO)/PVA MNs with near-infrared (NIR)-triggered self-unfolding ability. The unfolding behavior relies on NIR absorption by GO, generating a photothermal effect. This enabled minimally invasive implantation with a 4-mm incision and rapid reshaping (~10 s) in an animal MI model. NIR exposure was reported to increase nitric oxide (NO) release from CMs, leading to attenuated caspase-3 activity, reduced annexin binding, and decreased cytochrome c release from mitochondria. NIR absorption by cytochrome c further initiated signaling pathways and gene regulation that enhanced therapeutic efficiency. MN-treated groups achieved the highest EF (~70%) and FS (~42%). Angiogenesis (VWF (von Willebrand factor) and α -SMA markers) was also improved, facilitated by GO's large surface area and functional groups that supported controlled, sustained VEGF release [41].

In another smart system, double-layered MNs sensitive to **reactive oxygen species (ROS)** and ultrasound stimulation (US) were developed to alleviate oxidative stress and fibrotic remodeling post-MI (Figure 2B–D). The upper layer consisted of PVA/cerium dioxide NPs (CeNPs) and was crosslinked with ROS-sensitive binders (Figure 2B). During acute MI, this layer rapidly released CeNPs to scavenge excessive ROS in the ischemic environment, reduce cell damage, regulate inflammation, and catalyze oxygen (O_2) production via enzyme-like activities (Figure 2C–D). The lower layer was designed to activate NO release under US during the chronic phase of MI (Figure 2D). *In vitro*, the MNs achieved ~75% H_2O_2 clearance, ~10 mg/l O_2 generation, and a ~50% reduction in $\bullet OH$ production. The synergistic anti-inflammatory effects of CeNPs and NO led to decreased CD86 expression and increased CD206 expression in treated groups. Additionally, the MNs promoted angiogenesis and improved cardiac function, increasing EF from ~25% to ~65% and FS from ~7.5% to ~25% [42]. Similarly, conductive MNs were developed from GelMA/Polypyrrole/Polydopamine (GelMA/PPY/PDA) combined with mitochondria-targeted, adenosine triphosphate (ATP)-activated NPs. These NPs were degraded by mitochondrial ATP and released L-arginine to stimulate NO production. This MN design reduced oxidative stress and apoptosis, improved electrical coupling between CMs, and increased Cx43 expression [43].

Growth factors and peptides initiate cellular activities and stimulate the formation of new vascular structures through paracrine signaling. However, they are highly susceptible to enzymatic degradation and temperature-induced denaturation, leading to rapid breakdown and loss of biological activity. To preserve the structural integrity of protein-based therapeutics, researchers have encapsulated them into NPs such as PLGA [52] or liposomes [53], employed PEGylation, incorporated them into microgels [54], embedded them within 3D scaffolds [14], or delivered them

oxygen (O_2) (I) through cascade reactions mimicking SOD and CAT activities. This process alleviates myocardial hypoxia (II), reduces mitochondrial damage (III), and decreases cardiomyocyte apoptosis (IV). In parallel, the nanozymes suppress the (iNOS) pathway, thereby reducing M1 macrophage polarization and attenuating inflammation. Subsequently, US stimulation induces NO release, promoting angiogenesis and preventing thrombosis. Together, this dual-therapy strategy addresses both the acute and chronic phases of MI. Adapted, with permission, from [42], Copyright 2024 Elsevier. (BFPs: bifunctional peptides; CAT: catalase; CeNPs: cerium dioxide nanoparticles; CS: chitosan; DEX: dextran; DL-AMNB: double-layered adhesive MN bandage; H&E: hematoxylin and eosin; iNOS: inducible nitric oxide synthase; L-Arg: L-arginine; LV: left ventricular; MAP: mussel adhesive protein; MI: myocardial infarction; MN: microneedle; PVA: polyvinyl alcohol; ROS: reactive oxygen species; SA: sodium alginate; SOD: superoxide dismutase; TSPBA: N1-(4-boronobenzyl)-N3-(4-boronophenyl)-N1,N1,N3,N3-tetramethylpropane-1,3-diaminium; US: ultrasound stimulation).

using stimuli-responsive systems [55]. Similarly, MNs protect these biomolecules by retaining them within the polymer matrix, shielding them from environmental challenges such as enzymatic degradation, hypoxic conditions, shear stress, and oxidative stress, while enabling direct delivery into the tissue. Core-shell MN systems also represent a promising platform for protecting molecules or cells by embedding them within the core [56]. Consequently, the localized and sustained release achieved through MNs helps overcome the inherently short half-lives of these molecules, offering the potential for a more effective therapeutic response [14,21,22].

