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REVIEW

Nanomedicine for Cardiac Repair in Heart Failure: From Targeted Delivery to Regenerative Modulation

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Abstract: Heart failure is a progressive syndrome in which the heart fails to maintain adequate output and remains a leading cause of mortality and healthcare utilization despite guideline-directed pharmacological and device-based therapies. A major contributor to this residual burden is the limited myocardial specificity of conventional treatments, which act systemically and incompletely address the heterogeneous microenvironment of the failing ventricle. Nanomedicine employs nanoscale carriers to reshape pharmacokinetics, protect labile cargo, and enhance delivery to injured myocardium. Preclinical studies in predominantly heart failure with reduced ejection fraction (HFrEF) models, including post-myocardial infarction and pressure-overload injury, demonstrate that targeted nanoplatforms can improve left ventricular ejection fraction by approximately 5–15 percentage points, reduce infarct size by 20–50%, and attenuate fibrosis, inflammation, or cardiomyocyte apoptosis by 30–60% compared with control treatments. Spatially and temporally controlled delivery of small molecules, proteins, and nucleic acids is possible using organic and inorganic nanoparticles and catalytic systems, biomimetic and bioderived carriers, extracellular vesicles, and nanostructured hydrogels or patches, with some also providing mechanical support or theranostic imaging. There is limited evidence in heart failure with preserved ejection fraction (HFpEF). Early studies have focused on inflammation, fibrosis, and microvascular dysfunction rather than on contractile recovery. Importantly, the majority of nanomedicine strategies discussed remain at the preclinical stage, with clinical experience largely confined to early-phase safety and feasibility studies. This review summarizes information from in vitro systems, small- and large-animal models, and newly developed clinical studies, and critically examines translational issues such as toxicity, immunogenicity, scalability, and regulatory complexity. New approaches to cardiac regeneration, such as local delivery of pro-regenerative signals, are also supported by nanomedicine, which facilitates the delivery of pro-regenerative cues, such as regulatory RNAs and extracellular vesicles, to promote cardiomyocyte survival, angiogenesis, and limited myocardial tissue renewal.

Keywords: heart failure, nanomedicine, cardiac regeneration, nanoparticle drug delivery, extracellular vesicles, cardiac fibrosis

Introduction

Heart failure is a progressive clinical syndrome where the heart cannot sustain the production that can be able to meet the metabolic requirements of the body. Heart failure is an increasing burden on health care all over the world. Recent epidemiological studies suggest that over 64 million people in the world are living with heart failure, and the prevalence of heart failure is more than 10% among those aged above 70 years.[1–3] High-income countries have lifetime risk rates of between 20–25%, and low- and middle-income regions are fast growing due to ageing and the increase of cardiometabolic disease. Irrespective of treatment progress, symptomatic heart failure has a 5-year mortality of about 50%, and the syndrome consumes more than 1–2% of overall health care spending in most healthcare systems because of the frequency of readmission and the need for long-term care.[1,4–6] It has tens of millions of victims all over the world, and it causes significant mortality rates, high frequency of hospitalizations, and huge medical expenses. The prevalence increases sharply as age increases, and a good

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number of patients live with recurrent incidences of decompensation, low activity levels, and severe deterioration in the quality of life. Long term prognosis of symptomatic heart failure is poor in most areas despite the advancements made in terms of pharmacological treatment and device-based intervention.[7]

Conventional medical treatment of heart failure is aimed at systematic adjustment of neurohormonal processes and at the regulation of congestion. Antihypertensive drugs, which are renin-angiotensin-aldosterone system blockers, beta-adrenergic antagonists, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 blockers, lower hospitalization rates and improve survival among the selected patients. Implantable cardioverter defibrillators, cardiac resynchronization systems, and ventricular assist devices are other devices that reduce the chance of sudden death and facilitate the process of advanced disease. These measures have changed clinical practice, but lots of patients, still symptomatic, restructure their body and finally end up with end-stage heart failure or undergo heart transplantation.[8] Nanomedicine has already made significant progress in cancer and other inflammatory diseases, but its application to heart failure remains limited.[9] The non-viable myocardium contains a heterogeneous microenvironment characterized by microvascular rarefaction, dense fibrosis, prolonged inflammation, and dysfunctional lymphatic or interstitial clearance, which restricts the entry of nanoparticles into cardiac tissue. This is contrary to the tumors that often present as sustained vascular hyperpermeability.[9,10] These disease-specific features profoundly restrict nanoparticle accumulation, retention, and cellular uptake, leading many nanotechnologies that perform well in other organs to exhibit only modest myocardial delivery.[9,11] Consequently, this raises fundamental questions regarding appropriate disease-specific target selection, carrier design, and delivery strategy in heart failure.[9]

One important reason for this residual burden is that most current therapies act in a diffuse manner on the circulation and on systemic signalling, rather than acting directly on the injured myocardium. Orally and intravenously administered drugs distribute widely, and only a small fraction of the dose reaches the heart at any given time. In the failing ventricle, capillary rarefaction, altered endothelial function, increased interstitial fibrosis, and heterogeneous perfusion further limit penetration and retention of therapeutics. Attempts to increase the dose to overcome these barriers are constrained by side effects in other organs, including hypotension, renal dysfunction, and electrolyte disturbance.[12] At the same time, knowledge of the cellular and molecular mechanisms that underlie heart failure has expanded. It is now clear that adverse ventricular remodelling reflects a complex interaction between cardiomyocyte loss, mitochondrial dysfunction, ROS, immune cell activation, fibroblast-driven matrix deposition, and microvascular disturbance. These processes occur in specific regions of the ventricle and follow distinct temporal patterns after an insult such as myocardial infarction (the leading cause of death worldwide, accounting for more than 800 deaths daily) or persistent pressure overload. The spatial and temporal heterogeneity of these events suggests that more localised and mechanism-directed intervention could provide additional benefits beyond global neurohormonal blockade.[13,14]

Nanomedicine has increasingly demonstrated the ability to actively facilitate cardiac repair after myocardial injury. Recent multifunctional nanoparticle platforms enable targeted delivery to ischemic myocardium, regulate local micro-environments, and modulate cellular responses critical to repair. For example, nanoparticle-mediated strategies can deliver anti-oxidative, anti-inflammatory, and pro-angiogenic agents directly to infarct zones, reducing cardiomyocyte death and functional deterioration more effectively than untargeted agents alone.[7] Nanomedicine facilitates regenerative techniques beyond the healing of acute injuries by delivering gene treatments, growth factors, or microRNAs that support endogenous heart regeneration. Nanocarriers can overcome major challenges to regenerative treatment in adult hearts, which lack intrinsic proliferative ability, by protecting these delicate biological cargos from degradation, improving cellular absorption, and achieving regulated release.[15,16] Current perspectives demonstrate how cell-free nanotherapies, such as scaffolds and injectable nanocomposites that maintain tissue structure and attract reparative cells, might enhance myocardial regeneration.[17] In order to treat heart failure and its pathological causes, such as inflammation, oxidative stress, and remodeling, precision medication delivery is still important. Systems based on nanoparticles allow for both passive and active targeting to damaged myocardium, reducing off-target toxicity and managing pharmacokinetics. Designer nanoparticles with controlled release kinetics, cardiac-endothelial targeting, and stimuli-responsive behaviors that react to the local pathophysiological milieu are examples of recent developments.[18,19] Heart failure with preserved ejection fraction (HFpEF) accounts for approximately 50% of all heart failure cases and has a unique pathophysiology that includes systemic inflammation, microvascular dysfunction, diastolic stiffness, and comorbidity-driven structural

remodeling. However, a large portion of nanomedicine research in heart failure focuses on HFrEF, which is characterized by impaired systolic function and cardiomyocyte loss. Although HFpEF patients have a high rate of morbidity and a low quality of life, current treatments only slightly improve severe outcomes.[20] The need for nanomedicine approaches specific to HFpEF pathomechanisms, such as targeted anti-inflammatory delivery, endothelial modulation, and microvascular repair, is highlighted by this increasing clinical burden.

Nanomedicine has already made significant progress in cancer and other inflammatory diseases, but its application to heart failure remains limited. The non-viable myocardium contains a microenvironment that is heterogeneous and comprised of microvascular rarefaction, dense fibrosis, prolonged inflammation, and dysfunctional lymphatic or interstitial clearance that restricts the entry of nanoparticles into cardiac tissue. This is contrary to the tumors that are often presented as sustained vascular hyperpermeability. It first outlines key aspects of heart failure pathophysiology that create both barriers and targets for nanomedicine. It then discusses major classes of nanoplatforms relevant to cardiac disease and considers their use in drug delivery, repair and regeneration, and imaging-guided intervention. Evidence from preclinical and emerging clinical studies is summarized, and the safety, regulatory, and translational challenges that must be overcome for routine clinical adoption are explored.[21,22] This narrative review was developed, including studies related to preclinical (in vitro, small animal, or large animal) or early clinical investigations of nanomedicine-based platforms with therapeutic or theranostic relevance to cardiac injury, repair, regeneration, or heart failure. Particular emphasis was placed on studies reporting functional, structural, molecular, or imaging-based cardiac outcomes.

Pathophysiology of Heart Failure and Implications for Nanomedicine

Structural Remodelling and Regional Heterogeneity

Heart failure usually develops after a sustained insult such as myocardial infarction, chronic pressure overload, volume overload, or primary cardiomyopathy. The ventricle responds with a sequence of structural changes that are collectively described as remodelling. Chamber size increases, wall thickness and geometry alter, and the ventricle often becomes more spherical. These macroscopic changes increase wall stress and place a persistent load on surviving cardiomyocytes.[23] At the cellular level, cardiomyocytes are enlarged, misaligned, and exhibit disordered sarcomere organization and calcium regulation. These cells also increase the extracellular collagen matrix, and the balance between matrix synthesis and degradation favors accumulation. Fibrosis occurs in the interstitial space and vessel peri-infarction, and scar tissue that replaces the infarcted necrotic myocardium is dense. The final product is a patchwork of surviving myocardium, hibernating tissue, and fibrotic scar in the same ventricle.[24] In nanomedicine, such structural heterogeneity is both a challenge and an opportunity. It makes it more difficult to deliver drugs in the same way into the circulation and into the tissue, but also offers region-specific molecular and mechanical signatures that can be targeted. Activated fibroblasts and stressed cardiomyocytes, full of collagen-rich scar, express surface molecules and matrix components, which are not found in healthy myocardium. An example of such signatures that nanocarriers can carry is their ligand, which could accumulate preferentially in regions of remodeling.[25] An overview of nanoparticle applications in optical imaging, nuclear imaging, ultrasound imaging, and multimodal imaging to investigate the inflammatory microenvironment of cardiovascular injury is presented in Figure 1.[26]

