

Designing siRNA nanocarriers for myocardial ischemia/reperfusion injury: pathobiological targets, delivery barriers, platform strategies, and translational constraints

Baihao Mei¹, Ying Li¹, Zhaoyu Gao¹

School of Nursing, Mudanjiang Medical University; No. 3 Tongxiang Street, Aimin District, Mudanjiang, Heilongjiang 157011, China

Corresponding author: Zhaoyu Gao (gzy721031@163.com)

Academic editor: Tatyana Avtina ♦ **Received** 15 June 2026 ♦ **Accepted** 08 September 2026 ♦ **Published** 30 September 2026

Citation: Mei B, Li Y, Gao Zh (2026) Designing siRNA nanocarriers for myocardial ischemia/reperfusion injury: pathobiological targets, delivery barriers, platform strategies, and translational constraints. *Research Results in Pharmacology* 12(3): 104–117. <https://doi.org/10.18413/rrpharmacology.12.1206>

Abstract

Introduction: Reperfusion remains the only effective way to salvage myocardium after acute infarction, yet restoring blood flow can itself aggravate injury through gene-regulated oxidative, inflammatory, mitochondrial, endothelial, and cell-death programs. Small interfering RNA (siRNA) can silence such transcripts with high sequence specificity, but its value in myocardial ischemia/reperfusion (MI/R) injury depends on delivery to the right cardiac cell population at the right phase of reperfusion, not on target discovery alone. This traditional narrative review builds a barrier-to-design framework for MI/R siRNA nanocarriers and is not an efficacy ranking; it was motivated by a delivery gap (the injured microvasculature can deny access to any payload) that existing platform-organized reviews leave unexamined.

Materials and Methods: Literature was screened across four domains (MI/R pathobiology and cardioprotection; RNA interference and cardiovascular RNA therapeutics; nanocarrier design for nucleic-acid delivery; preclinical cardiac nanomedicine) using structured Crossref-based searches (13 keyword groups, coverage 1982–2026, with a dedicated 2023–2026 recency pass); screening produced 152 unique candidates, of which 97 sources were retained in the evidence bank and 69 are cited, 71 % published in 2021–2026.

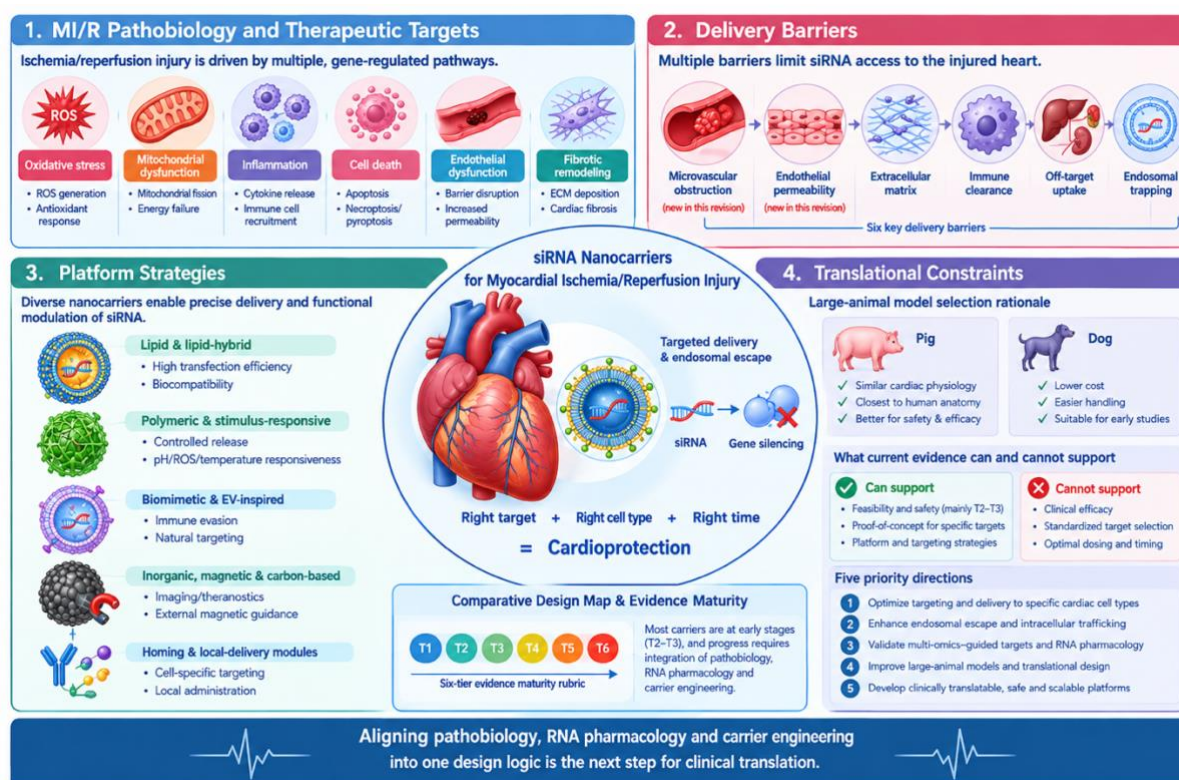
Results: the review reports (1) an MI/R target map governed by five explicit inclusion criteria and evidence-maturity tiers; (2) six delivery barriers, naming microvascular obstruction and endothelial permeability as the sixth, an independent access barrier added in this revision; (3) a platform-by-function analysis of lipid and lipid-hybrid, polymeric and stimulus-responsive, biomimetic and extracellular-vesicle-inspired, and inorganic, magnetic, and carbon-based carriers, including homing and local-delivery modules; (4) a comparative design map with an explicit six-tier evidence-maturity rubric (T1–T6); (5) a statement of what current evidence can and cannot support, closing with five priority directions; and (6) translational constraints, including a large-animal model-selection rationale (pig versus dog).

Conclusion: most surveyed carriers sit at early maturity tiers (T2–T3), which is the honest state of the field rather than a deficit; the next advance is more likely to come from aligning pathobiology, RNA pharmacology, and carrier engineering into one design logic than from adding new material names.



Copyright: © Baihao Mei et al. This is an open access article distributed under terms of the Creative Commons Attribution License (Attribution 4.0 International – CC BY 4.0).

Graphical Abstract



Keywords

cardiac drug delivery; endosomal escape; evidence maturity; ischemia/reperfusion injury; microvascular obstruction; nanocarrier; RNA interference; siRNA

Introduction

Reperfusion therapy has changed the prognosis of acute myocardial infarction, but it has not eliminated reperfusion injury. Restoring blood flow is necessary to rescue ischemic tissue, yet oxygen re-entry, ionic disequilibrium, mitochondrial dysfunction, endothelial activation, and innate-immune recruitment can aggravate cell injury after reperfusion (Kalogeris et al. 2012; Hausenloy and Yellon 2013; Heusch 2020). The paradox makes MI/R injury a persistent translational problem: the therapeutic window is short, the tissue environment changes over minutes to days, and the biology consists of several mutually reinforcing, gene-regulated pathways rather than one isolated lesion (Liu et al. 2023).

Those features explain why RNA-based interventions are attractive. Because oxidative stress, mitochondrial fission, inflammatory signaling, regulated cell death, endothelial dysfunction, and fibrotic remodeling are all gene-regulated processes, a molecule that suppresses a selected transcript upstream of protein expression could modulate pathways that are difficult to inhibit pharmacologically. Since the discovery of potent and sequence-specific RNA interference (Fire et al. 1998), RNA therapeutics have matured from molecular-biology tools into licensed and clinical platform technologies (Damase et al. 2021). The question for the injured heart is not whether siRNA can silence a target, but whether a carrier can bring it intact to the correct cell population before the pathological program runs its course.

siRNA is not a conventional small molecule. It is hydrophilic, anionic, nuclease-sensitive, and inefficient at crossing cell membranes; after systemic injection it can be degraded in serum, filtered by the kidney, sequestered in liver and spleen, trapped in endosomes, or taken up by cells that play no role in the injury. In the infarcted and reperfused heart these obstacles are compounded by a vasculature whose permeability, patency, and perfusion change rapidly, and

whose microcirculation can remain obstructed even when the epicardial artery is open. Target identification is therefore only half of the therapeutic argument; the other half is delivery, and the vascular barrier belongs to the delivery argument.

Many recent reviews of cardiac nanomedicine are organized by carrier type – lipid nanoparticles, polymeric particles, biomimetic systems, inorganic materials – and this taxonomy produces descriptive rather than analytical writing. A carrier is not valuable because it belongs to a fashionable class; it is valuable if it solves a defined delivery problem in a biologically relevant way. For MI/R injury, the design questions are: Which cell type should receive the siRNA? At which phase of reperfusion? Which barrier prevents effective delivery, and which carrier feature answers that barrier? What evidence proves payload delivery and knockdown rather than nanoparticle accumulation alone? These questions already separate this review from the nearest predecessors: comprehensive cardiovascular RNA-delivery surveys (Gil-Cabrero et al. 2024), reviews of RNA delivery to diseased heart tissue (Nicoletti et al. 2025), platform surveys of MI/R nanotherapy (Wang et al. 2025a), and engineered-delivery analyses for ischemic heart disease (Lu et al. 2026) all stop before microvascular obstruction is treated as a design variable, and none attaches explicit evidence-maturity criteria or model-selection logic to carrier development.