While proteins provide precise biological signaling, recent advancements have expanded MN platforms to include cellular and genetic interventions. These strategies aim to modulate the cardiac microenvironment and repair or reprogram damaged tissue. By integrating therapeutic cells, extracellular vesicles, especially their subsets, i.e., **exosomes** [57], or gene-delivery vectors into MN systems, researchers are now addressing the root causes of MI at the molecular and cellular levels, opening new frontiers in regenerative cardiology.

Cellular and genetic approaches

Cell therapies play a significant role in regenerating the damaged myocardium by inhibiting adverse remodeling and alleviating the inflammatory response (Table 1) [58]. In the first study of this kind, **cardiac stromal cells (CSCs)** were encapsulated into PVA MNs (300 μm base, 5 μm tip, 600 μm height) to address the problem of poor cell retention. The slow dissolution of porous PVA enabled the sustained release of regenerative factors from the encapsulated cells. This approach significantly enhanced myocyte proliferation (from ~ 2.5 to ~ 10 cells/ mm^2), increased angiogenesis (from ~ 11 to ~ 22 cells per high-power field (cell number (n)/HPF)), and improved cardiac function within 3 weeks (from $\sim 38\%$ to $\sim 60\%$ EF) in an *in vivo* MI model [28]. In another study, **mesenchymal stromal cell-derived biological factors (MSCFs)** were encapsulated into PLGA NPs in elastin-like polypeptide gel-based MN tips. Higher cellular uptake of MSCFs in CMs was reported than in cardiac fibroblasts. MNs improved proliferation of CMs while reducing apoptosis. The MNs reduced infarct size from $\sim 20\%$ to $\sim 10\%$ in an MI model. These therapeutic MNs enhanced particle penetration into the infarcted area and attenuated adverse cardiac remodeling [44]. Similarly, **induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs)** were integrated into GelMA MNs, which combined a VEGF/IL-10-loaded base, a carbon nanotube (CNT) middle layer, and a GelMA hydrogel upper layer (Figure 3A). Pre-differentiation of iPSCs into CMs addressed the heterogeneity and inefficiency associated with *in vivo* differentiation, thereby ensuring cellular consistency. These MNs provided drug delivery ($\sim 70\%$ release within 110 h; VEGF and IL-10 levels reaching ~ 1000 pg/ml within 4 days), electrical conductivity, and structural support for cell organization. Furthermore, MNs facilitated electrical integration of transplanted CMs with the host myocardium, contributing to myocardial repair. Collectively, these synergistic effects improved cardiac function (EF: $\sim 20\%$ to $\sim 50\%$) (Figure 3B and D) and increased ventricular wall thickness (from ~ 500 μm to ~ 700 μm) (Figure 3B–C), demonstrating the therapeutic advantage of conductive MNs loaded with pre-differentiated cells [45].

Mei *et al.* developed a snakebite-mimicking MN system inspired by the grasp-and-release mechanism of a snake's jaw, enabling minimally invasive delivery to internal organs. Stem cell-derived exosomes were incorporated into HA-based MNs and evaluated in both rat and porcine MI models. The simplicity of this design highlights its potential to address key limitations associated with open-heart surgery. *In vivo* studies demonstrated efficient myocardial targeting with minimal tissue damage [59].

Several MN studies have focused on strategies to modulate fibrosis using exosomes, gene therapies, or viral vectors. Gelatin-based MNs carrying exosome-microRNA-29b (miR-29b) mimics were developed for post-MI fibrosis treatment (Figure 3E). MNs increased miR-29b