Inflammation, Oxidative Stress and Cell Death

The main characteristic of the progression of acute cardiac injury to chronic heart failure is inflammation. The danger signals released by necrotic cells after myocardial infarction attract neutrophils and monocytes. Such cells are clearance cells that also release proteases, cytokines, and chemokines, thereby defining the local microenvironment. In simple healing, an inflammatory response is followed by a more reparative response, in which macrophages acquire repair-promoting phenotypes.[27] Inflammatory activity is also sustained in most patients. Chronic invasion of immune cells and continued cytokine synthesis contribute to the perpetual stress of myocytes, the disruption of the extracellular matrix, and functional deterioration. In non-ischaemic heart failure, systemic inflammatory stimuli from conditions such as obesity, diabetes, and chronic kidney disease further drive myocardial injury.[28]

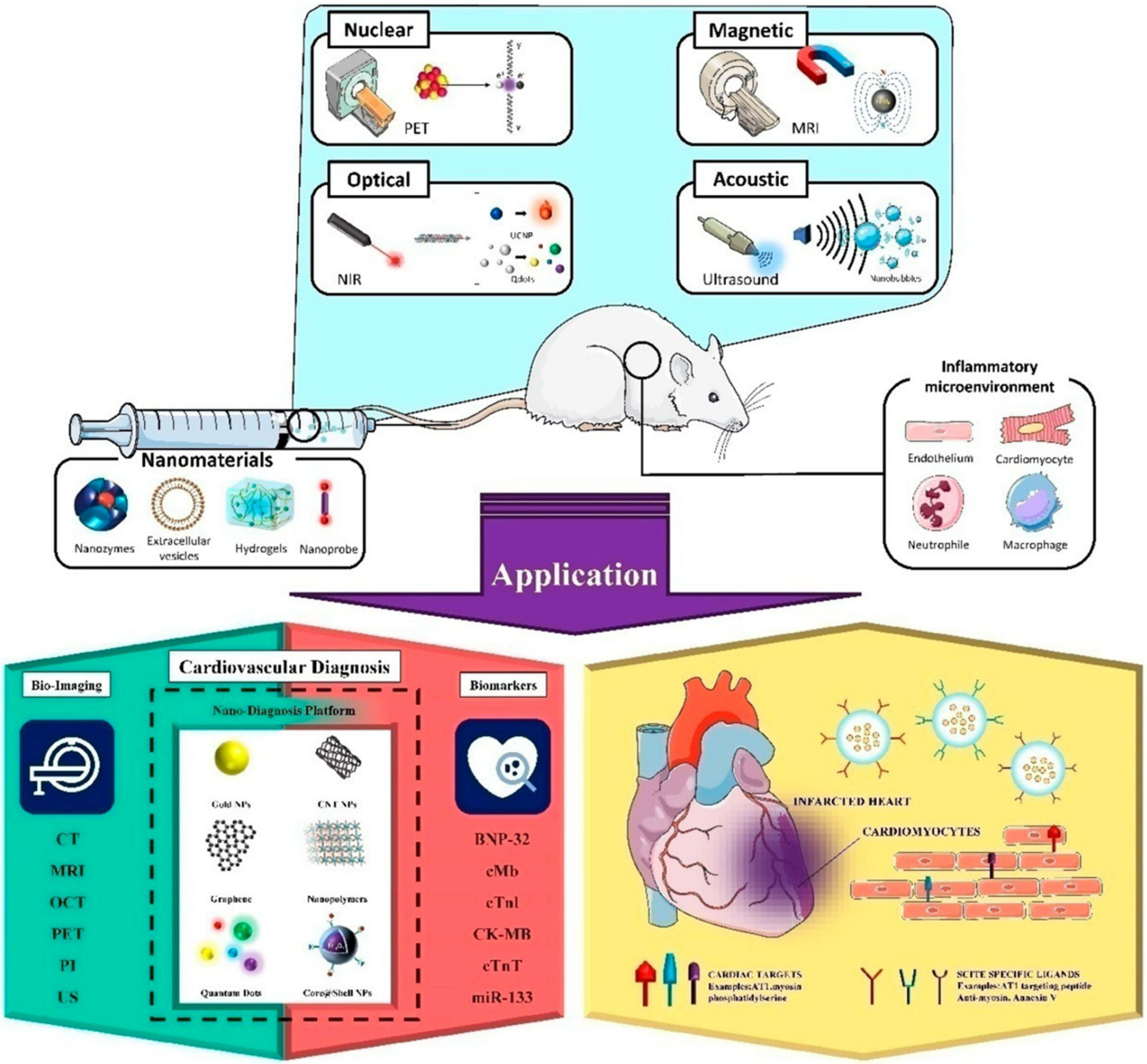

Figure 1 Application of nanotheranostics in the diagnosis and treatment of the myocardial inflammatory microenvironment.[26]

Oxidative stress intersects with these inflammatory pathways. Mitochondria and enzyme systems generate ROS that exceed the capacity of endogenous antioxidant defences. ROS damage proteins, lipids, and nucleic acids, impair mitochondrial function, and trigger cell death programmes. Apoptosis, necroptosis, pyroptosis, and other regulated forms of cell death have all been observed in the failing heart.[29] These processes present several attractive targets for nanomedicine. Particles that scavenge ROS, deliver antioxidants, or modulate mitochondrial function can be directed toward stressed cardiomyocytes. Nanocarriers loaded with anti-inflammatory agents, cytokine inhibitors, or nucleic acids that reprogrammed immune cells can act within inflamed regions while limiting systemic exposure. Systems that deliver regulators of cell death pathways offer the possibility of preserving endangered but still viable myocardium in the peri-infarct zone.[9] The persistent inflammation in heart failure is characterized by elevated circulating and myocardial inflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), C-reactive protein, and chemokines such as CCL2. These mediators continue to attract immune cells, stimulate fibroblasts, and promote cardiomyocyte failure. Maladaptive phenotypes of infiltrating macrophages maintain matrix

remodeling and oxidative stress. Using nanocarriers to target these inflammatory signals reduces systemic immunosuppression while enabling targeted immune regulation inside the myocardium.[26,30,31]

Microvascular Dysfunction and Extracellular Matrix Barriers

Heart failure is accompanied by changes in the coronary microcirculation. The density of capillaries can decrease, the endothelial cells can lose their normal production of nitric oxides and their responses to vasodilators, and the small vessels can have abnormal tone. Flow disturbance at a capillary level can also be caused by leukocyte adhesion, platelet activation, and microthrombi. These variations result in areas of relative hypoperfusion and hypoxia despite the presence of great epicardial vessels.[32] Concerning delivery, it means that a homogeneous vascular bed is not applied to nanocarriers and systemically administered drugs. Some of these territories are violently flooded, and some are underflowed. Traditional small-molecule therapy is not capable of reversing this trend, as higher dosages merely increase systemic concentrations without a selective correction of local deficits.[33] The extracellular matrix is also a barrier. In fibrotic tissue, there are tight interwoven bundles of collagen and other matrix proteins that are more cross-linked. Interstitial pressure can be increased, and lymphatic drainage can be affected. All these characteristics slow down diffusion and impede the diffusion of particles and macromolecules.[34] These barriers should therefore be taken into consideration when designing nanomedicine. The size, form, and surface chemistry of particles affect permeation across the microvascular wall and transit through the matrix. Particles that are extremely large or very strong adhesives might be stuck in the vessel, but those of extremely small size could be removed quickly. Surface alterations and targeting ligands may be selected to prefer attachment to specific structures in the microvasculature or the matrix, but excessive binding can result in obstruction. One of the design challenges in cardiac applications is achieving the correct balance.[35]

Systemic Barriers and Organ Interactions

Heart failure should be understood as a disorder that develops within a systemically compromised organism rather than as an isolated cardiac condition. Patients commonly exhibit concurrent renal dysfunction, hepatic congestion, pulmonary hypertension, and skeletal muscle wasting, each of which can substantially influence the biodistribution, biotransformation, and elimination of therapeutic agents and nanoscale delivery systems. The regular macrophage populations in the liver and spleen efficiently absorb the particles in the blood, and the kidneys help to eliminate low molecular weight substances and some of the products of degradation. Reduced organ perfusion, venous congestion, and prolonged neurohormonal activation break these pathways in heart failure by complex and interdependent processes.[36] In most nanomedicine platforms, not a large percentage of the dose that is delivered gets to the myocardium, and a significantly greater percentage is retained in the liver, spleen, and other peripheral organs. Whereas this distribution pattern may be tolerated in certain therapeutic settings, it turns out to be a significant limitation where the goal is to achieve selective cardiac repair. Simultaneously, the off-target effects on noncardiac tissues expose the risk of organ toxicity, which must be assessed stringently.[37] An accurate perception of these systemic obstacles is thus the key to rational design and effective clinical translation of cardiac nanotherapeutics. The surface alterations reducing the recognition of phagocytic cells can increase the time of circulation and thus make it more likely that the nanocarriers will survive the coronary vasculature. Membrane biomimetic-derived erythrocytes, platelets, or stem cell-derived membranes can also be improved to increase immune evasion and localize to vascular injury sites. In addition, localized delivery strategies, including intracoronary infusion, transendocardial injection, and epicardial patch-based administration, can circumvent several systemic constraints, although they introduce greater procedural complexity.[38]

Classes of Nanomedicine Platforms for Cardiac Therapy

The quadruple therapy of beta-blockers, mineralocorticoid receptor antagonists, angiotensin receptor neprilysin inhibitors (ARNI), and SGLT2 inhibitors is part of the standard guideline-directed medical therapy (GDMT) for heart failure. These medications significantly lower hospitalization and mortality across heart failure phenotypes and ejection fractions. The therapeutic significance of SGLT2 inhibitors as primary therapy is demonstrated by their recent addition to the list of approved drugs to include HFpEF.[39,40] Therefore, rather than replacing GDMT, nanomedicine should be considered as an additional, complementary component. Nanocarrier systems have the potential to improve therapy delivery or targeting (eg., enhancing cardiac absorption of ARNI or SGLT2 inhibitors), reduce off-target effects, and facilitate precision medicine approaches.[16]

However, it is uncertain that nanomedicine would quickly replace current therapies without synergistic integration due to lengthy research periods, inconsistent preclinical results, and strict safety regulations.[39,41]

Organic Nanocarriers

Organic nanocarriers are among the most mature tools in nanomedicine and include liposomes, polymeric nanoparticles, micelles, and dendrimers. They are built from lipids or polymers that are usually biocompatible and often biodegradable. They can be encapsulated with water-soluble and lipid-soluble drugs, or encapsulate peptides, proteins, and nucleic acids because of their internal structure.[42] The liposomes are made of one or several bilayers of phospholipids and an aqueous core. They are capable of transporting hydrophilic and hydrophobic agents in the core and in the membrane, respectively. The amphiphilic polymers self-assemble into polymeric nanoparticles and micelles in water to create a hydrophobic interior and an exterior that is hydrophilic. Dendrimers are very branched macromolecules that have terminal groups to which drugs or targeting ligands can be conjugated.[18] These carriers can be designed with dimensions large enough to restrict renal clearance, but small enough to allow the carriers to pass through the coronary microvasculature in the case of heart failure. Their surface properties, such as electrical charge and hydrophilicity, can be carefully modulated, along with reducing macrophage-mediated uptake and increasing residence time in the circulation. Moreover, ligands that bind receptors or components of the extracellular matrix that are concentrated in injured myocardium can be targeted to the carrier surface. Organic nanocarriers can be designed to increase the concentration of drugs in the failing ventricle and decrease the exposure of drugs to the whole system through these design features.[43]