This review therefore develops a traditional narrative synthesis rather than a systematic review. It claims neither exhaustive coverage nor meta-analytic certainty; the search is described truthfully in the next section with its real screening counts, and evidence drawn from adjacent fields (tumor nanomedicine, general RNA delivery, hepatic models) is used as design context, never as proof of cardiac efficacy. The route through the material is: pathobiology to targets (section on pathobiological rationale), targets and barriers to design (six-barrier analysis), platforms to function (platform-by-function analysis), function to comparison (comparative design map and evidence maturity), comparison to honest limits and priorities (what current evidence can and cannot support), and limits to models (translational constraints and model selection).

Materials and Methods

This article is a traditional literature review. Literature was considered from four overlapping domains: (i) MI/R pathobiology and cardioprotection; (ii) RNA interference and cardiovascular RNA therapeutics; (iii) nanocarrier design for nucleic-acid delivery; and (iv) preclinical nanomedicine addressing myocardial injury, inflammatory recruitment, or cardiac RNA delivery. Priority was given to studies that helped answer one of three questions: which MI/R pathway is being targeted, which delivery barrier is being addressed, and what level of evidence supports the carrier design.

Because the journal's five-year currency rule demands a recent reference base, searches were run through the Crossref REST API as the structured metadata source on 2026-09-09, organized in 13 keyword query groups: cardiac siRNA/RNAi delivery; cardiac nanocarrier delivery; biomimetic cell-membrane coating; extracellular-vesicle cardiac delivery; microvascular obstruction and no-reflow; endothelial-targeted siRNA; lipid-nanoparticle cardiac delivery; polymeric stimulus-responsive cardiac carriers; inorganic, magnetic, and carbon cardiac platforms; MI/R pathobiology and cardioprotection; regulated cell death in MI/R; large-animal models of myocardial infarction; and evidence-maturity criteria for cardioprotection. Records were limited to English-language metadata with resolvable DOIs and covered the period 1982–2026, with a dedicated recency pass for 2023–2026 publications that supplied most of the current reference base.

The screening pipeline is reported with its real numbers. The 13 query groups requested 165 raw API rows; 112 records survived filtering on relevance and record quality, and DOI deduplication reduced these to 103 unique records. A second, DOI-level verification round added 73 lookups (24 overlapping with the first set), giving 152 unique screened candidates. Of these, 97 sources were retained in the evidence bank on the grounds that they substantiated at least one planned claim, and 69 are cited in this article. The final list is 71 % recent (49 of 69 references published 2021–2026), above the journal's 50 % rule. Candidate records that were screened but not cited were set aside for one of four recorded reasons: unresolved date or volume metadata, redundancy with a stronger cited record, payload outside the siRNA scope, or supersession of a classic statement by a canonical anchor already included.

The review is not a systematic review: no PRISMA-style flow diagram, pooled effect estimate, or formal risk-of-bias table is reported, and screening relied on metadata-level queries rather than dual independent full-text extraction. This boundary matters for interpretation. The review uses the published literature to synthesize concepts and to identify design criteria; it does not rank interventions by efficacy, and statements of absence (for example, that no in-window

study met a criterion) are bounded to the screened literature as of September 2026. Evidence from adjacent fields is treated as design context; where a cited study uses a permanent-ligation infarction model rather than true ischemia/reperfusion, or carries a non-siRNA payload, the text says so at the point of use.

Pathobiological rationale for siRNA therapy in MI/R injury: a target map

The value of an siRNA approach depends on whether silencing can influence a disease-driving transcript at the right time, in the right cell. MI/R injury is dynamic. In the earliest reperfusion phase, reactive-oxygen bursts, mitochondrial permeability transition, calcium overload, and endothelial activation dominate; shortly afterwards, neutrophil recruitment, macrophage polarization, inflammasome activation, and cytokine release shape both injury and repair; later, cardiomyocyte death, extracellular-matrix remodeling, angiogenesis, and fibrosis determine ventricular function (Hausenloy and Yellon 2013; Heusch 2020; Liu et al. 2023). A transcript that is a rational target in one window may be neutral or protective in another, so target suitability is time- and cell-dependent. Four target axes emerge from the screened literature and structure (Table 1).

The oxidative and mitochondrial axis is the most intensively studied. Reperfusion-driven mitochondrial calcium uptake and permeability-transition opening sit upstream of cell death (Bertero et al. 2024), and regulatory long non-coding RNAs modulate the fission machinery: the lncRNA Oip5-as1 limits excessive mitochondrial fission in MI/R by controlling DRP1 phosphorylation, and its silencing biology has been characterized in the injured myocardium (Niu et al. 2024). The lncRNA MIAT is a second validated regulator, for which siRNA chemistry has been optimized for cardioprotection in MI/R (Ma et al. 2025). Ferroptosis, an iron- and lipid-peroxidation-dependent death program active in reperfused myocardium, adds a further set of silenceable regulators (Jin et al. 2024; Zhu et al. 2026). The translation difficulty of this axis is intrinsic: mitochondria-driven injury matures within minutes to hours of reperfusion, so a carrier must reach cardiomyocytes and release its payload before the irreversible phase – a timing constraint developed in section on translational constraints.

The inflammatory axis is attractive for a different reason: immune cells are both disease drivers and natural delivery vehicles. Neutrophils and macrophages contribute endothelial adhesion, reactive-oxygen production, cytokine amplification, inflammasome activation, and, later, repair (Li et al. 2025). Regulators such as S100A9 and the macrophage transcription factor ARID3A, which promotes neutrophil-extracellular-trap formation via THBS1/CD47 signaling after cardiac ischemia-reperfusion (Tian et al. 2025), are silenceable transcripts, and macrophage- and neutrophil-camouflaged siRNA systems that exploit the same trafficking biology are described in the platform section. The strength of this axis is biological congruence – inflammatory cells naturally accumulate in reperfused tissue — and its risk is that inflammation also contributes to healing, so complete or mistimed suppression could be counterproductive.

Regulated cell death other than ferroptosis forms a third axis. Apoptosis, pyroptosis, and necroptosis are all implicated in MI/R injury, and their executioners, inflammasome components, and non-coding regulators are in principle silenceable (Bertero et al. 2024; Jin et al. 2024; Zhu et al. 2026). The delivery problem is familiar: cell-death signaling can outrun carrier pharmacokinetics, so for this axis the intracellular-release barrier (fourth barrier below) and speed of accumulation may matter more than molecular specificity.

The endothelial and vascular axis is the most underused, and the closest to the central argument of this review. Reperfused myocardium is reached through a damaged microvascular network: endothelial swelling, glycocalyx injury, leukocyte adhesion, and microvascular obstruction (no-reflow) can restrict carrier access even when the epicardial vessel is patent. Endothelial transcripts are demonstrably addressable – endothelial S1PR2 drives mitochondrial dysfunction, NLRP3 inflammasome activation, and pyroptosis in cardiac ischemia-reperfusion (Duan et al. 2024), and an endothelial-cell-targeted, reactive-oxygen-ultrasensitive drug/siRNA co-delivery system has been reported against MI/R injury (Hou et al. 2022). Endothelial-targeted silencing is not a substitute for solving the access barrier itself; however; the two problems meet in the sixth barrier below.

Which targets deserve a row in a review table is a methodological decision, and this review applies five explicit criteria: transcript-level mechanistic evidence in MI/R injury or a directly adjacent cardiac-injury model; an identifiable cell population and time window; plausible siRNA addressability; a published outcome link; and a recency preference for 2021–2026, with canonical older anchors allowed. Table 1 maps the resulting rows to the delivery consequences that each target axis imposes and to the evidence-maturity vocabulary defined in the section on the comparative design map (tiers T1–T6; only exemplar-based tiers are assigned here, never an efficacy statement). Refer to Table 1 for further information.