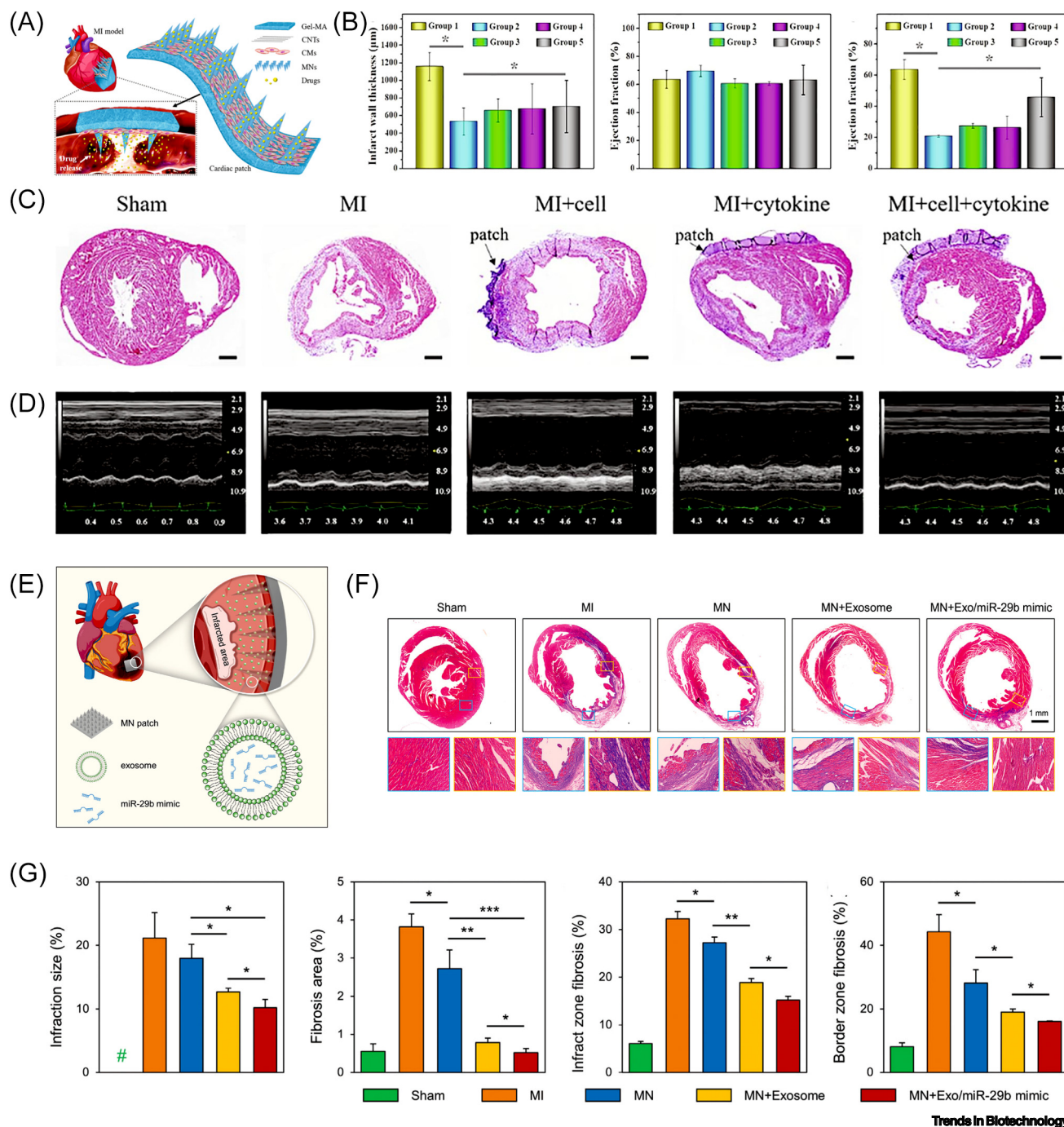


Figure 3. Schematic overviews of cell- and exosome-containing microneedle (MN) systems for myocardial infarction (MI) treatment. (A) Illustration of a carbon nanotube (CNT)-integrated, stem cell-derived cardiomyocyte (CM)-aligned, cytokine-loaded GelMA-based MN system designed for treating infarcted myocardium. (B) Quantitative analysis of infarct wall thickness and ejection fraction measured by echocardiography 1 day before treatment (baseline) and after 7 days of treatment across five groups; Group 1: sham; Group 2: MI without treatment; Group 3: MI + cell patch; Group 4: MI + cytokine patch; Group 5: MI + cell + cytokine patch. (C) Representative hematoxylin and eosin (H&E)-stained heart sections from each group, illustrating myocardial morphology and infarct thickness (scale bar: 500 μm). (D) Representative M-mode echocardiographic images of the corresponding groups. Together, the H&E images and echocardiography measurements demonstrate that incorporation of cells and cytokines into the MN patch enhances therapeutic efficacy. Adapted, with permission, from [45]. Copyright 2021 Elsevier.