Inorganic Nanoparticles and Catalytic Systems

The lack of biodegradability of inorganic nanoparticles, such as metallic, silica, and carbon-based systems, is a significant barrier to clinical translation and regulatory approval. Their retention in tissues can be persistent and, therefore, can result in retention, result in the clearance being ineffective, and causes chronic toxicity. Comparatively, more advanced therapeutic nanoparticles, such as lipid-based nanoparticles, polymeric micelles, biodegradable formulations of poly-lactic-glycol-acrylate (PLGA), and PEGylated systems have a superior safety and regulatory profile because of the fact that they are more readily broken down into biocompatible products. Biodegradable nanocarriers have traditionally been more accepted by regulatory bodies, such as the FDA and EMA, since their pharmacokinetic properties and clearance routes are more predictable. The continuous deposition of nonbiodegradable substances, including iron oxide, in cardiac tissue or the reticuloendothelial system could lead to the promotion of oxidative stress, iron homeostasis, and maintenance of chronic inflammatory reactions. These issues are significant hindrances in the cardiovascular use of such materials.[44–46] However, the inorganic nanoparticles have functional qualities that cannot be easily imitated by organic carriers. Gold, silica, iron oxide, manganese, and other related metals or metal oxides on platforms have high structural stability, highly defined morphology, and specific optical or magnetic characteristics. In some cases, these materials also demonstrate enzyme-like catalytic activity toward reactive oxygen species and are therefore classified as nanozymes.[47]

Gold nanoparticles can be synthesised with precise control over size and surface chemistry. They are readily functionalised with thiol-containing ligands, peptides, and polymers. In cardiac research, they have been explored as drug carriers, as components of conductive cardiac patches, and as contrast enhancers for imaging. Iron oxide particles are detectable by magnetic resonance and can be guided or concentrated by external magnetic fields. Manganese and other catalytic particles can decompose reactive oxygen and nitrogen species, which are abundant in ischemia-reperfusion injury and in chronic heart failure.[48] These features make inorganic systems attractive for combined diagnostic and therapeutic purposes. However, many inorganic cores are not fully degradable, and long-term accumulation in the liver, spleen, or other organs is a concern. Before the possible long-term use in heart failure patients, careful selection of materials, dose control, and complete safety assessment are necessary.[49,50]

Biomimetic and Bioderived Carriers

Nanocarriers based on biomimetic and bioderived materials aim at taking advantage of natural cell communication and tissue homing pathways. This category includes extracellular vesicles, exosomes, viral vectors such as adeno-associated viruses, and synthetic nanoparticles with or without cell membrane coating.[51]

The extracellular vesicles of mesenchymal stromal cells, cardiac progenitor cells, and cardiomyocytes generated by induced pluripotent stem cells have a wide repertoire of proteins, lipids, and RNA species that can regulate cell survival, inflammatory reactions, and angiogenesis. These vesicles are endogenous nanocarriers after isolation and concentration. Their therapeutic value can be further extended with the usage of the chosen nucleic acids or pharmacological compounds, and by surface modification approaches aimed at enhancing myocardial targeting.[52] Viral vectors are very effective vehicles of gene delivery, the capsid composition of which defines cell specificity. Already under clinical investigation, engineered adeno-associated virus variants with enhanced cardiomyocyte tropism are being studied for cardiomyopathies and inherited cardiomyopathies. Nanoparticles covered with cell membranes consist of a synthetic core as well as an outer coating based on platelets, red blood cells, or stem cells. This membrane cloak can also contain natural proteins that prevent immune recognition and can home to sites of vascular injury or inflammation.[53] The regenerative and gene-based treatments of heart failure are particularly attractive to these bioderived strategies, but those also raise such issues as large-scale production, batch-to-batch consistency, and immunogenicity, which, however, remain to be dealt with before such methods can be applied on a large scale in clinics. Representative nanomedicine platforms that have been explored for myocardial ischemia, ischemia reperfusion injury, and myocarditis are summarized in Figure 2.[26]

Stimuli Responsive and Theranostic Platforms

A defining advantage of nanoscale design is the ability to create systems that respond to cues in the disease microenvironment. Stimuli-responsive platforms incorporate components that change conformation or degrade when they encounter specific conditions such as acidic pH, high concentrations of ROS, or elevated activity of proteases.[54] In heart failure, injured and remodelling myocardium often displays lower pH, higher oxidative stress, and increased expression of matrix metalloproteinases and other enzymes compared with healthy tissue. Nanocarriers can be constructed with

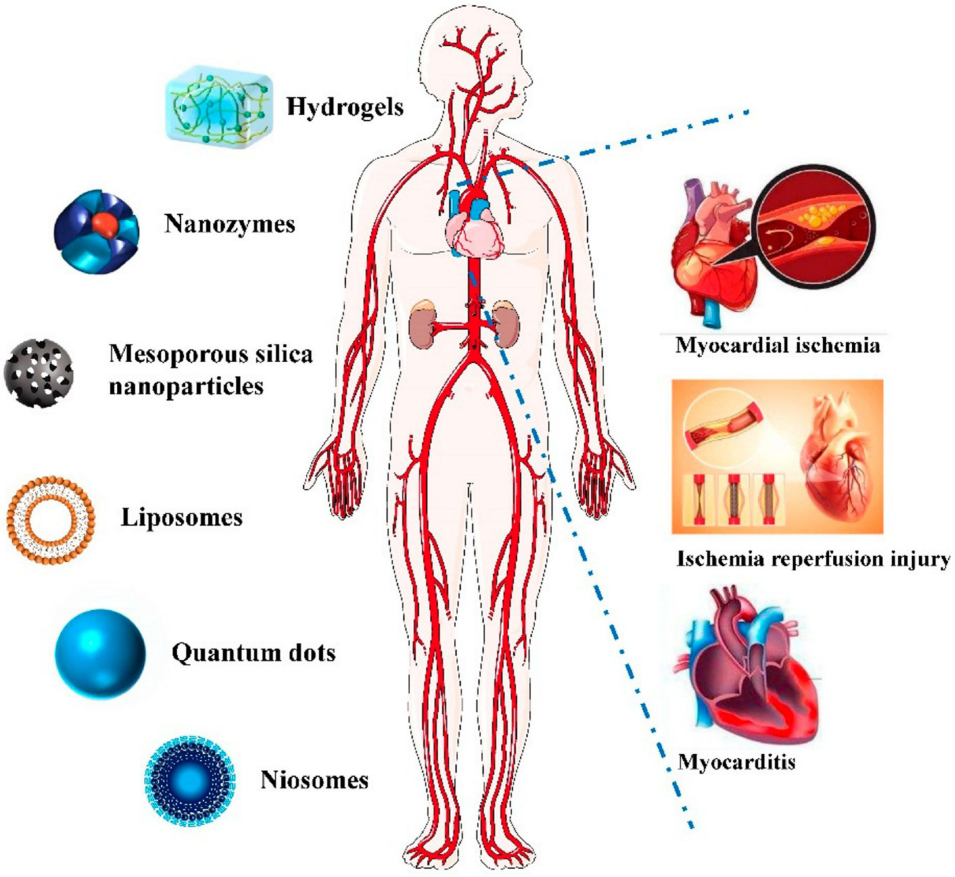

Figure 2 Application of Nano-theranostics for myocardial injury.[26]

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linkers that are cleaved by these enzymes or with polymers that are sensitive to local pH or redox state. Consequently, the payload is released in favour of diseased areas and is relatively safe elsewhere.[55] Theranostic platforms go further by integrating diagnostic and therapeutic functions within a single system. A single particle can be designed to incorporate both an imaging probe for magnetic resonance imaging, computed tomography, or nuclear imaging and a therapeutic payload such as a drug or gene. This integrated approach enables visualization of particle accumulation and, by inference, the localization of the therapeutic cargo. In heart failure, such multifunctional platforms may facilitate patient stratification, optimization of dosing strategies, and early evaluation of therapeutic response, because the same formulation simultaneously provides information regarding both biodistribution and biological effect.[56]

Nanostructured Scaffolds and Cardiac Patches

A distinct subdivision of nanomedicine is nanostructured scaffolds and cardiac patches, the primary action of which is not through the systemic circulation but biomechanical support and control of the microenvironment of the local tissues. Their therapeutic application can be attributed to the nanoscale structural features that govern the cell adhesion, electrical connections, and controlled release of bioactive factors into the myocardium.[57] Hydrogels are injectable natural or synthetic hydrogel polymers that may be injected by a catheter into the infarct border zone and hardened, causing thickening of the wall. They can contain nanoparticles, growth factors, or cells that can be released into the adjacent tissues on a slow basis. Overlaid wounds can be seeded with cardiomyocytes or progenitor cells on nanofibrous scaffolds, electrospun or made by similar lead-free techniques, and electrospun onto the epicardial surface. The combination of conductive nanostructures with this arrangement of fibers is helpful to recapitulate the anisotropic structure and electrical activity of native myocardium.[58] These readings address the mechanical nature of heart failure and the biological nature of heart failure. They are able to alleviate the burden on the walls, alleviate the ventricular egression, create a positive environment to live in, and incorporate the functional activities of the cell. At the same time, they require invasive delivery; their long-term operations and interactions with host tissue should be taken into account.[59] Combining all these nanomedicine platforms creates a multimodal therapeutic platform that can address the complex pathophysiology of heart failure. Organic carriers, inorganic nanoparticles, biomimetic systems, stimuli-responsive constructs, and nanostructured scaffolds can be combined or adapted to support targeted drug delivery, regenerative strategies, and imaging-guided therapy in a way that conventional formulations cannot easily match.[60]

Systems for stimuli-responsive nanomedicine have been developed to take advantage of the biochemical environment of the failing heart. While matrix metalloproteinase-sensitive carriers break down preferentially in fibrotic or remodeling tissue, ROS-responsive nanoparticles selectively release antioxidants in oxidative microenvironments. Drug release in the ischemic myocardium, where acidosis is common, is made possible by pH-responsive polymers. These methods decrease the exposure of healthy tissue and improve the spatial accuracy of treatment.[26,54,55]