Table 1. MI/R processes, candidate RNA-silencing targets, and delivery consequences

MI/R process	RNA-silencing target logic	Primary cell/time window	Delivery consequence	Evidence maturity
Oxidative stress and mitochondrial dysfunction	Silence regulators of ROS generation, mitochondrial fission (e.g., Oip5-as1/DRP1 axis), or mitochondrial death signaling	Cardiomyocytes; early reperfusion, minutes to hours	Fast-acting carriers with strong endosomal escape; route and timing dominate	T3
Neutrophil recruitment and macrophage activation	Modulate S100A9, ARID3A, or inflammasome-linked regulators	Neutrophils and macrophages; minutes to days	Immune-cell-interface targeting; membrane-camouflaged carriers	T3
Endothelial dysfunction and microvascular obstruction	Reduce endothelial activation, S1PR2 signaling, leukocyte adhesion	Endothelium; early reperfusion onward	Vascular-interface access; size, timing, endothelial-targeted modification	T2–T3
Regulated cell death	Suppress apoptosis, pyroptosis, necroptosis, or ferroptosis regulators	Cardiomyocytes and infiltrating cells; reperfusion onward	High cellular uptake and cytosolic release before irreversible injury	T2
Remodeling and fibrosis	Silence late pro-fibrotic or maladaptive signaling	Fibroblasts and myocytes; days to weeks	Repeatable dosing; local or depot formats	T1–T2

This mechanistic map shows why a simple material list is insufficient. Different targets imply different cells, time windows, and pharmacological risks: a carrier suited to inflammatory-cell delivery may be poorly suited to cardiomyocyte mitochondrial targets, and a system optimized for intracellular delivery may miss the inflammatory interface that drives early reperfusion injury. Design therefore starts from the barrier that separates a chosen target from its carrier — the subject of the next section.

Six delivery barriers that define carrier design

Carrier design for cardiac siRNA is best organized around the delivery barriers themselves rather than around material classes. Cross-field RNA-delivery experience (Zhang et al. 2023), cardiovascular RNA surveys (Gil-Cabrerizo et al. 2024; Nicoletti et al. 2025), and the evidence assembled here converge on six barriers. The first five are familiar from the broader RNA-delivery literature. The sixth, microvascular obstruction and endothelial permeability, is where cardiac delivery differs most sharply from delivery to other organs, and it is treated here as an independent access barrier with its own evidence chain and design responses.

Extracellular stability

The first barrier is degradation before the target organ is reached. Naked or poorly shielded siRNA is nuclease-sensitive in serum and tissue fluid, and a carrier must condense, encapsulate, or chemically shield the payload without preventing its later cytosolic release (Damase et al. 2021; Hou et al. 2021). The design balance is delicate: over-stable binding prolongs circulation but can convert the particle into a biologically silent depot.

Systemic disposition

The second barrier is biodistribution at the level of organs. Nanoparticles are not automatically delivered to the heart: size, charge, PEG density, protein corona, deformability, and membrane composition govern circulation time and uptake by liver and spleen. A hard-won lesson of nanoparticle medicine is that enhanced tissue signal must not be equated with efficient cellular delivery (Wilhelm et al. 2016); for cardiac carriers, the same caution applies in both directions. Intravenously infused mRNA-lipid nanoparticles in swine express protein in all major organs, with the heart far from the dominant compartment (Ferraresso et al. 2024), and even after direct intramyocardial injection of lipid nanoparticles in pigs, reporter expression localizes to discrete cell populations rather than distributing uniformly across the wall (Labonia et al. 2024). Both studies define the honest modern benchmark for cardiac disposition data.

Myocardial localization

The third barrier is arrival in the injured region at therapeutic concentrations. Passive accumulation in reperfused myocardium is inconsistent because perfusion and microvascular permeability are heterogeneous in space and time; active-targeting concepts — peptides, antibodies, aptamers, extracellular-matrix-binding domains, and cell-membrane coats — aim to improve this step, but targeting claims deserve scrutiny. Conjugate analyses show that peptide-directed nanoparticles frequently fail to achieve true cellular selectivity in vivo (Beitzinger et al.

2025), so the term “targeting” should be reserved for evidence of cell- or tissue-selective payload delivery rather than nanoparticle presence in the injured region (Song et al. 2024).

Intracellular release

The fourth barrier is cytosolic access. Productive RNA interference requires siRNA in the cytosol, and endocytosis without endosomal escape produces no knockdown. Ionizable lipids, pH-buffering polymers, and membrane-disruptive motifs are therefore not technical details but the determinants of biological activity (Shrestha et al. 2012; Hou et al. 2021). Endosomal escape is one of the least visible and most decisive barriers in siRNA nanomedicine, and its assessment in cardiac studies is often indirect.

Safety and repeatability

The fifth barrier concerns the patient rather than the particle. MI/R patients are frequently older, inflamed, and hemodynamically unstable, and often receive antiplatelet or anticoagulant therapy; nanocarriers intended for this context require early assessment of complement activation, cytokine release, hemolysis, coagulation interaction, arrhythmogenic potential, organ retention, degradation products, and repeat-dose behavior (Heusch 2017). The cautionary precedent from large animals is real: microRNA therapy intended to repair the infarcted pig heart produced uncontrolled, arrhythmogenic repair when the biological response escaped the intended program (Gabisonia et al. 2019). Safety cannot be inferred from short-term cell viability, and cardioprotection-experiment standards demand rigor before efficacy claims (Lecour et al. 2014; Lecour et al. 2021).

Microvascular obstruction and endothelial permeability

The sixth barrier is access through the acutely injured microcirculation, and it is where cardiac delivery differs most sharply from delivery to other organs. Clinically, microvascular obstruction (MVO, the no-reflow phenomenon) is a documented feature of reperfused infarction: angiographic no-reflow correlates with MVO detected by cardiovascular magnetic resonance, and both predict outcome (Eitel et al. 2025). Mechanistically, reperfusion injures the endothelial glycocalyx and the microvascular endothelium itself – glycocalyx preservation reduces microvascular obstruction after MI/R in experimental models (Fernandes et al. 2026) – and MVO has identifiable pharmacology, such as the ALOX12 axis (Wu et al. 2024). The delivery consequence is direct: an obstructed, glycocalyx-denuded microcirculation can deny circulating particles access to precisely the tissue that needs the payload, so the injured vasculature is an independent access barrier and not merely a targeting opportunity.

The access-evidence chain for nanoparticles crossing this barrier is short but consistent. Systemically administered nanoparticles accumulate in a size-dependent manner immediately after cardiac ischemia-reperfusion, with smaller particles entering more efficiently (Lundy et al. 2016); lipid-based nanoparticles distribute into reperfused and infarcted myocardium in mouse models (Paulis et al. 2012; Geelen et al. 2013); and in a myocardial-infarction model, nanoparticle-mediated antithrombotic intervention reduced ischemia-reperfusion injury and no-reflow, reported initially at conference level (Pan et al. 2019) and extended in later work combining inhibition of thrombosis and inflammation (Vargas et al. 2023). This chain supports a permeability-window concept: particle entry is best shortly after reperfusion, when vascular injury is maximal, and declines as the barrier re-forms.

The sixth barrier therefore has its own design responses. Small particle diameter exploits the post-reperfusion permeability window (Lundy et al. 2016); administration timed to the permeability window does the same at the level of dosing; membrane camouflage that borrows leukocyte trafficking carries particles across the inflamed endothelium (Zhou et al. 2023; Lu et al. 2024); endothelial-targeted modification adds selectivity at the interface, as shown by ROS-ultrasensitive endothelial-targeted drug/siRNA co-delivery in MI/R (Hou et al. 2022); and antithrombotic or glycocalyx-preserving modules attack the barrier itself (Vargas et al. 2023; Fernandes et al. 2026). Adjacent-field support for the endothelial-targeting logic comes from hepatic ischemia-reperfusion, where endothelial-targeted exosomes carrying IL-6 siRNA ameliorate injury (Huang et al. 2026a) – a hepatic model, cited as design context and not as cardiac proof. Each of these counter-strategies maps onto a platform family in the next section.

Nanocarrier platforms and their barrier functions

Platforms are compared here by the barriers they answer, not by their material pedigree. The six-barrier frame keeps the comparison analytical: every family below is scored implicitly against extracellular stability, systemic disposition, myocardial localization, intracellular release, safety and repeatability, and microvascular/endothelial access. Full quantitative scores would overstate

the literature, so the comparative design map in the next section grades evidence maturity instead, and this section states functions and their limits.

Lipid and lipid-hybrid nanoparticles

Lipid nanoparticles (LNPs) are the most mature non-viral nucleic-acid platform, with scalable formulation, tunable ionizable lipid chemistry, and proven endosomal release (Hou et al. 2021). They establish the benchmark grammar for cardiac RNA delivery, but their biology works against cardiac use: after systemic injection most LNP formulations accumulate in the liver, and a formulation optimized for hepatic silencing is not automatically a cardiac formulation. Adaptation toward the injured heart is being demonstrated from several directions. An extracellular-matrix-lipid nanoparticle composite achieved site-specific siRNA delivery to improve cardiac repair after myocardial infarction (Wang et al. 2025b); intramyocardial injection of LNP-formulated modified mRNA in pigs produced localized, cell-type-restricted expression (Labonia et al. 2024, mRNA payload – design context); and intravenous mRNA-LNP in swine expressed protein broadly outside the heart, quantifying the systemic-disposition problem (Ferraresso et al. 2024, mRNA payload). Lipid-hybrid systems add modularity – a polymeric, extracellular-matrix-affine, or targeting component carries localization or release duties while the lipid handles packaging and escape (Wang et al. 2025b) – at the price of characterization burden: as hybrid complexity rises, so do the demands on reproducibility, release testing, and safety evaluation. The honest summary is that LNPs are the benchmark, not the answer: whether their grammar can be rewritten for an acutely injured, heterogeneous, and difficult-to-transfect organ remains an open design problem.