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expression *in vitro* (~15-fold), while enhancing exosome retention, reducing infarct size (from ~22% to ~10%), and decreasing total fibrosis area (from ~4% to ~1%) in a murine MI model (Figure 3F,G). Collectively, these findings suggest that exosomes play an important role in modulating the post-infarction inflammatory response [46].

Chen *et al.* developed conductive HA methacryloyl (HAMA) MNs to deliver miR-30d via zeolitic imidazolate framework-8 (ZIF-8) NPs. By exploiting the proton sponge effect, in which ZIF-8 NPs induce endosomal swelling and rupture through proton buffering, the MNs facilitated efficient endosomal escape of miR-30d, thereby preventing lysosomal degradation and enabling sustained release (100% over 16 days). The MN platform supported miR-30d expression in CMs, reduced CM apoptosis (from 9.72% to 4.59%), achieved a ~sixfold increase in transfection efficiency, and downregulated fibrotic marker expression. Functionally, treatment improved cardiac performance, as evidenced by increases in EF ($16.31 \pm 3.5\%$) and FS ($9.85 \pm 2.06\%$). Collectively, this conductive MN-based nanodelivery strategy mitigated myocardial damage and addressed key limitations of conventional RNA delivery approaches [47].

Researchers have also explored RNA-based MN therapies to modulate post-MI remodeling at the molecular level. N6-methyladenosine (m6A) mRNA modification plays a critical role in fibrosis. To address this, double-layered MNs with N6-adenosine-methyltransferase-3/14 (METTL3/14) inhibitor were developed. The HA-based first layer (with S-adenosylhomocysteine (SAH)) enabled rapid release (~10 min), while the second layer (SAH-loaded PLGA) provided sustained release (~10 days) to suppress fibroblast overproliferation, excessive collagen synthesis, and deposition. In a cell model of fibrosis induced by hypoxia and TGF- β 1, METTL3/14 inhibition reduced mitochondrial fragmentation and CM death. *In vivo*, infarct size decreased (~70% to ~50%), and cardiac function improved. Mechanistically, Drp1 expression was suppressed at the m6A level, mitigating mitochondrial damage and fibrotic progression [48].

In another study, MNs were coated with an adeno-associated virus (AAV) vector to achieve homogeneous distribution of VEGF. MNs containing AAV-VEGF promoted angiogenesis by increasing VEGF expression, activating the Akt signaling pathway, and increasing capillary density (~fourfold) in the infarct and border zones. Moreover, MNs reduced infarct size (from ~70% to ~45%) and improved cardiac function, as reflected by increased EF (from ~22% to ~37%) and FS (from ~12% to ~17%). Overall, this study demonstrated that MN-mediated AAV delivery provides homogeneous distribution when compared with direct injection [49].

Stem cells repair the myocardium primarily through paracrine mechanisms by secreting regenerative factors [28,45,60]. To protect cells, bioactive factors, and genes from degradation under harsh environmental conditions—such as enzymatic activity, oxidative stress, rapid clearance, and mechanical stress in the ischemic environment—polymeric encapsulation strategies or vector-based carrier systems have been widely employed. Among these, AAV vector-based approaches are often preferred due to their ability to maintain long-term gene expression, lower immunogenicity compared with other viral vectors, and high transduction efficiency in target cells [61]. However, the use of viral vectors remains associated with several concerns,

(E) Illustration of an MN patch loaded with exosomes containing miR-29b mimics, designed for post-MI antifibrotic therapy. (F) Representative H&E-stained heart sections from the treated groups, demonstrating reduced fibrosis following treatment with MN-based systems, including the exosome/miR-29b mimic platform (scale bar: 1 mm). (G) Quantitative analysis of cardiac remodeling outcomes, including infarction size, total fibrosis area, infarct zone fibrosis, and border zone fibrosis for each group, illustrating the therapeutic efficacy of the MN-based exosome/miR-29b mimic system. Adapted, with permission, from [46], Copyright 2023 Wiley. (CM: cardiomyocyte; H&E: hematoxylin and eosin; MI: myocardial infarction; MN: microneedle; miR-29b: microRNA-29b (* $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$)).

including dose-dependent toxicity, potential long-term side effects, and induction of innate or adaptive immune responses.

These studies underscore the versatile role of MNs in delivering biologics for cardiac repair. Tunable mechanics, geometry, and payloads support multifunctional strategies, including fibrosis mitigation, angiogenesis, immunomodulation, and gene editing. As MN designs progress toward clinical translation, they hold transformative potential in minimally invasive cardiac therapeutics.