Illustrative Case Studies: Successes and Limitations

Although several nanomedicine platforms have been suggested for cardiac treatment, only a small number have consistently shown functional efficacy beyond proof-of-concept delivery in preclinical models.[61] For instance, by reducing mitochondrial oxidative stress, myocardium-targeted polymeric micelles carrying antioxidant payloads have demonstrated promise in reducing infarct size and maintaining ejection fraction in acute ischemia–reperfusion injury. However, in chronic heart failure, options where fibrosis and microvascular dysfunction limit penetration and durable functional recovery, their therapeutic efficacy frequently declines.[62,63] Batch-to-batch variability and limited scalability remain major obstacles to clinical translation. By comparison, extracellular vesicle-based systems derived from mesenchymal stromal cells have shown reproducible improvements in capillary density, resolution of inflammation, and ventricular performance across a range of preclinical models. At least to some degree, such effects are attributed to the natural membrane composition, which is biased towards cellular uptake and immunocompatibility.[64,65] The other example representative is the inorganic nanozymes having reactive oxygen species scavenging ability, such as cerium oxide and manganese-based nanozymes. These systems are capable of reducing the oxidative damage of acute ischemic conditions, but their use in chronic therapy is limited by the issue of long-term retention of the compounds in tissue and their safety.[66,67] Taken together, these illustrations suggest that therapeutic efficacy in cardiac nanomedicine is not primarily determined by the novelty of materials but rather by the level to which the platform properties are aligned to particular pathophysiological goals.[61,64]

Nanomedicine Mediated Drug Delivery in Heart Failure

Rationale and Effects on Pharmacokinetics

The conventional medicines used to treat heart failure are administered orally or by injection and then circulate through the body. Only a small fraction of the dose delivered to the diseased myocardium reaches the target at any given moment, and this fraction decreases with microvascular dysfunction and fibrosis. Hypotension, renal failure, or electrolyte disturbances are among the systemic side effects that may constrain dose increases. This has resulted in a very high number of agents being given dosage levels that are not governed by tissue-level requirements but rather by tolerability.[68] Nanomedicine-mediated delivery aims to redefine this state of affairs. The absorption, distribution, and clearance can be controlled by putting a therapeutic agent in a carrier whose size and surface characteristics are controllable. Encapsulation prevents the removal of labile molecules by enzymes, enhances the solubility of those drugs that cannot be dissolved in water, and enables prolonged release of the carrier. Macrophage recognition in the liver and spleen can be evaded by surface coating to extend circulation time and increase the likelihood that carriers traverse the coronary circulation. In preclinical models, such formulations often produce higher drug exposure in the heart and lower exposure in off-target organs when compared with free drug at the same nominal dose.[69]

Targeted Delivery to Injured and Remodelling Myocardium

A central advantage of nanomedicine is the ability to deliver drugs and other therapeutic agents with precision. Injured and remodelling myocardium expresses molecules that are scarce in healthy tissue, including endothelial adhesion molecules, integrins on angiogenic vessels, receptors on activated fibroblasts, and exposed matrix proteins such as collagen fragments. Nanocarriers can be decorated with ligands that recognize these structures, which increases retention in diseased areas.[70] Short peptides that bind to integrins on sprouting endothelium, antibodies or fragments that recognize neoepitopes in the infarct border zone, and small molecules with affinity for collagen can all be used as targeting moieties. At least when attached to the vesicles of liposome surfaces, polymeric particles or extracellular vesicles, they facilitate selective accumulation in areas where remodelling occurs. This specifically applies during the initial stages following myocardial infarction, when there is a temporary increase in vascular permeability and passive pressure of blood into tissue.[71] Active targeting is also appealing in the case of chronic heart failure, where patchy fibrosis and microvascular dysfunction make it difficult to deliver drugs uniformly. In that regard, ligand selectivity assists in focusing anti-inflammatory, anti-fibrotic, or anti-apoptotic agents in those areas that cause the greatest amount of progressive loss of functionality, but not in the comparatively intact myocardium and other organs.[72]

Delivery of Nucleic Acids and Gene Based Therapies

Many pathways that drive heart failure are regulated at the level of gene expression. Changes in transcription, post-transcriptional control by microRNAs, and epigenetic marks alter the expression of contractile proteins, calcium-handling components, metabolic enzymes, and cell-cycle regulators. Alteration of these pathways directly would need the safe and efficient transfer of nucleic acids or gene editing systems to heart cells.[73]

There are several paths that nanomedicine offers to create. The most effective method of delivering genes to cardiomyocytes remains the subject of viral vectors, such as adeno-associated virus. It can be considered an example of a natural nanocarrier, the capsid proteins of which determine tropism. Capsid engineering and peptide display have resulted in better cardiac selectivity versions following systemic administration. But the issue of immunogenicity, complexity of manufacture, and long-term control prompts simultaneous development of non-viral systems[74] Plasmid DNA, messenger RNA, small interfering RNA, or microRNA mimics can be encapsulated by polymeric nanoparticles, lipid-based carriers, or engineered extracellular vesicles. Ligands that prefer uptake by cardiomyocytes, endothelial cells, or fibroblasts can be modified onto their surfaces. After internalization, pH-sensitive or enzyme-sensitive elements activate the release of the nucleic acids into the cytosol, and other properties can be used to facilitate entry into the nucleus. Experimental models have been utilized to improve pro-survival and pro-angiogenic factor expression, silence pro-apoptotic and pro-fibrotic genes, and to tune microRNA networks that regulate regeneration when these carriers are used.[75] Nanomedicine strategies have enabled targeted delivery of multiple RNA modalities, including messenger RNA (mRNA) encoding cardioprotective proteins, small

interfering RNA (siRNA) to silence pro-apoptotic or pro-fibrotic genes, and microRNA mimics or inhibitors that regulate networks governing hypertrophy, angiogenesis, and inflammation. Lipid nanoparticles and polymeric carriers protect RNA from degradation, facilitate cellular uptake, and promote endosomal escape, while surface ligands enhance targeting to cardiomyocytes, fibroblasts, or endothelial cells.[73,74]

Local and Procedure Assisted Delivery Strategies

Though systemic administration is convenient, it is not the only method of nanomedicine in heart failure. Local and procedure-assisted delivery techniques may position in or close to the myocardium, thus minimizing dilution in the general circulation. These techniques are intracoronary infusion during catheterization, transendocardial injection using mapping-guided catheters, and epicardial gel/patch application in surgery.[76] Infusion into the coronary artery subjects the microvasculature of the heart to a short-term, large number of carriers. During the infusion, the flow and pressure can be manipulated to increase the deposition in the downstream tissue. The pathway is the best suited for the application of vectors as gene therapies and carrier systems within the peri-infarct region upon reperfusion. Transendocardial injections are direct injections of suspensions or hydrogel into the ventricular wall images. The approach may be applied to specifically treat the border zone or hibernating areas of the myocardium with defective contractility and maintain its viability.[23] During open or minimally invasive surgical operations, epicardial patches and spray-based preparations are typically administered. These platforms may incorporate nanoparticles, growth factors, or cells within biodegradable matrices. Such constructs create a localized reservoir that supports sustained release into the underlying tissue and may also provide mechanical reinforcement in regions of pronounced wall thinning. Although invasive, these strategies are particularly attractive in patients already undergoing interventions such as coronary artery bypass grafting or valve surgery.[77]

Combination Therapies and Theranostic Drug Delivery

The combination of many pathways results in heart failure, and thus, the interventions aimed at one of the targets may not be enough at the advanced stage of the disease. Platforms of nanomedicine are naturally susceptible to combination therapy, where multiple agents are co-delivered in a predetermined proportion. A single carrier can co-encapsulate an antioxidant and an anti-apoptotic drug, or an anti-inflammatory agent and a pro-angiogenic growth factor. Release profiles can be tuned so that one component acts quickly to stabilize acutely injured myocardium, while another is released over days or weeks to support longer-term remodelling.[78]

Nanomedicine platforms are especially well-suited for combination treatment in heart failure, because they allow for the co-delivery of drugs that target complementary pathways, including oxidative stress, inflammation, angiogenesis, and fibrosis. Both acute damage and long-term remodeling processes can be addressed by controlled release kinetics, which enable sequential or prolonged exposure. The overview of delivery routes for cardiovascular nanomedicine is shown in Figure 3.[79] Compared to passive delivery methods, nanocarriers functionalized with cardiac endothelium targeting peptides (such as CRPPR) greatly increase localized drug accumulation in damaged myocardium. When compared to traditional methods, stimuli-responsive nanoparticles that release payloads during ischemia exhibit better retention and therapeutic indices.[18] Nanoparticle systems have been shown to deliver anti-inflammatory agents to neutrophils and macrophages, reducing excessive inflammation and improving myocardial recovery more effectively than systemic administration of the same agents.[19]

Nanomedicine for Cardiac Repair and Regeneration

Concepts of Repair and Regeneration in the Failing Heart

After a myocardial infarction or other major injury, the adult human heart has a very limited ability to regenerate lost muscle. The necrotic cardiomyocytes are mostly substituted with fibrotic scar, which maintains the ventricular wall stable, but does not aid in contraction. The remaining cardiomyocytes hypertrophy, change their metabolism, and fibroblasts and immune cells rebuild the extracellular matrix. This repair process is critical to short-term survival, but it tends to escalate into chronic deleterious remodelling of the chamber with dilatation and deteriorating pump performance.[80] The real regeneration would entail functional myocardium regeneration with the help of cardiomyocyte proliferation, progenitor cell recruitment, or reprogrammed non-myocytes. The animal models show that such regenerative responses can be achieved under certain