Polymeric and stimulus-responsive carriers

Polymeric systems offer tunability: molecular weight, charge density, degradability, and responsive linkages can be adjusted to shape loading, circulation, release, and toxicity, and cationic polymers condense siRNA while disulfide, pH-, enzyme-, or ROS-responsive linkages support triggered release. The injured myocardium supplies plausible triggers, because reperfusion elevates reactive oxygen species, inflammatory cells release enzymes, and local pH shifts; responsive co-delivery systems attempt to match activation to disease chemistry, exemplified by CD11b-modified ROS/pH-responsive nanoparticles that co-deliver dioscin and siRNA to reduce neutrophil recruitment and improve cardiac repair after myocardial infarction (Xu et al. 2025) and by ROS-responsive injectable microgels for myocardial infarction (Wang et al. 2024). Responsiveness must be demonstrated, not assumed: a carrier described as ROS-responsive should show stability under normal conditions, release at pathologically relevant trigger levels, knockdown in the relevant cell type, and an outcome beyond what the non-siRNA component explains. When a small molecule and siRNA are co-delivered – dioscin and siRNA in the example above – the contribution of each component must be separated, or the platform becomes mechanistically attractive but pharmacologically ambiguous. Safety is the counterweight: highly cationic materials can damage membranes, activate complement, and adsorb protein nonspecifically, and slowly degrading polymers can persist in tissue (Heusch 2017).

Biomimetic and extracellular-vesicle-inspired carriers

Biomimetic carriers are the most distinctive recent direction in cardiac siRNA delivery, and their rationale is strong because MI/R injury is organized around immune-cell trafficking, endothelial adhesion, and extracellular-vesicle communication. Cell-membrane coating and vesicle-inspired design borrow natural homing, immune evasion, and interface behavior. The 2023–2026 literature contains a coherent wave of direct MI/R evidence: reversibly camouflaged biomimetic nanocomplexes delivering siRNA against MI/R injury (Zhou et al. 2023); macrophage-membrane-coated S100A9-siRNA systems (Lu et al. 2024); neutrophil-membrane-camouflaged siRNA nanocomplexes (Jiang et al. 2025); exosome-based WTAP-siRNA delivery (Yin et al. 2024); membrane-coated nanoparticles suppressing macrophage pyroptosis (Yue et al. 2026); and microneedle-patch delivery of mesenchymal-stem-cell exosomes carrying EGR1 siRNA (Huang et al. 2025). Adjacent and adjacent-payload systems extend the logic: FAP-aptamer-functionalized extracellular vesicles deliver TGF- β 1 siRNA to injured cardiac tissue (Kang et al. 2025), NOX4-siRNA small extracellular vesicles were validated in a cardiac-hypertrophy model rather than MI/R (Kang et al. 2023, model-adjacent), cardiac-targeted extracellular-vesicle formulations co-delivering quercetin target the infarcted heart (Zhang et al. 2026, non-RNA payload – design context), and macrophage-membrane-biomimetic nanoparticles delivering melatonin address MI/R (Huang et al. 2026b, non-RNA payload – design context). The synthesis is clear: these systems can address several barriers at once – circulation, immune recognition, lesion homing, endothelial interaction, and cell-specific uptake. The critical interpretation is

equally clear: such advantages are difficult to standardize. Membrane source and donor variability, isolation method, residual proteins, orientation, storage stability, and batch-to-batch reproducibility can alter biological behavior, and it is often difficult to prove which membrane component produces the targeting (Gil-Cabrerizo et al. 2024; Zhao et al. 2025). Biomimetic carriers are therefore a leading frontier, not a shortcut: their promise is strongest when membrane biology is mechanistically matched to the injury process, and weakest when “natural targeting” substitutes for quantitative cell-type delivery, payload release, and manufacturing evidence.

Inorganic, magnetic, and carbon-based systems

Inorganic and carbon materials contribute functions that organic carriers do not offer, but those functions are only useful if they answer a real barrier. Gold nanoparticles bring well-established surface chemistry (Daniel and Astruc 2004); superparamagnetic iron-oxide nanoparticles bring magnetic guidance and magnetic-resonance visibility (Laurent et al. 2008); and magnetic nanovesicles targeted to injured cardiac tissue have been reported for mRNA treatment of myocardial infarction (Mun et al. 2026, mRNA rather than siRNA payload, labelled design context). Carbon materials load nucleic acids efficiently and offer large surfaces, but no in-window MI/R-siRNA study met the inclusion criteria of this review, so their cardiac-siRNA case rests on general material arguments and is stated here without citation burden. The practical test for this entire family is the one applied in the evidence-limits section: does the platform carry siRNA stably in serum, reach reperfused myocardium through the injured microcirculation, enter the correct cell type, release siRNA into the cytosol, avoid long-term retention, and produce knockdown in an MI/R model? Metal retention, oxidative stress, coating degradation, and dose-related toxicity must be answered before theranostic elegance matters. These systems are conditional opportunities – useful if their special function solves a barrier that lipid, polymeric, or biomimetic systems do not solve.

Cross-cutting targeting and local-delivery modules

Some design features are class-agnostic and worth separating from platform chemistry. Cardiac homing peptides direct liposomal and mesoporous-silica carriers to the injured heart, demonstrated with small-molecule payloads after myocardial infarction (Yu et al. 2026; You et al. 2022, non-siRNA payloads – design context). Extracellular-matrix targeting is an alternative localization handle: Type-I-collagen-targeted liposomes delivering Serca2a modulate calcium handling and fibrosis after myocardial infarction (Chen et al. 2024, non-siRNA payload – design context). And local-depot formats – ROS-responsive injectable microgels (Wang et al. 2024) and microneedle patches (Huang et al. 2025) – trade systemic exposure for regional retention and repeatability. The shared trade-off is manufacturing: each added selectivity module must remain reproducible, or the design becomes an experiment rather than a product (see translational constraints).

Comparative design map and evidence maturity

Grading the carrier landscape requires criteria, and this review applies explicit evidence-maturity tiers adapted from cardioprotection guidance rather than a material-based scale. The ladder follows the ESC position paper on preclinical cardioprotection assessment (Lecour et al. 2014), the IMPACT criteria of the EU-CARDIOPROTECTION COST Action (Lecour et al. 2021), their application in the multicenter IMPACT pig study (Kleinbongard et al. 2024), and IMPACT-based re-evaluations in the literature (Pędzińska-Betiuk et al. 2024). Six tiers are used here: T1, design or in-vitro proof; T2, delivery evidence in small animals (quantitative biodistribution, cell-type localization, or knockdown); T3, efficacy in small-animal MI/R models; T4, independent replication or head-to-head comparison against a simpler optimized carrier; T5, large-animal (pig before dog) validation with clinically plausible timing; T6, clinical-trial presence. Grading describes study design and evidence depth, never efficacy; a tier label is not a verdict on the merits of a material.

Table 2 applies the rubric to the platform families of this review. The stated basis column records what the grade rests on, including absence statements, which are bounded to the screened literature as of September 2026.

Three conclusions follow. First, no platform solves all six barriers; each family answers some and leaves others to formulation work. Second, evidence maturity differs sharply between classes even when functional overlap is large – biomimetic systems reached T3 through replication while carbon systems remain at T1. Third, the field's heterogeneity makes design matching, not material ranking, the defensible conclusion: the most convincing future studies will not introduce a new material but will show that a chosen design solves a defined barrier better than a simpler optimized carrier.