Current challenges and limitations

Despite strong preclinical evidence, key barriers remain for clinical translation. The major challenge is mechanical integration: achieving stable anchoring on the continuously contracting myocardium, particularly in large animal or human-scale hearts, which requires further optimization of MN geometry, elasticity, and fixation strategies. Modulus-matched hydrogels, elastic backings, and tissue-adhesive chemistries (such as barbed or MAP-based interfaces) may improve MN–epicardial contact [62,63]. However, long-term performance remains uncertain, as chronic epicardial implantation may trigger foreign-body immune responses or induce subtle conduction disturbances that could increase arrhythmogenic risk. These concerns highlight the need for extended safety evaluations in large animal models.

In addition, current implantation workflows remain procedurally limited. In preclinical studies, MN patches are typically applied to the epicardium through small thoracic incisions or thoracoscopic access, followed by brief manual pressure to ensure engagement with the beating heart. These approaches, however, are unfamiliar to most clinicians and lack standardized operating protocols. Catheter-based MN delivery concepts have been proposed but remain technically constrained due to difficulties in stabilizing the penetration angle on the moving myocardium and achieving uniform engagement across curved epicardial surfaces [59]. Moreover, unlike cutaneous MNs, no dedicated applicator has been developed for cardiac use, and reproducible deployment will likely require controlled pressure and angle stabilization compatible with minimally invasive procedures. Emerging advances in soft robotics, flexible applicators, and image-guided thoracoscopic tools may ultimately enable more consistent deployment and help bridge the gap toward clinically scalable delivery strategies [64]. These translational gaps also reflect the current maturity of the field. Most cardiac MN platforms remain at early-stage technology readiness levels (approximately TRL 2–4), with only a few prototypes tested in large animal models, underscoring the remaining distance from clinical application. *In vivo* efficacy studies also rely on heterogeneous myocardial injury models, primarily permanent left anterior descending (LAD) artery ligation and ischemia/reperfusion (IR), which differ substantially in infarct size, inflammatory signaling, and molecular remodeling. These differences complicate cross-study comparisons and necessitate careful interpretation when extrapolating MN performance [61]. Furthermore, clinical translation must account for major anatomical and physiological disparities. Rodents exhibit LV wall thicknesses of ~1–2 mm, whereas human LV myocardium ranges from ~8 to 15 mm and displays distinct mechanical properties, immune responses, and tissue architecture [65,66]. Such differences must guide adjustments in needle length, penetration mechanics, and myocardial drug distribution to ensure both safety and therapeutic efficacy during clinical translation.

Furthermore, biodegradability and biosafety require careful validation. Polymers such as PLGA or gelatin can generate acidic degradation products that alter local pH; proposed solutions include adjusted PLGA ratios, pH-neutral hydrogels, or buffered micro-reservoirs [67]. Standardizing batch reproducibility, sterilization compatibility, and storage stability is also essential to meet manufacturing requirements. Scaling MN fabrication to clinically meaningful volumes will likely require advances in high-throughput 3D printing [68], microfabrication workflows [69], and

validated sterilization pipelines (such as gamma irradiation or low-temperature plasma), each of which must preserve polymer integrity and drug stability.

Drug loading capacity is another limitation. The microscale structure restricts therapeutic payloads, particularly for large biomolecules or cell-based therapies. Incorporating multiple agents within a single MN platform complicates fabrication and quality control, while achieving reliable spatiotemporal release profiles remains technically challenging. Potential solutions include multi-layer MNs, nanocarrier-loaded formulations, and tip-specific loading strategies, all designed to increase payload capacity while enabling programmable release profiles [70,71]. Ultimately, meaningful clinical translation will require close collaboration among cardiac surgeons, materials scientists, device engineers, and regulatory experts, as such interdisciplinary integration is essential for optimizing implantation workflows, ensuring safety, and navigating complex combination-product approval pathways.

Concluding remarks and future perspectives

MNs represent a transformative platform for cardiac therapy, enabling localized, sustained, and minimally invasive delivery of drugs, biologics, and cells. Their modular properties make them adaptable for diverse cardiovascular applications, yet their clinical potential remains underexplored. Immediate priorities include clinically relevant milestones such as demonstrating reproducible efficacy in porcine MI models, which closely recapitulate human cardiac anatomy and physiology; assessing long-term biocompatibility and arrhythmia risk; and validating chronic epicardial implantation under physiological loading conditions. Beyond these near-term goals, emerging directions may further expand the therapeutic potential of MN-based systems (see [Outstanding questions](#)). Bioprinting and patient-specific modeling could optimize MN geometry and release profiles, while biosensing may enable closed-loop therapy. Advances in gene editing and RNA platforms further support MN-based delivery of CRISPR tools or mRNA [72], though such approaches require evaluation of off-target effects, vector biodistribution, exposure control, and ethical considerations.