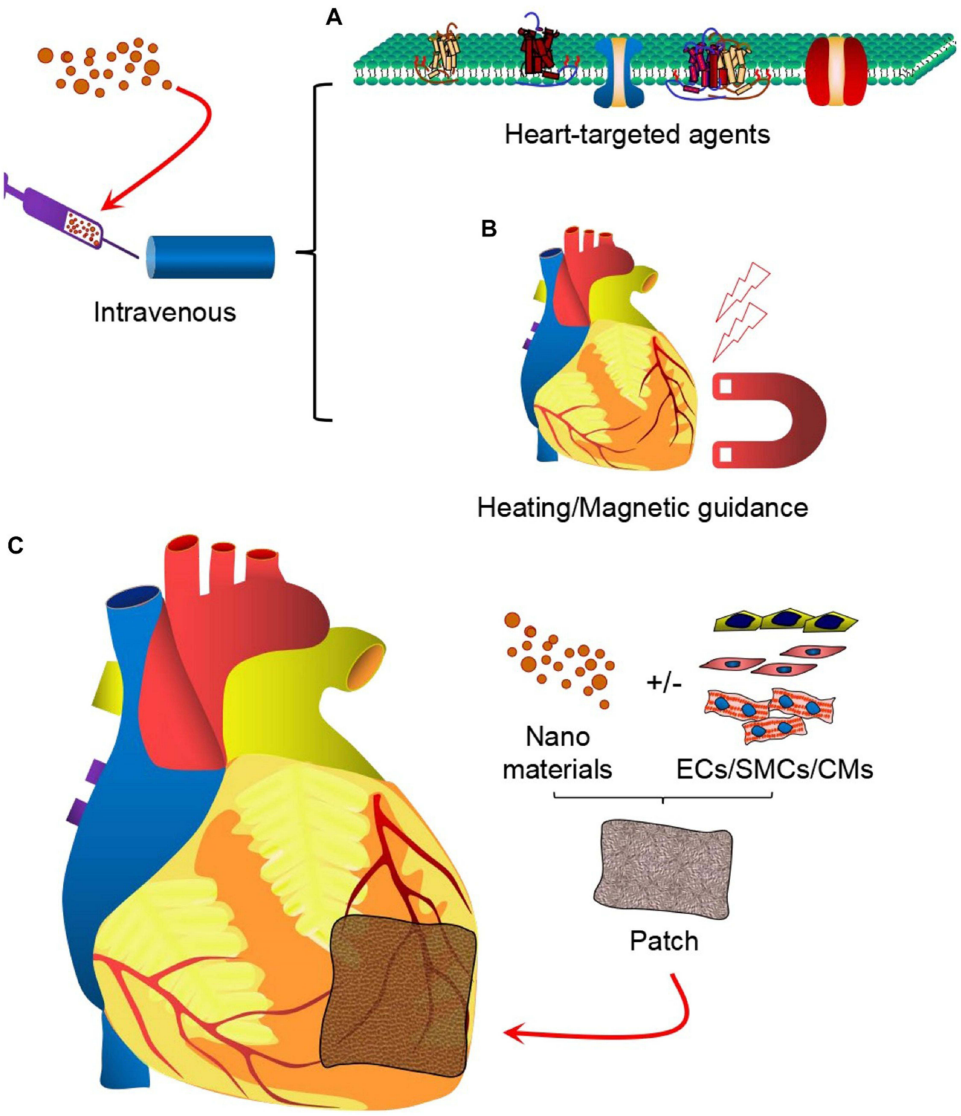

Figure 3 Overview of delivery routes for cardiovascular nanomedicine. (**A**) Intravenous administration of heart targeted agents. (**B**) Use of external heating or magnetic guidance to concentrate nano systems in the heart. (**C**) Application of an epicardial patch that combines nanomaterials with endothelial cells, smooth muscle cells and cardiomyocytes for local cardiac repair.[79]

conditions, but they are poor in adult human beings. The primary realistic therapeutic objective is thus to preserve endangered myocardium, enhance the quality of scar formation, facilitate neovascularization, and enhance constrained regenerative activity when feasible.[81] Nanomedicine helps with these objectives in two major ways. First, it facilitates the delivery of cargo that determines survival, inflammation, angiogenesis, and matrix turnover to the injured areas more specifically than systemic drugs. Second, nanostructured scaffolds like hydrogel and patches are able to offer mechanical stability and local microenvironmental conditions that favour cell survival and integration.[82]

Recent studies highlight mechanisms by which nanocarriers support regenerative biology. For example, nanoparticles transporting miRNA or growth factors demonstrate enhanced cardiomyocyte proliferation signals both in vitro and in vivo, overcoming delivery barriers that have hindered conventional regenerative therapies.[16] Cell-free nanotherapies using injectable nanocomposites provide structural scaffolding that supports endogenous cell recruitment and extracellular matrix remodeling, promoting regeneration after myocardial infarction.[17] Nanomaterial-enhanced biomimetic scaffolds allow controlled growth factor presentation, correlating with improved tissue regeneration in preclinical ischemic cardiomyopathy models.[83]

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Cell Free Nanomedicine Based on Paracrine Signalling

Many of the benefits observed in early cell therapy experiments for cardiac disease are now thought to arise from paracrine signalling rather than long-term engraftment of transplanted cells. Mesenchymal stromal cells, cardiac progenitor cells, and induced pluripotent stem cell-derived cardiomyocytes release extracellular vesicles that contain proteins, lipids, and regulatory RNAs. These vesicles influence apoptosis, inflammation, angiogenesis, and metabolism in recipient cells.[84] Cell-free nanomedicine builds on this concept by isolating and using these vesicles directly, or by engineering synthetic carriers that mimic their behaviour. Extracellular vesicles can be collected from conditioned culture medium, purified, and concentrated. When administered systemically or locally in models of myocardial infarction, they reduce cardiomyocyte apoptosis, enhance capillary density, and improve ventricular function. Their natural membrane composition confers intrinsic biocompatibility and supports uptake by cardiac cells.[7] Engineered vesicles take this strategy further. Specific microRNA mimics or small interfering RNA sequences can be loaded into exosomes or lipid-based particles to modulate defined molecular pathways. Surface modification with peptides that recognize injured myocardium, or inflamed endothelium, enhances targeting. In this way, paracrine factors and nucleic acids that promote survival and angiogenesis or suppress excessive inflammation can be delivered with higher concentration at the site of injury and lower systemic exposure.[85] This cell-free approach avoids many of the logistical and safety challenges associated with transplanting living cells. There is no risk of unwanted differentiation or uncontrolled proliferation, and storage and handling are closer to those of biologic drugs. However, large-scale production, standardization of vesicle content, and long-term safety still require careful study before routine clinical use.[86]

Nanomedicine Assisted Cell and Tissue Engineering Strategies

Cell-based strategies remain attractive for cardiac repair, particularly for large or transmural infarcts where native myocardium is severely depleted. Transplantation of mesenchymal stromal cells, cardiac progenitor cells, and induced pluripotent stem cell-derived cardiomyocytes has been tested in several animal models and early clinical trials. A recurring challenge is that most transplanted cells are lost within hours or days due to mechanical washout, ischemic stress, and immune responses.[87]

Nanomedicine offers tools to improve the retention and survival of transplanted cells. One approach is to encapsulate cells in microscale or nanoscale protective shells made from alginate or related polymers. The shells permit the diffusion of nutrients or signalling molecules but protect cells against mechanical deformation and immune attack. Encapsulated cells are more persistent in the infarct border zone and yield more benefit in terms of functionality when compared to unprotected cells in models of myocardial infarction.[88] The other method is to pretreat cells with nanoparticle-based agents before transplantation. Cells in culture can absorb nanocarriers into which anti-apoptotic molecules, antioxidants, or microRNA modulators have been loaded. Post-transplantation, such pretreated cells are better able to withstand oxidative stress, as well as produce increased amounts of beneficial paracrine factors.[89] Tissue engineering provides a structural aspect. Contractile patches can be seeded using nanofibrous scaffolds prepared using degradable polymers and cardiomyocytes and other support cells. The nanoscaled geometry of such scaffolds, such as fibre orientation and surface chemistry, directs cell orientation and formation of functional syncytia. Electrical coupling of cells with the scaffold is enhanced by the incorporation of conductive nanoparticles, including gold or carbon-based structures, into the scaffold, and can facilitate contraction synchronization with the host myocardium after implantation.[90] In situ forming injections of hydrogels will provide a less invasive option. These materials can be loaded with cells, growth factors, or vesicles and injected into the infarct border zone through catheters. As the gel sets, it thickens the wall, reduces local stress, and serves as a depot for the gradual release of bioactive cargo.[91]

According to recent research, electrically conductive nanomaterials (such as carbon nanotubes, graphene, and gold nanostructures) in cardiac scaffolds should be used with precaution because of the possibility of arrhythmogenic hazards resulting from abnormal conduction coupling or heterogeneous electrical integration with the host myocardium. Uncontrolled electrical coupling across scaffold surfaces may interfere with natural conduction routes, raising the possibility of ectopic automaticity, conduction block, or re-entrant arrhythmias. Preclinical evaluations therefore recommend rigorous electrophysiological characterization (eg., action potential mapping, conduction velocity measurements) in vitro and in vivo before clinical translation.[92,93] Representative functional nanomaterials that have been evaluated for myocardial repair by modulation of the inflammatory microenvironment are summarized in Table 1.

Table 1 The Application of Functionalized Nanomaterials in Myocardial Repair

Nanocarrier	Size	Effective Constituent	Cargo Loading	Model	Type of Disease	Clinical Outcomes (Very Concise)	Reference
Nanofibrous gelling microspheres (NF-GMS)	60–90 μm	Human embryonic stem cell-derived cardiomyocytes (hESC-CMs)	Coincubation	Myocardial infarction rat model	Myocardial infarction	Enhanced CM engraftment, reduced infarct size, and improved cardiac function.	[94]
Triazole (TMTD–alginate) capsules	1.5 mm	Mesenchymal stem cells (MSCs)	Coincubation	Post-MI rat model	Acute myocardial infarction	Improved ventricular function and limited adverse remodeling after MI.	[95]
Recombinant human ferritin nanocage (FTn)	12 nm	Manganese (Mn) within nanocage	In situ synthesis	Cardiac ischemia–reperfusion mouse model	Cardiac ischemia–reperfusion	Reduced mitochondrial oxidative injury and supported heart function recovery.	[96]
NOS-like nanoplatform (NanoNOS)	130 ± 2.3 nm	Noble metal nanostructure	Modified seed-mediated method	HUVEC and THP-1 cell systems	Cardiovascular injury models	Raised NO levels and reduced monocyte–endothelial adhesion, protecting vessels.	[97]
CM-derived CD172a$^+$ extracellular vesicles (EVs)	0.1–0.5 μm	CM-derived CD172a$^+$ EVs	–	Hypoxic hiPSC-derived CMs	Cardiovascular diseases	Served as potential biomarkers for myocardial disease, especially aortic stenosis.	[98]
Cardiac progenitor cell-derived exosomes (CPC-Exo)	30–100 nm	CPC-derived exosomes	–	Viral myocarditis rat model	Viral myocarditis	Decreased cardiomyocyte apoptosis and improved function in viral myocarditis.	[99]
Primary CM-conjugated, 17β-estradiol-loaded PFP nanoprobes (PCM-E2 /PFPs)	418 ± 11 nm	Primary CMs and 17β-estradiol	Click chemistry	Cardiac hypertrophy rat model	Cardiac hypertrophy	Enabled targeted estradiol delivery and ultrasound imaging in hypertrophic hearts.	[100]
Lanthanide MOF nanoprobes (Eu–QPTCA)	150–250 nm	Europium-based MOF	Solution reaction	Human serum samples	Acute myocardial infarction (diagnosis)	Detected creatine kinase with high selectivity for early MI diagnosis.	[101]

Modulation of Inflammation, Angiogenesis and Fibrosis

The quality of cardiac repair depends strongly on the balance between inflammation, formation of new vessels, and deposition of extracellular matrix. Excessive or prolonged inflammation leads to further myocyte loss and disorganized scar, while inadequate inflammation prevents proper clearance of debris and can predispose to mechanical complications. Similarly, limited angiogenesis leaves surviving myocardium in a state of chronic hypoxia, and excessive fibrosis stiffens the ventricle and impairs both contraction and relaxation.[102] Nanomedicine enables more nuanced control of these processes. Targeted nanoparticles that are preferentially taken up by pro-inflammatory macrophages can deliver agents that reprogram them toward reparative phenotypes. Such agents include small-molecule inhibitors of inflammatory kinases, glucocorticoids at low local doses, and nucleic acids that modulate key transcription factors and microRNAs. These interventions can be limited to areas of inflammation in the heart, which can consequently reduce harmful levels of inflammation, but do not generally suppress systemic immunity. Another area with specific benefits of nanoscale delivery is the promotion of angiogenesis. Growth factors such as vascular endothelial growth factor and fibroblast growth factor can stimulate new vessel formation but are rapidly cleared when given in free form and may cause unwanted vascular effects in other tissues. Encapsulation in nanoparticles or incorporation into hydrogels prolongs their presence in the myocardium and enables controlled release. Co-delivery of pro-angiogenic factors with agents that protect endothelial cells from oxidative stress may further enhance the formation of stable and functional micro vessels.[103]