Table 2. Comparative design map of siRNA nanocarrier platforms for MI/R injury

Platform class	Main strengths (barriers answered)	Main limitations	Evidence maturity (stated basis)	Best-fit MI/R application
LNP and lipid-hybrid	Payload protection, endosomal release, scalable formulation (barriers 1, 4)	Liver tropism; cardiac selectivity not demonstrated (barrier 2)	T3: small-animal MI/R efficacy for adapted designs; large-animal cardiac LNP data exist for mRNA and are payload-adjacent; T4–T5 absent (n = 0 for MI/R siRNA)	Foundational platform for cardiac-adapted delivery
Polymeric and stimulus-responsive	Tunable release, disease-triggered activation, co-delivery (barriers 1, 4)	Cationic toxicity; responsiveness and component attribution often unproven; local formats needed (barrier 5)	T2–T3: delivery and efficacy in small-animal infarction models with permanent ligation; co-delivery attribution caveat	Matching activation to reperfusion chemistry
Biomimetic and EV-inspired	Immune evasion, lesion homing, endothelial interface (barriers 3, 6)	Source variability, QC, scale-up, mechanism attribution (barrier 5)	T3: multiple independent 2023–2026 small-animal MI/R siRNA studies (T4 partially met by independent replication); T5 absent (n = 0)	Inflammatory-cell and endothelial-interface delivery
Inorganic and magnetic	Imaging, magnetic guidance, theranostics (barrier 3)	Retention, toxicity, unproven cytosolic release (barriers 4, 5)	T2: delivery-adjacent large-animal/theranostic exemplars; in-window MI/R-siRNA efficacy absent; mRNA exemplar payload-adjacent	Guided delivery where imaging matters
Carbon-based	High loading and functionalization surface (barrier 1)	Persistence, purity, inflammatory risk; no in-window MI/R-siRNA evidence (barriers 2–6)	T1: design/in-vitro only; no qualifying study in the screened window	Exploratory, conditional

What current evidence can and cannot support

Grading the field by the rubric above produces a finding that is more useful than another catalogue: most surveyed MI/R siRNA carriers sit at T2–T3, with no carrier class at T5 or T6. That is the honest state of a field at its translation inflection point, not a deficit, and it converts the review's job from describing platforms to naming what evidence would move a design up the ladder.

What the evidence supports is biological plausibility and increasingly disease-aware design. Multiple preclinical studies connect RNA silencing to MI/R pathways, and engineered carriers improve delivery-related behavior compared with naked RNA: protection from nucleases, immune-cell-interface targeting, responsiveness to reperfusion chemistry, and, at the level of individual studies, functional improvement in small-animal MI/R models (Hou et al. 2022; Zhou et al. 2023; Lu et al. 2024). What the evidence cannot support is clinical readiness of any current class: no MI/R siRNA nanocarrier has reached randomized clinical testing, and the maturity grades in Table 2 are absence statements bounded to the screened literature as of September 2026.

The more consequential gap is the incomplete delivery-evidence chain. The field's question has shifted from whether nanocarriers can carry siRNA in principle – shown across many platforms – to whether a carrier delivers enough siRNA to the correct cardiac compartment, at the correct disease phase, with enough safety margin. Most studies report injury markers, fluorescence accumulation, or histological improvement without a full chain: quantitative organ distribution, cell-type-level payload accounting, cytosolic delivery, target knockdown, pathway modulation, and functional recovery in one study. The exceptions define the standard: cell-level tracing of intramyocardially injected LNP-mRNA in pigs mapped which cardiac cells actually received the payload (Labonia et al. 2024, mRNA payload – design context), and whole-body protein-expression mapping in swine quantified the disposition problem that cardiac delivery must beat (Ferraresso et al. 2024). Most studies also omit delayed dosing relative to revascularization, comorbid or aged animals, sex as a variable – female hearts differ reproducibly in ischemia-reperfusion susceptibility and cardioprotection (Fischer and Collins 2024) – and repeat administration. A further weakness is comparative: most studies benchmark against naked siRNA or saline rather than against a simpler optimized carrier, so the added value of camouflage, responsiveness, magnetic guidance, or hybridization frequently remains unproven. Adjacent-field evidence can inform such comparisons, but it is not a substitute for MI/R-specific validation; this review applies that rule at each point of use.

Five priority directions follow from these gaps, each stated with its design consequence:

P1. Cell-level delivery-evidence chains. Future studies should combine quantitative organ biodistribution, cell-type-level payload accounting (flow sorting, spatial methods), knockdown, and functional outcome in single experiments. Whole-organ fluorescence is not a delivery measurement.

P2. Clinically plausible timing and model realism. Administration windows must be tested at or after revascularization, including delayed dosing, and age, sex, diabetes, and comorbidity must enter the model design rather than the discussion section (Fischer and Collins 2024).

P3. Pig-first large-animal validation with MVO-relevant readouts. The next evidence tier (T5) requires large-animal studies in clinically plausible models that report infarct size, microvascular obstruction, and hemorrhage, not only ejection fraction (Dharmakumar et al. 2025; Kleinbongard et al. 2024); the model rationale is developed in the next section.

P4. Head-to-head comparators with payload attribution. New designs should be compared with a simpler optimized carrier of the same payload, and co-delivered components separated, so that camouflage, responsiveness, or targeting earns its complexity (Xu et al. 2025).

P5. Standardized dosing protocols and integrated safety and manufacturability data. Complement activation, coagulation interaction, arrhythmia monitoring, and organ retention belong in early study design, together with batch-level reproducibility of size, charge, loading, membrane composition, sterility, and release behavior.

Translational constraints and model selection

If priorities name the evidence to collect, constraints define the frame in which it can be collected at all. Four constraints dominate, and a fifth step – model selection – decides whether the collected evidence transfers to patients.

Biodistribution first

Translation begins with quantitative biodistribution: where the carrier goes, how long it remains, which cell type receives the payload, and how much target knockdown results. The modern benchmark studies in swine, cited above, show what this standard requires even for the most advanced platforms (Ferraresso et al. 2024; Labonia et al. 2024). Delivery evidence is the gate for everything downstream.

Timing

MI/R injury evolves faster than any chronic disease program, and a carrier given before ischemia in an experimental model does not reproduce clinical reperfusion, where treatment begins at or after revascularization. Administration windows, including delayed delivery, must be tested rather than assumed, and the phase-dependence of the target (harmful in early reperfusion, possibly useful during repair) must enter protocol design (Hausenloy and Yellon 2013; Heusch 2020).

Safety integration

Acute-cardiac nanocarriers act on patients who are hemodynamically unstable, inflamed, and frequently anticoagulated. Complement activation, cytokine release, coagulation interaction, arrhythmogenic potential, and organ retention should therefore be integrated into early design (Heusch 2017); the pig microRNA experience – therapeutic intent converting into uncontrolled, arrhythmogenic repair (Gabisonia et al. 2019) – is the cautionary benchmark for biological, not only material, safety.

Manufacturability

A carrier that cannot be reproduced cannot become a product, regardless of conceptual elegance. Size, charge, loading, membrane composition, sterility, endotoxin, storage stability, and release behavior must be controllable at batch scale, which is the least glamorous and most binding constraint for biomimetic and multi-component systems (Zhao et al. 2025).

Model selection: why the pig and the dog matter

The fifth step decides in which species the T5 evidence is generated, and the choice between pig and dog is a matter of coronary anatomy, infarct geometry, readouts, and delivery precedent – not of convenience. Coronary collateral flow determines how an infarction evolves during coronary occlusion: measured with radiolabelled microspheres, collateral flow during acute ischemia is approximately 0.6 % of non-ischemic flow in the pig, the lowest among the species examined, versus approximately 15.9 % in the dog, with a transmural gradient in the dog that spares the subendocardium (Wartier et al. 1982; Maxwell et al. 1987). The consequences are geometric: porcine infarction after coronary occlusion is reproducibly transmural, whereas canine infarction is variable and subendocardium-sparing, a difference that made the dog a poor default for testing interventions intended to limit transmural infarct size. Pigs additionally offer clinically relevant cardiac mass and hemodynamics, an in-situ regional ischemia/reperfusion preparation that is considered ready for translation (Heusch et al. 2011), cardiovascular-magnetic-resonance readouts of microvascular obstruction and hemorrhage in large animals

(Dharmakumar et al. 2025), and quality-assurance guidance for large-animal infarction models (Zwetsloot et al. 2017). Delivery precedent now favors the pig as well: myocardial lipidoid-nanoparticle delivery of modified mRNA produced rapid, transient cardiac expression (Turnbull et al. 2016, mRNA payload), intramyocardial LNP-mRNA mapped cellular targets in pigs (Labonia et al. 2024), intravenous mRNA-LNP expressed protein across organs in swine (Ferraresso et al. 2024), and the uncontrolled-repair miRNA study was itself porcine (Gabisonia et al. 2019). For an MI/R siRNA carrier, the defensible T5 sequence is therefore pig-first, with the dog retained only where a specific question (collateral-dependent biology, chronic remodeling with pre-existing collaterals) demands the canine circulation; model quality, not model availability, is the standard (Heusch et al. 2011; Zwetsloot et al. 2017).

Conclusion

siRNA nanomedicine offers a compelling but still immature strategy for MI/R injury. The biological rationale is strong because reperfusion injury is gene-regulated across oxidative, mitochondrial, inflammatory, endothelial, and cell-death programs; the translational challenge is equally strong because the payload must be protected, localized across an acutely injured microcirculation, internalized, released into the cytosol, and validated in a cardiac environment that changes within hours.