An additional future opportunity lies in leveraging MN design to modulate the effective half-life of therapeutics. Variations in polymer degradation rate, crosslinking density, and drug-matrix affinity already produce substantial differences in release kinetics, underscoring the need for a unified framework. MNs inherently enable this tunability: highly crosslinked or slowly degradable matrices prolong local retention, whereas lightly crosslinked or rapidly dissolving formulations permit fast initial release. Multilayer architectures can further support programmable release profiles in which outer layers provide a rapid bolus and deeper layers enable sustained delivery. These strategies are particularly relevant for growth factors, RNA therapeutics, and immunomodulators that rely on tightly controlled exposure windows to achieve maximal therapeutic efficacy.

Future MNs may also function as immuno-instructive biomaterials, promoting regenerative rather than suppressive immune responses [40]. Beyond MI, they could address heart failure, congenital disease, or transplant care. Translation will require scalable fabrication, improved surgical delivery, and clear regulatory pathways for combination products. Biosensing MNs, conductive cell-integrating platforms, or gene-editing patches should be viewed as emerging opportunities whose success will depend on manufacturability, safety, and regulatory acceptance. Rigorous comparative studies, particularly in large animal models, are essential to validate both efficacy and safety. Together, a feasible translational path includes (i) porcine MI validation, (ii) good manufacturing practice (GMP)-compliant fabrication and sterilization testing of MNs, and (iii) standardized minimally invasive deployment strategies, which represent the next critical milestones toward clinical readiness.

Outstanding questions

Can 3D printing and microfabrication technologies enable patient-specific microneedles (MNs) tailored to individual myocardial geometries and fibrotic patterns?

How can MNs be integrated with cardiac tissue engineering platforms to enhance myocardial regeneration beyond conventional drug delivery?

Could bioinspired or artificial intelligence-designed MN geometries improve mechanical stability and achieve more precise targeted delivery in the dynamic epicardial environment?

Is it feasible to combine MNs with non-pharmacological therapies such as phototherapy, electrical stimulation, or thermal modulation for multifaceted cardiac treatment?

Can MNs be engineered for temporally controlled, multiagent drug release that aligns with the dynamic phases of cardiac healing?

Are micro-robotic or catheter-assisted delivery systems viable for noninvasive or minimally invasive deployment of epicardial MNs?

Could MN systems be developed as theranostic platforms by integrating sensors to monitor local inflammation, fibrosis, or tissue perfusion in real time?

How can biodegradable MN platforms be optimized to minimize immune activation or fibrotic responses during long-term application?

What are the implications of MN therapy in pediatric or congenital heart disease, where anatomical variability and tissue fragility may necessitate novel design principles?

Can intelligent MN systems dynamically adjust drug release profiles in response to physiological cues from ischemic or inflamed myocardium?

Could machine learning platforms be developed to recommend the optimal therapeutic dose and MN type for specific cardiovascular conditions, based on large-scale clinical and experimental data?

In conclusion, MNs are uniquely positioned at the interface of engineering, regenerative medicine, and clinical cardiology. With interdisciplinary commitment, they may transform cardiovascular care in the coming decade.

Acknowledgments

S.A.B. gratefully acknowledges support from the *Chaire d'Excellence de Normandie*. F.I., A.Y., and E.E. gratefully acknowledge support from the Scientific and Technological Research Council of Turkey (TÜBİTAK) 2232 International Fellowship for Outstanding Researchers (project no: 118C254). However, the entire responsibility of the publication/article belongs to the authors. The financial support received from TÜBİTAK does not mean that the content of the publication is approved in a scientific sense by TÜBİTAK. F.I. gratefully acknowledges support from the TÜBİTAK Incentive Award, Turkish Academy of Sciences Outstanding Young Scientists Awards Program (TÜBA-GEBİP), Young Scientist Awards Program (BAGEP) from the Science Academy, TÜSEB Aziz Sancar Incentive Award, Dr. Nejat Eczaıbaşı Medicine Incentive Award, and the Science Award from Izmir Biomedicine and Genome Center (İBG).

Declaration of interests

The authors declare no conflicts of interest.

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