Fibrosis is both a necessary component of repair and a major contributor to chronic dysfunction. Nanocarriers that bind to activated fibroblasts or to specific matrix components can deliver agents that temper pro-fibrotic signalling pathways, such as inhibitors of transforming growth factor beta or modulators of renin-angiotensin-aldosterone signalling. In parallel, some scaffolds release matrix metalloproteinase inhibitors or modulators in a controlled fashion to adjust the balance between matrix deposition and degradation. It is not aimed at total inhibition of the formation of scar but at the establishment of an organized, mechanically competent scar, which is not excessively expanding or intrusive of viable myocardium.[104] The repair and regeneration plans demonstrate how nanomedicine can intervene in the healing process at multiple stages. Nanoscale systems represent an approach to translating the knowledge of post-infarction biology into targeted interventions that can limit the development of chronic heart failure and enhance the performance of existing disease management by acting on paracrine pathways, enhancing cell- and tissue-based therapies, and modulating inflammation, angiogenesis, and fibrosis.[105]

Theranostic and Imaging Guided Nanomedicine in Heart Failure

Role of Imaging in Cardiac Nanomedicine

Spatial heterogeneity is detected in heart failure. Hibernating tissue, viable myocardium, and dense scar coexist within the same ventricle, and across regions, microvascular dysfunction and inflammation are present. Traditional systemic biomarkers provide limited spatial data, whereas contemporary cardiac imaging can visualize anatomy, perfusion, viability, and fibrosis at the finest resolution. In conjunction with nanomedicine, imaging may go beyond diagnosis to direct delivery, track distribution, and determine treatment response in vivo.[106] Theranostic nanomedicine combines therapy and diagnosis. In this paradigm, a single nanoparticle or scaffold carries both a therapeutic payload and an imaging label. The imaging label is capable of tracing the path the carrier moves and gathering and correlating this pattern with alterations in the structure and functioning of regions. In heart failure, where each patient's response to treatment varies in many ways, this integration provides a path towards more adaptive and individualized therapy.[107]

Nano Enabled Contrast Agents and Molecular Imaging

Several nanomedicine platforms have been designed as contrast agents for cardiac imaging. Iron oxide particles, manganese-based particles, and other magnetic materials alter relaxation times and create signal changes on magnetic resonance images. When these particles are functionalized with ligands that recognize macrophages or activated endothelium, they highlight areas of inflammation in the myocardium. Other systems target activated fibroblasts or matrix components, thereby delineating regions of active fibrosis rather than mature scar.[108] Computed tomography can use high-atomic-number materials, such as gold, as contrast agents. Nanoparticles made of gold, since they are engineered in a manner that they have the desired size and surface properties, can circulate and extravasate in injured myocardium over a long period of time. When such particles are also loaded with drugs or genes, computed tomography can provide a map of therapeutic distribution at the organ level. Radionuclide-labelled nanoparticles are used in nuclear imaging techniques to detect minute quantities of material with high sensitivity.[109] Molecular imaging with these tools provides information beyond simple measurement of ejection fraction or volumes. It can reveal whether inflammation is ongoing or resolving, whether fibrosis is still active, and whether new vessels are forming in response to pro-angiogenic therapies. This information can help select patients for specific nanomedicine interventions and serve as an early marker of treatment success or failure.[110]

Theranostic Platforms that Combine Imaging and Therapy

Theranostic platforms combine imaging capability and therapeutic action in a single nano system. In heart failure and ischemic heart disease, such platforms typically carry a drug, biologic or nucleic acid together with a contrast element. Imaging then provides a surrogate for local drug concentration and for target engagement.[111] Iron oxide-based cores coated with polymers can encapsulate anti-inflammatory or antioxidant drugs. The iron oxide permits detection by magnetic resonance imaging, and the shell releases the drug preferentially in inflamed or oxidatively stressed myocardium. Gold or bismuth-based cores used for computed tomography imaging can be linked to ligands that direct the particle to fibrotic tissue and to small molecules that modulate fibrotic signalling. In gene therapy, vectors can be engineered to express both a therapeutic gene and a reporter gene whose product can be detected by nuclear imaging or

fluorescence, which allows noninvasive assessment of transduction patterns. Extracellular vesicles and other biological carriers can also be adapted for theranostic use. Labelling vesicles with suitable imaging tracers while retaining their regenerative cargo makes it possible to follow their biodistribution and persistence. This knowledge can guide dosing intervals and clarify reasons for variable treatment response between individuals.[112]

Image Guided Delivery and Future Perspectives

Many nanomedicine strategies in heart failure are delivered either perioperatively or via catheters. The planning and execution of such procedures revolve around imaging. The amount and transmural extent of scar, the existence of hibernating segments, and wall thickness and strain could be defined by preprocedural magnetic resonance or computed tomography. This data is used in the decision on the infusion route, the number and placement of injections, and the placement of hydrogels or patches.[113] Theranostic constructs present instantaneous feedback during and after delivery. Early imaging can verify whether a carrier is in the desired location or diffuses to other areas. Follow-up imaging can record the duration of the carrier's presence in the myocardium and whether it localizes with functional or perfusion changes in the region. In cases of low uptake in a particular patient, clinicians can increase the dose, repeat the procedure, or adopt alternative therapy.[114]

Looking ahead, the combination of imaging and nanomedicine is likely to play an increasing role in the development and clinical use of cardiac nano-therapeutics. It supports rational dose selection, improves understanding of variability in patient response, and may reduce the number of patients needed in trials by providing sensitive mechanistic endpoints. With the simultaneous growth in the imaging and nano-engineering fields, the distinction between diagnosis and treatment in heart failure could become blurrier, and integrated theranostic approaches could be the main component of the future personalized treatment. Figure 4[115] illustrates how nanoparticle systems can be used both for non-invasive

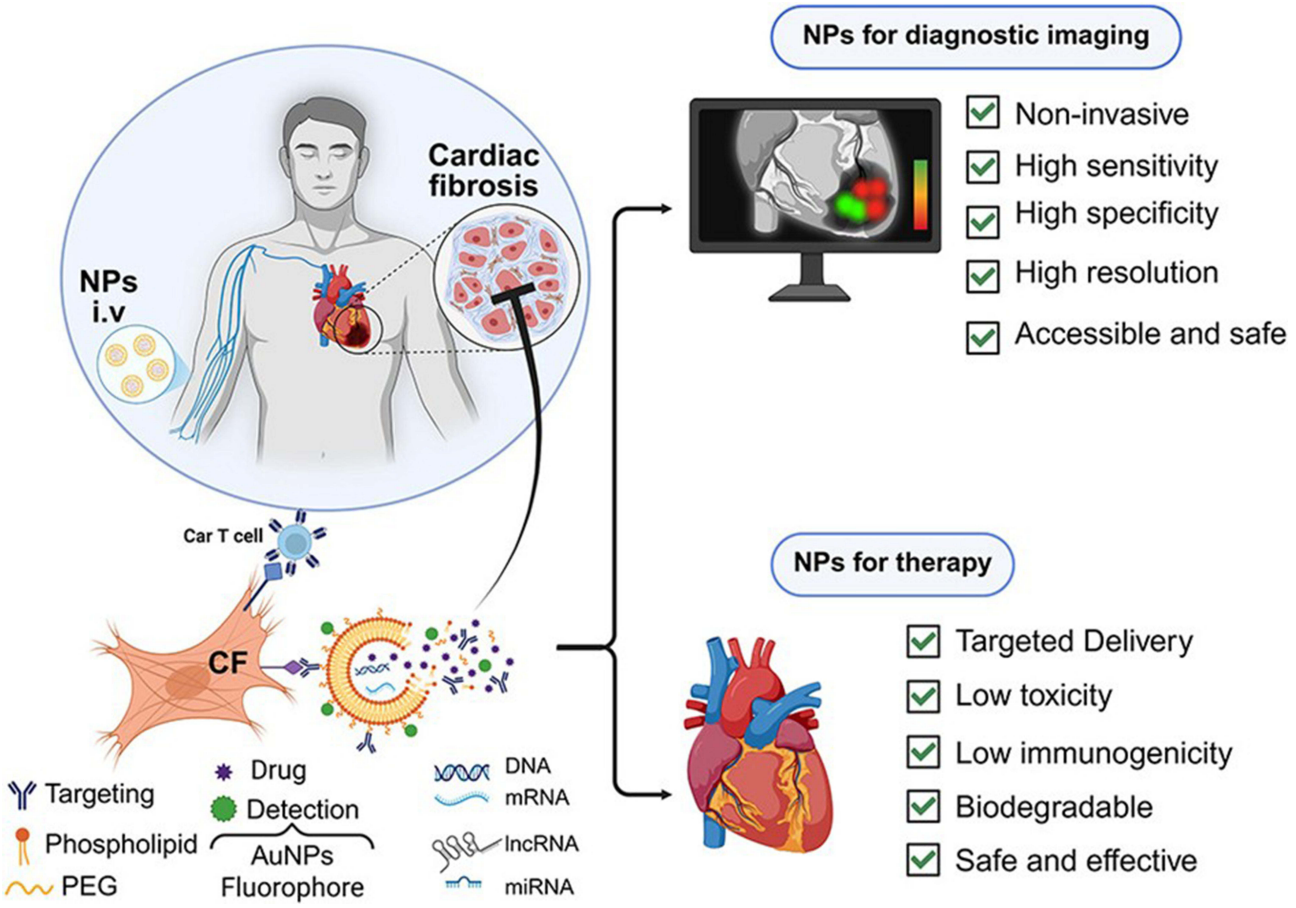

Figure 4 Nanoparticle (NPs) based theranostic strategies for cardiac fibrosis.[115]

https://doi.org/10.2147/IJN.S592274

imaging of cardiac fibrosis and for targeted delivery of anti-fibrotic therapies.[116] Cardiac fibrosis is considered a common pathological process that occurs in many cardiovascular diseases, including hypertension, myocardial infarction, idiopathic dilated cardiomyopathy, aortic stenosis, and myocarditis.[117] Theranostic and imaging-guided nanomedicine used in heart failure are given in Table 2.