The central message of this review is that carrier design should begin with the delivery barrier, not with the material category – and that for the heart, the barrier chain includes microvascular obstruction and endothelial permeability as an independent access step that platform-organized reviews have not yet treated as a design variable. The barrier-to-design framework, the target map with explicit inclusion criteria, the maturity rubric, and the model-selection logic give a pharmacology reader a single map on which any current or future MI/R siRNA-carrier study can be placed: which target, which barrier, which design answer, at what evidence level. The honest finding of that map is that most systems sit at T2–T3 and that the field's next advance is more likely to come from aligning pathobiology, RNA pharmacology, and carrier engineering into one coherent translational design – full delivery-evidence chains, clinically realistic timing and models, head-to-head comparators, and reproducible manufacturing – than from adding another nanomaterial name.

Additional Information

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

The authors have no funding to report.

Acknowledgments

The figures were created with BioRender.com.

Data availability

All of the data that support the findings of this study are available in the main text.

References

- Beitzinger B, Draphoen B, Hald J, Krämer M, Rudolf T, Schmitt F, Schwarz P, Lindén M (2025) On the cellular selectivity of targeting peptide-nanoparticle conjugates – a nanoparticle perspective. *Expert Opinion on Drug Delivery* 22(9): 1345–1358. <https://doi.org/10.1080/17425247.2025.2522245> [PubMed]
- Bertero E, Popoiu TA, Maack C (2024) Mitochondrial calcium in cardiac ischemia/reperfusion injury and cardioprotection. *Basic Research in Cardiology* 119(4): 569–585. <https://doi.org/10.1007/s00395-024-01060-2> [PubMed] [PMC]
- Chen W, Liu L, Tang M, Li J, Yuan W, Yin D, Cao Y, Tian J (2024) Type I collagen-targeted liposome delivery of Serca2a modulates myocardium calcium homeostasis and reduces cardiac fibrosis induced by myocardial infarction. *Materials Today Bio* 28: 101162. <https://doi.org/10.1016/j.mtbio.2024.101162> [PubMed] [PMC]
- Damase TR, Sukhovshin R, Boada C, Taraballi F, Pettigrew RI, Cooke JP (2021) The limitless future of RNA therapeutics. *Frontiers in Bioengineering and Biotechnology* 9: 628137. <https://doi.org/10.3389/fbioe.2021.628137> [PubMed] [PMC]
- Daniel MC, Astruc D (2004) Gold nanoparticles: assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology. *Chemical Reviews* 104(1): 293–346. <https://doi.org/10.1021/cr030698> [PubMed]

- Dharmakumar S, Vora KP, Huo H, Yoosefian G, Yang HJ, Krishnam M, Kumar A (2025) Detecting hemorrhagic myocardial infarction with T2 CMR at 3T: initial evidence from a large animal model. *Journal of Cardiovascular Magnetic Resonance* 27: 101231. <https://doi.org/10.1016/j.jocmr.2024.101231>
- Duan Y, Li Q, Wu J, Zhou C, Liu X, Yue J, Chen X, Liu J, Zhang Q, Zhang Y, Zhang L (2024) A detrimental role of endothelial S1PR2 in cardiac ischemia-reperfusion injury via modulating mitochondrial dysfunction, NLRP3 inflammasome activation, and pyroptosis. *Redox Biology* 75: 103244. <https://doi.org/10.1016/j.redox.2024.103244> [PubMed] [PMC]
- Eitel I, Saraei R, Jurczyk D, Stiermaier T (2025) Correlation of angiographic microvascular obstruction (no reflow phenomenon) with CMR derived microvascular obstruction: implications and future opportunities for paradigm-shifting. *Journal of Cardiovascular Magnetic Resonance* 27: 101205. <https://doi.org/10.1016/j.jocmr.2024.101205>
- Fernandes PLM, de Castro Silva PA, Miranda CH (2026) Fucoidan preserves endothelial glycocalyx and reduces microvascular obstruction after myocardial ischemia-reperfusion. *Microvascular Research* 167: 104985. <https://doi.org/10.1016/j.mvr.2026.104985> [PubMed]
- Ferraresso F, Badiou K, Seadler M, Zhang Y, Wietrzny A, Cau MF, Haugen A, Rodriguez GG, Dyer MR, Cullis PR, Jan E, Kastrup CJ (2024) Protein is expressed in all major organs after intravenous infusion of mRNA-lipid nanoparticles in swine. *Molecular Therapy – Methods & Clinical Development* 32(3): 101314. <https://doi.org/10.1016/j.omtm.2024.101314> [PubMed] [PMC]
- Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC (1998) Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature* 391(6669): 806–811. <https://doi.org/10.1038/35888> [PubMed]
- Fischer A, Collins HE (2024) Female cardioprotection in ischemia/reperfusion: isn't a SUR thing anymore? *Journal of Molecular and Cellular Cardiology Plus* 10: 100089. <https://doi.org/10.1016/j.jmccpl.2024.100089> [PubMed] [PMC]
- Gabisonia K, Prosdocimo G, Aquaro GD, Carlucci L, Zentilin L, Secco I, Ali H, Braga L, Gorgodze N, Bernini F, Burchielli S, Collesi C, Zandonà L, Sinagra G, Piacenti M, Zacchigna S, Bussani R, Recchia FA, Giacca M (2019) MicroRNA therapy stimulates uncontrolled cardiac repair after myocardial infarction in pigs. *Nature* 569(7756): 418–422. <https://doi.org/10.1038/s41586-019-1191-6> [PubMed] [PMC]
- Geelen T, Paulis LEM, Coolen BF, Nicolay K, Strijkers GJ (2013) Passive targeting of lipid-based nanoparticles to mouse cardiac ischemia-reperfusion injury. *Contrast Media & Molecular Imaging* 8(2): 117–126. <https://doi.org/10.1002/cmmi.1501> [PubMed]
- Gil-Cabrero P, Simon-Yarza T, Garbayo E, Blanco-Prieto MJ (2024) Navigating the landscape of RNA delivery systems in cardiovascular disease therapeutics. *Advanced Drug Delivery Reviews* 208: 115302. <https://doi.org/10.1016/j.addr.2024.115302> [PubMed]
- Hausenloy DJ, Yellon DM (2013) Myocardial ischemia-reperfusion injury: a neglected therapeutic target. *The Journal of Clinical Investigation* 123(1): 92–100. <https://doi.org/10.1172/JCI62874> [PubMed] [PMC]
- Heusch G (2017) Critical issues for the translation of cardioprotection. *Circulation Research* 120(9): 1477–1486. <https://doi.org/10.1161/CIRCRESAHA.117.310820> [PubMed]
- Heusch G (2020) Myocardial ischaemia-reperfusion injury and cardioprotection in perspective. *Nature Reviews Cardiology* 17(2): 773–789. <https://doi.org/10.1038/s41569-020-0403-y> [PubMed]
- Heusch G, Skyschally A, Schulz R (2011) The in-situ pig heart with regional ischemia/reperfusion – ready for translation. *Journal of Molecular and Cellular Cardiology* 50(6): 951–963. <https://doi.org/10.1016/j.yjmcc.2011.02.016> [PubMed]
- Hou M, Wu X, Zhao Z, Deng Q, Chen Y, Yin L (2022) Endothelial cell-targeting, ROS-ultrasensitive drug/siRNA co-delivery nanocomplexes mitigate early-stage neutrophil recruitment for the anti-inflammatory treatment of myocardial ischemia reperfusion injury. *Acta Biomaterialia* 143: 344–355. <https://doi.org/10.1016/j.actbio.2022.02.018> [PubMed]
- Hou X, Zaks T, Langer R, Dong Y (2021) Lipid nanoparticles for mRNA delivery. *Nature Reviews Materials* 6: 1078–1094. <https://doi.org/10.1038/s41578-021-00358-0>
- Huang C, Zhang X, Wu SX, Chang Q, Zheng ZK, Xu J (2025) Cardioprotective effects of hUCMSCs-Exosi-EGR1 MN patch in MI/RI by modulating oxidative stress and mitophagy. *Materials Today Bio* 31: 101500. <https://doi.org/10.1016/j.mtbio.2025.101500> [PubMed] [PMC]
- Huang K, Zhang X, Yan X, Qin M, Lv L, Yang S, Zheng Y, Yin G, Tian X, Wang X, Deng W, Yan Y, Wu W, Yuan H, Fan Z, Wang C, Ma J (2026a) Endothelial-targeted modification of ginseng-derived exosomes for IL-6 siRNA delivery ameliorates hepatic ischemia-reperfusion injury. *Journal of Nanobiotechnology* 24(1): 22. <https://doi.org/10.1186/s12951-025-03954-2> [PubMed] [PMC]
- Huang T, Zhang Z, Hou R, Lin B, Wang D, Xu G (2026b) Macrophage membrane-biomimetic nanoparticles for targeted delivery of melatonin in myocardial ischemia-reperfusion injury. *Nanomedicine: Nanotechnology, Biology and Medicine* 75: 102962. <https://doi.org/10.1016/j.nano.2026.102962> [PubMed]
- Jiang Y, Jiang R, Xia Z, Guo M, Fu Y, Wang X (2025) Engineered neutrophil membrane-camouflaged nanocomplexes for targeted siRNA delivery against myocardial ischemia reperfusion injury. *Journal of Nanobiotechnology* 23(1): 134. <https://doi.org/10.1186/s12951-025-03172-w> [PubMed] [PMC]
- Jin B, Zhang Z, Zhang Y, Yang M, Wang C, Xu J, Zhu Y, Mi Y, Jiang J, Sun Z (2024) Ferroptosis and myocardial ischemia-reperfusion: mechanistic insights and new therapeutic perspectives. *Frontiers in Pharmacology* 15: 1482986. <https://doi.org/10.3389/fphar.2024.1482986> [PubMed] [PMC]
- Kalogeris T, Baines CP, Krenz M, Korthuis RJ (2012) Cell biology of ischemia/reperfusion injury. *International Review of Cell and Molecular Biology* 298: 229–317.
- Kang J, Mun D, Chun Y, Park D, Kim H, Yun N, Joung B (2023) Engineered small extracellular vesicle-mediated NOX4 siRNA delivery for targeted therapy of cardiac hypertrophy. *Journal of Extracellular Vesicles* 12(10): e12371. <https://doi.org/10.1002/jev2.12371> [PubMed] [PMC]
- Kang JY, Mun D, Park M, Yoo G, Kim H, Yun N, Joung B (2025) Injured cardiac tissue-targeted delivery of TGF- β 1 siRNA by FAP aptamer-functionalized extracellular vesicles promotes cardiac repair. *International Journal of Nanomedicine* 20: 2575–2592. <https://doi.org/10.2147/IJN.S497428> [PubMed] [PMC]
- Kleinbongard P, Arriola CG, Badimon L, Crisostomo V, Giricz Z, Gyöngyösi M, Heusch G, Ibanez B, Kiss A, de Kleijn DPV, Podesser BK, Carracedo RR, Rodríguez-Sinovas A, Ruiz-Meana M, Sanchez Margallo FM, Vilahur