Preclinical Evidence for Cardiac Nanomedicine

In vitro and Three-Dimensional Models

Cardiac nanomedicine preclinical investigations are normally initiated using controlled cell-based research. The cultures of the cardiac fibroblasts, cardiomyocytes of the ventricles, endothelial cells, and the macrophages are typically utilized to evaluate the internalization of nanocarriers, the clearance of intracellular trafficking, and the description of cargo release. The artificial pluripotent stem cell-derived cardiomyocytes are especially useful since they can offer an electrophysiological and contractile phenotype more akin to native myocardium than many other classical models.[122] The results of these studies usually include the preferred location of particles within the cells, transit between compartments like endosomes, cytosol, mitochondria, and nucleus, and the disturbance of the normal operation of the cell by the presence of the particles. Viability, apoptosis, calcium handling, action potential properties, and contractile performance are some of the key readouts in cardiomyocytes. Activation-associated markers and expression of extracellular matrix components in fibroblasts are used to deduce profibrotic/antifibrotic responses. Adhesion, migration, and cytokine secretion assays of endothelial cells and macrophages can give information on the effects of nanomedicine platforms on inflammatory programs and vascular behavior.[123] The three-dimensional tissues and organ-on-a-chip models are the foundation of more advanced model systems. Constructed heart tissues, which consist of cardiomyocytes, fibroblasts, and endothelial cells encapsulated in gel matrices, can produce measurable forces and have quantifiable conduction properties. Microfluidic platforms also provide controlled perfusion and mechanical stretch features of the dynamic cardiac environment that are selected. Under such conditions, the implications of nanomedicine systems when subjected to them can be evaluated in an environment more physiological than stagnant monolayer cultures.[124]

Small Animal Models of Myocardial Injury and Heart Failure

Small animals, such as mice and rats are commonly used in vivo models for cardiac nanomedicine. Coronary artery ligation results in myocardial infarction and later remodelling and systolic dysfunction. Transient ligation and reperfusion produce an ischemia-reperfusion injury model characterized by oxidative stress. It is possible to cause pressure overload by constricting the aorta, leading to hypertrophy and subsequent failure.[125] Models used to test nanomedicine platforms include systemic injection, intracoronary infusion, or direct intramyocardial administration. The results include survival, echocardiographic, and magnetic resonance imaging measurements of left ventricular ejection fraction, chamber volumes, infarct size, wall thickness, capillary density, and extent of fibrosis. Many studies report that targeted nanoparticles carrying antioxidants, anti-apoptotic agents, or inflammation modulators reduce infarct size and preserve function after ischemia-reperfusion injury. Nanostructured hydrogels injected into the infarct border zone thicken the wall and limit adverse remodelling. Extracellular vesicles and engineered exosomes have repeatedly been shown to decrease cardiomyocyte apoptosis, enhance angiogenesis, and improve contractile performance.[126] Gene and nucleic acid delivery systems based on viral and non-viral carriers have also shown benefit in small animals. Transfer of genes that facilitate

Table 2 Theranostic and Imaging Guided Nanomedicine in Heart Failure

Nanotherapeutic Agent	Imaging Modality	Therapeutic Function	References
Polymeric/Lipid NPs with imaging tags	MRI, PET, CT	Drug delivery, imaging	[118]
Metallic nanoparticles (eg., iron oxide)	MRI	Contrast, anti-inflammatory therapy	[119]
Nanocarriers (liposomes, micelles)	PET/CT	Targeted delivery, imaging	[120]
Theranostic nanocarriers in cardiotoxicity imaging	MRI/optical	Diagnostic imaging, cardioprotection	[107]
Emerging nano-imaging platforms	Multimodal imaging	Real-time diagnosis, therapy	[121]

calcium process, mitochondrial stability, or cell cycle regulation has enhanced activity and scar size in different models. Equally, nanocarriers have been employed to modulate expression networks that mediate survival, hypertrophy, and fibrosis using microRNA mimics or Inhibitors.[127]

Large Animal Models and Translational Signals

Translation from rodent models to human applications requires intermediate validation in large-animal systems, in which cardiac size, coronary anatomy, and electrophysiological properties more closely approximate those of humans. Pigs, dogs, and sheep are among the most frequently employed species for this purpose. In these models, myocardial infarction is typically induced through temporary or permanent coronary artery occlusion using surgical or catheter-based approaches. Chronic pacing, microembolization, and pressure overload may also be used to generate forms of heart failure that recapitulate important features of clinical syndromes.[128] Although cardiac nanomedicine investigations in large animals are not as prevalent as studies with rodent models, they still offer invaluable data for translational research. These models allow the assessment of delivery modes to be used clinically, including intracoronary infusion during angiography and transendocardial injection using conventional catheter systems. They make it possible to directly apply more complex magnetic resonance, computed tomography, and nuclear imaging techniques, and they enable device interactions to be conditions that are more realistic to clinical reality.[129] These models have confirmed that certain carriers can be delivered safely to the heart, that targeted particles can increase local concentration in infarcted regions, and that functional improvements observed in rodents can sometimes be reproduced at a larger scale. They have also highlighted new challenges, including lower retention of injected materials in thicker ventricular walls, more pronounced clearance by the reticuloendothelial system and greater variability between animals.[130]

Translating Cardiac Nanomedicine into Clinical Practice

Clinical translation of cardiac nanomedicine is beginning to move from concept toward practice, building on experience from oncology, infection and metabolic disease where most approved nano scale products currently reside, and the earliest cardiovascular applications already show that reformulation of known drugs in lipid based or polymer based carriers and the introduction of nanostructured contrast agents can improve pharmacokinetics and safety for agents that act on the heart and vasculature. More specific candidates for heart failure and ischaemic heart disease include nanoparticles that deliver antioxidants or anti-inflammatory agents to limit ischaemia reperfusion injury, viral and non-viral vectors for gene transfer to cardiomyocytes, and cell free preparations of extracellular vesicles intended to promote repair, which are now being tested mainly in early phase studies that prioritise feasibility, safety and pharmacodynamic signals, while initial experience with adeno associated virus vectors that target calcium handling or contractile proteins and with extracellular vesicle based products confirms technical feasibility but highlights issues such as preexisting immunity, vector dose and the need for careful patient selection.[131]

Regulatory agencies usually evaluate these products within established pathways for small molecules, biologics, gene therapies or devices, but require a more detailed description of nano specific features, including size distribution, shape, surface charge, composition, stability and impurity profile, together with evidence of batch consistency and assays that capture both carrier and cargo, and they demand extended non clinical programmes that address toxicities from the payload and from the carrier, long term organ accumulation, immune activation and interactions with implanted devices such as defibrillators, stents and ventricular assist systems.[132] At the same time, the step from laboratory preparation to large scale manufacture is demanding, because many platforms depend on precise control of mixing, solvent exchange, temperature and shear forces that must be re optimized at higher volumes, and clinical production must follow good practice standards with robust sterile processes, real time measurements of key particle properties, tightly controlled upstream cell culture and downstream purification for bioderived systems, and storage and distribution strategies that prevent aggregation or loss of activity, all of which favor simpler and more modular designs for broad use in heart failure.[133]

Clinical trials must then demonstrate benefit over existing therapy, with early clinical trials concentrating on safety, pharmacokinetics, biodistribution and target engagement using imaging and biomarkers demonstrating that the carriers successfully reach desired myocardial areas and mediate the action on the preferred pathway, and subsequent clinical trials on outcomes that are of clinical interest to patients and health systems like infarct size, post-acute-event heart

failure, mortality, hospital admission rates, ventricular function, exercise capacity and quality of life, preferably with enrichment strategies to select individuals in whom. Because nano scale products are likely to be more expensive than conventional drugs and may require specialized imaging, interventional facilities and intensive monitoring, health economic analyses must examine whether they reduce hospitalizations, delay the need for devices or transplantation and maintain quality of life at an acceptable cost, while policy makers and developers must also address access and equity so that advanced nanomedicine does not remain confined to a few well-resourced centers but, if it proves effective, becomes realistically available to populations that carry the greatest burden of heart failure.[134] Table 3 presents illustrative nanomedicine platforms that have advanced to early clinical trials or late preclinical evaluation in heart failure and closely related conditions. Entries are grouped by carrier type and intended indication, with emphasis on the nature of the cargo, the route of administration, and the main translational signals.

A number of challenges still prevent cardiac nanomedicine from becoming a standard clinical procedure, even in the face of compelling preclinical evidence. Less than 1% to 5% of the injected dosage usually reaches the heart after systemic administration, with the remainder accumulating in the liver, spleen, and kidneys. This usually leads to poor myocardial delivery efficiency. Off-target toxicity is a problem, especially for inorganic or slowly degradable compounds.[140–143] Another significant issue is manufacturing scalability. Large-scale, GMP-compliant production and batch-to-batch consistency are complicated by the fact that many nanoplatforms depend on complex synthesis processes, exact control over particle size and surface chemistry, or biologically derived components like extracellular vesicles.[9,69,144] From the perspective of biology, it is important to carefully assess immune activation, complement-mediated infusion responses, and the possibility of arrhythmogenic or microvascular consequences in the sick heart.[62,93,145] There are several translational obstacles in cardiac nanomedicine, despite promising

Table 3 Selected Nanomedicine Platforms Near Clinical Translation in Heart Failure and Related Cardiac Conditions

Platform type	Cargo or Principal Function	Primary Cardiac Indication	Route of Administration	Development Stage	Key Reported Findings	Reference
Viral vector-based gene carrier	Expression cassette for SERCA2a in cardiomyocytes to improve calcium handling	Advanced systolic heart failure with reduced ejection fraction	Intracoronary infusion or peripheral intravenous infusion	Early to mid phase clinical studies	Feasible delivery with acceptable short-term safety and mixed effects on ventricular function. Response depends on vector dose preexisting immunity and patient selection.	[135]
Extracellular vesicles from mesenchymal stromal cells	Paracrine factors and regulatory RNAs that support cardiomyocyte survival and angiogenesis	Acute myocardial infarction and early post infarction remodelling	Intracoronary or intravenous administration shortly after reperfusion	First in human pilot experience and extensive preclinical work	Procedures feasible with encouraging early safety in patients and consistent preclinical reduction in injury and improved vascularisation.	[136]
Lipid nanoparticle formulation of a small molecule drug	Encapsulated antioxidant or anti-inflammatory agent to limit ischaemia reperfusion injury	Patients undergoing reperfusion therapy for acute coronary syndromes and related preclinical models	Intravenous administration around the time of reperfusion	Late preclinical and early translational evaluation	Improved tolerability and exposure compared with free drug in models with attenuation of oxidative stress inflammation and cell death and exploratory reduction in infarct size.	[137]
Polymer based nanoparticle for microvascular and tissue targeting	Delivery of vasculotropic or cytoprotective agents to infarct zone microvasculature	No reflow or microvascular obstruction after reperfusion and early post infarction remodelling	Intracoronary or intravenous administration using standard catheters	Late preclinical and very early clinical evaluation	Enhanced delivery to the infarct territory with improved indices of microvascular flow and reductions in myocardial injury markers in experimental studies.	[138]
Injectable hydrogel or epicardial patch with embedded bioactive factors	Local depot for growth factors extracellular vesicles or cells that support wall strength angiogenesis and repair	Post infarction left ventricular remodelling in selected surgical or catheter-based candidates	Injection into the infarct border zone or placement on the epicardial surface during a planned procedure	Large animal studies and first in human trials	Well tolerated treatment with reduced wall thinning and improved regional function and early human data showing safety and feasibility of transendocardial or catheter based delivery.	[139]

preclinical findings. For example, Poor in vivo targeting efficiency and off-target retention due to nonspecific biodistribution and mononuclear phagocyte system uptake.[44] Insufficient understanding of long-term biodistribution, metabolism, and potential chronic toxicity, especially for non-biodegradable carriers.[44,45] Technical and manufacturing challenges, including reproducibility, scalable GMP production, and quality control of nanoparticle formulations.[24] Lack of standardized preclinical models with predictive human physiology, particularly for phenomena such as the EPR effect in non-tumor tissues.[24] To address such gaps, interdisciplinary cooperation (cardiology, materials science, pharmacology) and model creation, high-quality safety assessment procedures, and earlier advice on regulation should be prioritized in future studies.[44,45]