- G, Zamorano JL, Zaragoza C, Ferdinandy P, Hausenloy DJ (2024) The IMPACT multicenter pig study on the effect of ischemic preconditioning. *Basic Research in Cardiology* 119(6): 893–909. <https://doi.org/10.1007/s00395-024-01083-9> [PubMed] [PMC]
- Labonia M, Estapé Senti M, van der Kraak P, Brans M, Dokter I, Streef T, Smits A, Deshantri A, de Jager S, Schiffelers R, Sluijter J, Vader P (2024) Cardiac delivery of modified mRNA using lipid nanoparticles: cellular targets and biodistribution after intramyocardial administration. *Journal of Controlled Release* 369: 734–745. <https://doi.org/10.1016/j.jconrel.2024.04.018> [PubMed]
 - Laurent S, Forge D, Port M, Roch A, Robic C, Vander Elst L, Muller RN (2008) Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. *Chemical Reviews* 108(6): 2064–2110. <https://doi.org/10.1021/cr068445e> [PubMed]
 - Lecour S, Andreadou I, Botker HE, Davidson SM, Heusch G, Ruiz-Meana M, Schulz R, Zuurbier CJ, Ferdinandy P, Hausenloy DJ, European Union-CARDIOPROTECTION COST Action (CA16225) (2021) IMPACT criteria: guidelines of the EU-CARDIOPROTECTION COST Action (CA16225). *Basic Research in Cardiology* 116(1): 52. <https://doi.org/10.1007/s00395-021-00893-5> [PubMed] [PMC]
 - Lecour S, Botker HE, Condorelli G, Davidson SM, Garcia-Dorado D, Engel FB, Ferdinandy P, Heusch G, Madonna R, Ovize M, Ruiz-Meana M, Schulz R, Sluijter JP, Van Laake LW, Yellon DM, Hausenloy DJ (2014) ESC Working Group Cellular Biology of the Heart: position paper: Improving the preclinical assessment of novel cardioprotective therapies. *Cardiovascular Research* 104(3): 399–411. <https://doi.org/10.1093/cvr/cvu225> [PubMed] [PMC]
 - Li Y, Li P, Wang W, Zhang Y, Li S, Li D, Lin Q (2025) Nanoparticle-based drug delivery systems targeting inflammatory immune mechanisms in acute myocardial infarction: current advances and perspectives. *Frontiers in Cardiovascular Medicine* 12: 1657300. <https://doi.org/10.3389/fcvm.2025.1657300> [PubMed] [PMC]
 - Liu Y, Li L, Wang Z, Zhang J, Zhou Z (2023) Myocardial ischemia-reperfusion injury: molecular mechanisms and prevention. *Microvascular Research* 149: 104565. <https://doi.org/10.1016/j.mvr.2023.104565> [PubMed]
 - Lu H, Huang Q, Xiong Z, Wu C, Ren S, Wang X, Shi J (2026) Precision nanomedicine in cardiovascular disease: engineered siRNA delivery platforms for atherosclerosis and ischemic heart disease. *Chemical Engineering Journal* 529: 172968. <https://doi.org/10.1016/j.cej.2026.172968>
 - Lu H, Wang J, Chen Z, Wang J, Jiang Y, Xia Z (2024) Engineered macrophage membrane-coated S100A9-siRNA for ameliorating myocardial ischemia-reperfusion injury. *Advanced Science* 11(41): e2403542. <https://doi.org/10.1002/adv.202403542> [PubMed] [PMC]
 - Lundy DJ, Chen KH, Toh EKW, Hsieh PCH (2016) Distribution of systemically administered nanoparticles reveals a size-dependent effect immediately following cardiac ischaemia-reperfusion injury. *Scientific Reports* 6: 25613. <https://doi.org/10.1038/srep25613> [PubMed] [PMC]
 - Ma XR, Yan TM, Pan Y, Jiang ZH (2025) Optimization of siRNA therapeutics targeting MIAT for cardioprotection in myocardial ischemia/reperfusion injury. *Molecular Therapy – Nucleic Acids* 36(4): 102747. <https://doi.org/10.1016/j.omtn.2025.102747> [PubMed] [PMC]
 - Maxwell MP, Hearse DJ, Yellon DM (1987) Species variation in the coronary collateral circulation during regional myocardial ischaemia: a critical determinant of the rate of evolution and extent of myocardial infarction. *Cardiovascular Research* 21(10): 737–746. <https://doi.org/10.1093/cvr/21.10.737> [PubMed]
 - Mun D, Kang JY, Park M, Yoo G, Lee J, Yun N, Joung B (2026) Injured cardiac targeting magnetic nanovesicles for mRNA treatment of myocardial infarction. *Theranostics* 16(8): 4090–4112. <https://doi.org/10.7150/thno.124754> [PubMed] [PMC]
 - Nicoletti L, Coletto M, Stola GP, Paoletti C, Marcello E, Testore D, Tivano F, Zoso A, Mattu C, Chiono V (2025) Strategies for the delivery of RNA therapeutics to diseased heart tissue. *Expert Opinion on Drug Delivery* 22(10): 1583–1598. <https://doi.org/10.1080/17425247.2025.2539960> [PubMed]
 - Niu X, Zhang J, Hu S, Dang W, Wang K, Bai M (2024) lncRNA Oip5-as1 inhibits excessive mitochondrial fission in myocardial ischemia/reperfusion injury by modulating DRP1 phosphorylation. *Cellular & Molecular Biology Letters* 29(1): 72. <https://doi.org/10.1186/s11658-024-00588-4> [PubMed] [PMC]
 - Pan H, Lindon A, Grabau R, Dominguez W, Wickline S (2019) Anti-thrombin nanoparticles limit ischemia-reperfusion injury and no-reflow in myocardial infarction. *European Heart Journal* 40(Supplement 1): ehz745.0176. <https://doi.org/10.1093/eurheartj/ehz745.0176>
 - Paulis LE, Geelen T, Kuhlmann MT, Coolen BF, Schäfers M, Nicolay K, Strijkers GJ (2012) Distribution of lipid-based nanoparticles to infarcted myocardium with potential application for MRI-monitored drug delivery. *Journal of Controlled Release* 162(2): 276–285. <https://doi.org/10.1016/j.jconrel.2012.06.035> [PubMed]
 - Pędzńska-Betiuk A, Schlicker E, Weresa J, Malinowska B (2024) Re-evaluation of the cardioprotective effects of cannabinoids against ischemia-reperfusion injury according to the IMPACT criteria. *Frontiers in Pharmacology* 15: 1382995. <https://doi.org/10.3389/fphar.2024.1382995> [PubMed] [PMC]
 - Shrestha R, Elsabahy M, Florez-Malaver S, Samarajeewa S, Wooley KL (2012) Endosomal escape and siRNA delivery with cationic shell crosslinked knedel-like nanoparticles with tunable buffering capacities. *Biomaterials* 33(30): 7145–7153. <https://doi.org/10.1016/j.biomaterials.2012.07.054> [PubMed] [PMC]
 - Song L, Jia K, Yang F, Wang J (2024) Advanced nanomedicine approaches for myocardial infarction treatment. *International Journal of Nanomedicine* 19: 6399–6425. <https://doi.org/10.2147/IJN.S467219> [PubMed] [PMC]
 - Tian H, Xiong Y, Zhan J, Lu Z, Zhang Y, Leng Y, Huang Q, Xia Z (2025) Inhibition of macrophage ARID3A alleviates myocardial ischemia-reperfusion injury after heart transplantation by reducing THBS1/CD47 signaling-mediated neutrophil extracellular traps. *Advanced Science* 12(44): e09952. <https://doi.org/10.1002/adv.202509952> [PubMed] [PMC]
 - Turnbull IC, Eltoukhy AA, Fish KM, Nonnenmacher M, Ishikawa K, Chen J, Hajjar RJ, Anderson DG, Costa KD (2016) Myocardial delivery of lipidoid nanoparticle carrying modRNA induces rapid and transient expression. *Molecular Therapy* 24(1): 66–75. <https://doi.org/10.1038/mt.2015.193> [PubMed] [PMC]
 - Vargas I, Grabau RP, Chen J, Weinheimer C, Kovacs A, Dominguez-Viqueira W, Mitchell A, Wickline SA, Pan H (2023) Simultaneous inhibition of thrombosis and inflammation is beneficial in treating acute myocardial infarction. *International Journal of Molecular Sciences* 24(8): 7333. <https://doi.org/10.3390/ijms24087333> [PubMed] [PMC]
 - Wang H, Li L, Luo L, Cheng Y, Zhou F, Zhao S, Li Y, Yang Y, Zhou Q, Niu H, He J, Zhang C, Guo J, Tang L, Xu J (2025a) Advanced nanomaterial platforms for targeted therapy of myocardial ischemia-reperfusion injury. *Research (Washington, D.C.)* 8: 0822. <https://doi.org/10.34133/research.0822> [PubMed] [PMC]