Safety, Toxicity and Immune Responses in Cardiac Nanomedicine

Heart failure nanomedicine is induced to a heart having little structural and electrophysiological reserve. Thereby, electrical conduction, mechanical activity, or extracardiac safety alterations of any magnitude can lead to dire results. Myocardial structures are able to disrupt impulse conduction by acting on ion channels, gap junctions or local electrical heterogeneity. Although conduction nanomaterials have the potential to increase coupling in evenly dispersed material, focal deposition may create an arrhythmogenic substrate. Mechanical incompatibility is also important, with a too-stiff hydrogel or epicardial construct potentially damaging filling and putting stress on the wall, and fragile materials being unable to withstand repeated deformation. In addition to that, microvascular particle entrapment or uninhibited release of vasoactive cargo may increase reperfusion injury, hypotension, ischaemia, or tachyarrhythmia. Close early clinical trials ought to be preceded by a rigorous preclinical evaluation of rhythm, contractile performance, and scar architecture in centres with advanced cardiac support. It has been noted that systemic exposure is a major barrier as nanocarriers are likely to settle at the liver, spleen, kidneys, lungs, and lymphoid tissues. The persistent presence of inorganic cores and large doses of organic carriers may lead to the disruption of cellular homeostasis and the occurrence of hepatic, renal, pulmonary, or immunological toxicity, particularly upon the release of the off-target drug. Further uncertainty is in immune complications, where complement activation, adsorption of plasma proteins, and reactions to biologically derived carriers can have positive effects in clearing or incite an infusion reaction. Based on this, translation relies on material design, purification, antibody screening, administration, and immune monitoring. Because heart failure is a chronic syndrome, long term safety is critical, and although biodegradable polymers and lipids eventually generate small molecules that are cleared along known pathways, some inorganic or hybrid systems may persist in liver, spleen or bone marrow for years and could subtly alter metabolism, oxidative balance or gene expression with repeated dosing, particularly for gene based or regenerative nano therapies that act on proliferation and survival pathways, so risk management must begin at the design stage by favouring materials with clear degradation routes and prior clinical experience, by planning doses and schedules with an integrated view of exposure in both target and non-target organs using pharmacokinetic data, imaging and modelling, and by using theranostic systems where suitable to visualize biodistribution and identify individuals with unusual accumulation patterns; taken together, these considerations highlight that the ability of nanomedicine to deliver powerful interventions directly to the failing heart is matched by the possibility of new and sometimes unexpected harms, and that only careful design, rigorous preclinical work and vigilant clinical surveillance will ensure that benefits outweigh risks in this vulnerable population.[146]

Synthesis of Evidence and Common Limitations

Nanomedicine can positively influence a number of basic pathways involved in cardiac injury and heart failure, as preclinical evidence shows. Drug, biologic, and nucleic acid delivery platforms have the potential to increase drug, biologic, and nucleic acid concentrations in damaged myocardial tissue, protect labile therapeutic cargo against premature degradation, and facilitate target release at the injury site. In parallel, reactive oxygen species-scavenging systems attenuate oxidative injury, immunomodulatory nanoplatforms reprogram maladaptive inflammatory signalling, and regenerative formulations promote angiogenesis while preserving viable myocardium.[147] However, several shortcomings must be taken into consideration. The percentage of experimental studies using young, otherwise healthy animal models is high. Conversely, patients with heart failure are usually elderly and have complicated clinical histories that include diabetes, obesity, renal failure, and chronic inflammatory diseases. Moreover, animal experiments are often confined to weeks, whereas in normal human cases, heart failure develops over years. Translational interpretation is further complicated by interspecies differences in dose scaling and exposure profiles, and even targeted formulations often deliver only a modest proportion of the administered dose to the

heart.[148] There is also the possibility of publication bias that favours positive outcomes in the literature, and the methodological heterogeneity is present to a large degree in disease models, outcome measures, and comparator therapy. Moreover, some nanomedicine platforms that are demonstrated to be efficacious in rodent models are subsequently tested in large animal models; very few will undergo formal toxicological assessment and early-phase clinical development.[149] Although these limitations exist, the preclinical body of evidence provides a strong conceptual framework for further development. Collectively, these studies show that nanoscale engineering can address several pharmacokinetic and microenvironmental obstacles that restrict the effectiveness of conventional therapies, while also identifying specific platform classes and biological targets that warrant continued translational investigation. The challenge now is to refine these systems with an eye toward realistic clinical constraints, to test them in models that better reflect human disease, and to integrate imaging and biomarker readouts that will allow efficient translation into carefully designed human studies.[115]

Depending on the stage of the disease and the mode of distribution, nanomedicine systems perform very differently in preclinical research. Antioxidant and anti-inflammatory nanoparticles are beneficial in acute ischemia damage models.[66] On the other hand, unless distribution is coupled with local depots like hydrogels or patches, chronic heart failure models show declining results.[150] Although they are more difficult to manufacture, biomimetic carriers function better than synthetic nanoparticles in terms of immunological tolerance and myocardial retention.[63] Additionally, the failure of many platforms is not due to a lack of therapeutic potency, but rather to the fact that, during systemic distribution, less than 1–5% of the injected dosage reaches the myocardium. These results highlight the need for realistic expectations of myocardial targeting efficiency, integration with interventional delivery modalities, and endpoints that are in line with the biological action of the platform to achieve future success in cardiac nanomedicine.[18]

Challenges and Future Priorities

Although experimental work confirms that nanomedicine can influence many processes relevant to heart failure, several obstacles still separate these concepts from routine clinical care. Heart failure represents a spectrum of diseases that arise from ischaemic injury, pressure overload, genetic cardiomyopathy, metabolic disturbance, and inflammatory conditions, so a nano-scale platform that performs well in a young animal with a single coronary ligation may behave very differently in an older patient with diabetes, renal impairment, and diffuse vascular disease. A small percentage of the systemically administered carriers typically get into the human myocardium. A large part of the dose is sequestered by the liver and the spleen and other organs, making it harder to select the dose, and there is a fear of extra-cardiac toxicity. At the same time, most preclinical models do not reproduce the full complexity of human heart failure with its combination of ageing, metabolic disease, polypharmacy and long clinical course, and commonly used biomarkers such as ejection fraction and natriuretic peptides are too coarse to report directly on mitochondrial function, immune cell phenotype or microvascular tone, which are the targets of many nano interventions. Systems biology, quantitative modelling, and data science can help bridge these gaps by predicting how particle properties and dosing influence tissue exposure and by defining heart failure phenotypes in which mechanisms, such as inflammation or fibrosis, are dominant, but such tools must be transparent and free from bias if they influence trial design or patient selection. Ethical and distributive concerns also warrant careful consideration, particularly because certain nanoplatforms intervene in fundamental biological processes, including gene regulation and cellular proliferation, and are likely to remain expensive and confined to specialised centres during early implementation. In this regard, informed consent will have to be tight, benefits and risks should be clearly communicated, and pricing and reimbursement systems should be fair. The field is likely to grow optimally in the future by focusing on simple, robust platforms that can assist in enhancing the delivery of therapeutics with established clinical utility or providing localised mechanical assistance, and the directed release of a few reparative growth factors. It will also require an increased translational connection among preclinical and clinical research, which will be supported by the longer and more clinically reliable experimental models, and early human research that will entail an extensive analysis with rigorous examinations through the usage of rigorous imaging and biomarker-based evaluation. Another important consideration to be made is the integration of nanotherapeutic means within the existing treatment regimens, as opposed to considering them as alternatives to the traditional standards of care. This interdisciplinary collaboration of cardiologists, materials scientists, chemists, pharmacologists, imaging specialists, regulators, health economists, and patient communities will be needed to guarantee that something substantial is made, as

these potentially promising nanoscale interventions are made, tested, and deployed in a scientifically sound, clinically safe, and broadly available manner that people with heart failure can employ.[151,152] These developments have reiterated the potential of nanomedicine use in heart failure management within the past year, with some key developments including regenerative nanomaterials to induce endogenous repair programs that are mostly absent in the adult heart, multifunctional nanosystems to enable simultaneous targeted delivery and controlled release, and microenvironment sensing and translational approaches that are increasingly concerned with safety, manufacturability, and scalability.[61] At the same time, novel avenues of gene network regulation of cardiomyocyte survival and proliferative capacity have been created through new RNA-based nanotherapeutic platforms.[16]

Conclusion

The troubling systemic pharmacological mismatch between the failing ventricle and the rest of the body is the main cause of the persistent global burden of heart failure. Although today clinical protocols, medicines, and devices have some clinical use, they frequently do not adequately cover the heterogeneous cellular environment and hostile biochemical environment of diseased heart tissue. There is evidence that nanomedicine offers a platform through which enhanced therapeutic accuracy may be attained by radically reforming the mode of delivery and concentration of diagnostic and therapeutic agents in the myocardium. Biological molecules may be kept intact at the nanoscale by using highly designed nanoscale vehicles and cellular-type structures. These systems maximize the pharmacokinetic properties and support the focused concentration of payloads in areas characterized by ischemia, chronic inflammation, or fibrotic remodelling. Similarly, acellular approaches by employing extracellular vesicles and related biomimetic scaffolds permit the restoration of regenerative paracrine signaling without addressing the immunogenicity and logistical limitations of more conventional cell-based transplantation. Moreover, nucleic acid therapeutics are administered using viral or nonviral vectors, which facilitate direct regulation of the molecular programmes that determine cardiomyocyte survival, metabolic activity, and innate regenerative capability of the adult heart. The real-time quantification of biodistribution and target engagement can also be achieved through further integration of theranostic platforms, which incorporate imaging moieties and therapeutic cargo. In spite of this enormous potential, the area of clinical translation is still limited by a number of core challenges. These are the inefficient myocardial sequestration after delivering it systemically, the absence of detailed information on the safety of synthetic materials over a long period, and the deep intricacies of mass production and compliance with regulations. Importantly, emerging technologies should be able to prove a discernible incremental advantage over current guideline-based medical therapies to warrant their usage. The next generation development of the field must focus on the possible choice of robust and scalable platform design, imaging-driven, or biomarker-driven guidance of early-phase clinical evaluations, and nanomedicine as an integrative part of the existing treatment trajectory, as opposed to a direct substitute. Should these multidisciplinary problems be addressed in a structured manner, nanotechnology will become an important complement in the holistic prevention and treatment of ventricular dysfunction.

Data Sharing Statement

This is a review article, and all relevant information is provided in the article. No dataset is associated with this article.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report there are no competing interests to declare.

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