- Wang S, Yao Y, Song L, Zhai Z, Li S, Wang Z, Shen L, Zhu Y, Liu W, Gao C (2024) ROS-responsive drug-releasing injectable microgels for ameliorating myocardial infarction. *Biomaterials* 307: 122534. <https://doi.org/10.1016/j.biomaterials.2024.122534> [PubMed]
- Wang X, Zhong Y, Qian B, Huang S, Long Q, Zhang H, Zhao Q, Ye X (2025b) Self-assembled extracellular matrix-lipid nanoparticle composite for site-specific siRNA delivery to improve cardiac repair post-myocardial infarction. *Materials Today Bio* 34: 102205. <https://doi.org/10.1016/j.mtbio.2025.102205> [PubMed] [PMC]
- Warltier DC, Zyvoloski MG, Gross GJ, Brooks HL (1982) Subendocardial versus transmural myocardial infarction: relationship to the collateral circulation in canine and porcine hearts. *Canadian Journal of Physiology and Pharmacology* 60(12): 1700–1706. <https://doi.org/10.1139/y82-248> [PubMed]
- Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF, Chan WCW (2016) Analysis of nanoparticle delivery to tumours. *Nature Reviews Materials* 1: 16014. <https://doi.org/10.1038/natrevmats.2016.14>
- Wu Y, Lin Y, Liu B, Ma J, Xiang Y, Wang Y, Meng S (2024) Shexiang Tongxin dropping pill ameliorates microvascular obstruction via downregulating ALOX12 after myocardial ischemia-reperfusion. *International Journal of Cardiology* 416: 132481. <https://doi.org/10.1016/j.ijcard.2024.132481> [PubMed]
- Xu N, Chi Z, Zhang H, Wu J, Sun R, Tian C (2025) CD11b-modified ROS/pH-responsive nanoparticles co-deliver dioscin and siRNA to improve cardiac repair after myocardial infarction by reducing neutrophil recruitment. *Materials Today Bio* 34: 102226. <https://doi.org/10.1016/j.mtbio.2025.102226> [PubMed] [PMC]
- Yin T, Wang N, Jia F, Wu Y, Gao L, Zhang J, Hou R (2024) Exosome-based WTAP siRNA delivery ameliorates myocardial ischemia-reperfusion injury. *European Journal of Pharmaceutics and Biopharmaceutics* 197: 114218. <https://doi.org/10.1016/j.ejpb.2024.114218> [PubMed]
- You L, Wang Q, Ma Y, Li Y, Ye H, Xu L, Lei M (2022) Precise dapagliflozin delivery by cardiac homing peptide functionalized mesoporous silica nanocarriers for heart failure repair after myocardial infarction. *Frontiers in Chemistry* 10: 1013910. <https://doi.org/10.3389/fchem.2022.1013910> [PubMed] [PMC]
- Yu H, Li S, Niu H, Li Z, Gai Y, Sun B, Zhao L (2026) Precise atorvastatin delivery by cardiac homing peptide functionalized nanoliposomes for myocardial damage repair after myocardial infarction. *Nanomedicine (London)* 21(6): 789–801. <https://doi.org/10.1080/17435889.2026.2628309> [PubMed] [PMC]
- Yue R, Liu Y, Luo J, Huang Y, Li Y, Zhang Y, Wang K, Zhang Y, Rao C, Gou J, Hu H (2026) Macrophage pyroptosis suppression by membrane-coated nanoparticles ameliorates myocardial ischemia-reperfusion injury. *Chemical Engineering Journal* 537: 175926. <https://doi.org/10.1016/j.cej.2026.175926>
- Zhang B, Li J, Jiang J, Lin X, Sun X, Wang Q (2023) Overcoming delivery barriers for RNA therapeutics in the treatment of rheumatoid arthritis. *European Journal of Pharmaceutics and Biopharmaceutics* 192: 147–160. <https://doi.org/10.1016/j.ejpb.2023.10.010> [PubMed]
- Zhang X, Wang R, Li X, Song J, Wang Y, Chatterjee E, Li G, Jiang J, Yao J (2026) Cardiac targeting extracellular vesicles combined with quercetin co-delivery system enhances the therapeutic efficacy of myocardial infarction. *Biomaterials Advances* 185: 214880. <https://doi.org/10.1016/j.bioadv.2026.214880> [PubMed]
- Zhao X, Chen W, Wu J, Shen Y, Xu B, Chen Z, Sun Y (2025) Application of biomimetic cell membrane-coated nanocarriers in cardiovascular diseases. *International Journal of Nanomedicine* 20: 8249–8289. <https://doi.org/10.2147/IJN.S531558> [PubMed] [PMC]
- Zhou Y, Liang Q, Wu X, Duan S, Ge C, Ye H (2023) siRNA delivery against myocardial ischemia reperfusion injury mediated by reversibly camouflaged biomimetic nanocomplexes. *Advanced Materials* 35(23): e2210691. <https://doi.org/10.1002/adma.202210691> [PubMed]
- Zhu Y, Zheng H, Li H, Xue L, Cai H, Pei C (2026) Potential relationship between ferroptosis and pyroptosis in myocardial ischemia/reperfusion injury: molecular mechanisms and therapeutic targets. *Reviews in Cardiovascular Medicine* 27(7): 50196. <https://doi.org/10.31083/rcm50196> [PubMed] [PMC]
- Zwetsloot PP, Kouwenberg LHJA, Sena ES, Eding JE, den Ruijter HM, Sluijter JPG, Pasterkamp G, Doevendans PA, Hoefer IE, Chamuleau SAJ, van Hout GPJ, Jansen of Lorkers SJ (2017) Optimization of large animal MI models; a systematic analysis of control groups from preclinical studies. *Scientific Reports* 7(1): 14294. <https://doi.org/10.1038/s41598-017-14294-z> [PubMed] [PMC]

Author Contributions

- **Baihao Mei**, Master's Candidate in Nursing, Graduate Student, School of Nursing, Mudanjiang Medical University, Mudanjiang, China; e-mail: 3011891593@qq.com; **ORCID ID**: <https://orcid.org/0009-0002-9150-6703>. Conceptualization, methodology, formal analysis, investigation, data curation; writing – original draft, visualization, project administration.
- **Ying Li**, Master's Candidate in Nursing, Graduate Student, School of Nursing, Mudanjiang Medical University, Mudanjiang, China; e-mail: 18247983465@163.com; **ORCID ID**: <https://orcid.org/0009-0001-8410-7678>. Validation, resources, data curation, writing – review and editing, supervision (co-supervision).
- **Zhaoyu Gao**, Professor, School of Nursing, Mudanjiang Medical University, Mudanjiang, China; e-mail: gzy721031@163.com; **ORCID ID**: <https://orcid.org/0009-0009-3801-8592>. Conceptualization, supervision, funding acquisition, writing – review and editing, final approval of the version to be published.