HHS Public Access

Author manuscript

Chem Rev. Author manuscript; available in PMC 2020 November 13.

Published in final edited form as:

Chem Rev. 2019 November 13; 119(21): 11352–11390. doi:10.1021/acs.chemrev.8b00323.

Nanoscale Technologies for Prevention and Treatment of Heart Failure: Challenges and Opportunities

Mohammad Javad Hajipour[†,■], **Mehdi Mehrani**[§,■], **Seyed Hesameddin Abbasi**[§], **Ahmad Amin**[‡,*], **Seyed Ebrahim Kassaian**[§], **Jessica C. Garbern**[▲,Ω], **Giulio Caracciolo**[λ], **Steven Zanganeh**[‖], **Mitra Chitsazan**[‡], **Haniyeh Aghaverdi**[⊥], **Seyed Mehdi Kamali Shahri**[⊥], **Aliakbar Ashkarran**[†,⊥], **Mohammad Raoufi**[¶], **Holly Bauser-Heaton**[Δ], **Jianyi Zhang**[¥], **Jochen D. Muehlschlegel**[⊥], **Anna Moore**[†], **Richard T. Lee**[▲,ζ], **Joseph C. Wu**[▼,Θ,Φ], **Vahid Serpooshan**[#,Δ], **Morteza Mahmoudi**[†,⊥,Ŧ,*]

[†]Precision Health Program, Michigan State University, East Lansing, MI, United States

[§]Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran.

[‡]Rajaie Cardiovascular, Medical and Research Center, Iran University of Medical Science Tehran, Iran

[▲]Department of Stem Cell and Regenerative Biology, Harvard University, Harvard Stem Cell Institute, Cambridge, Massachusetts, United States

[Ω]Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts, United States

[λ]Department of Molecular Medicine, Sapienza University of Rome, V.le Regina Elena 291, 00161, Rome, Italy

[‖]Department of Radiology, Memorial Sloan Kettering, New York, NY 10065, United States

[⊥]Department of Anesthesiology, Perioperative and Pain Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, United States

[¶]Physical Chemistry I, Department of Chemistry and Biology & Research Center of Micro and Nanochemistry and Engineering, University of Siegen, Siegen, Germany

[¥]Department of Biomedical Engineering, The University of Alabama at Birmingham, Birmingham, Alabama, United States

[ζ]Department of Medicine, Division of Cardiology, Brigham and Women's Hospital and Harvard Medical School, Cambridge, Massachusetts, United States

[▼]Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, California, United States

[Θ]Department of Medicine, Division of Cardiology, Stanford University School of Medicine, Stanford, California, United States

[*]Corresponding Author: M.M.: mahmou22@msu.edu.

[■]Equal contribution

The authors declare no competing financial interest.

[Φ]Institute of Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, California, United States

[#]Department of Biomedical Engineering, Georgia Institute of Technology & Emory University School of Medicine, Atlanta, Georgia, United States

[Δ]Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, United States

[Ŧ]Connors Center for Women's Health & Gender Biology, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States

Abstract

The adult myocardium has a limited regenerative capacity following heart injury and the lost cells are primarily replaced by fibrotic scar tissue. Suboptimal efficiency of current clinical therapies to resurrect the infarcted heart results in injured heart enlargement and remodeling to maintain its physiological functions. These remodeling processes ultimately leads to ischemic cardiomyopathy and heart failure (HF). Recent therapeutic approaches (e.g., regenerative and nanomedicine) have shown promise to prevent HF post-myocardial infarction in animal models. However, these preclinical, clinical, and technological advancements have yet to yield substantial enhancements in the survival rate and quality of life of patients with severe ischemic injuries. This could be attributed largely to the considerable gap in knowledge between clinicians and nano-bioengineers. Development of highly effective cardiac regenerative therapies requires connecting and coordinating multiple fields, including cardiology, cellular and molecular biology, biochemistry and chemistry, and mechanical and materials sciences, among others. This review is particularly intended to bridge the knowledge gap between cardiologists and regenerative nanomedicine experts. Establishing this multidisciplinary knowledge base may help pave the way for developing novel, safer, and more effective approaches that will enable the medical community to reduce morbidity and mortality in HF patients.

Graphical Abstract

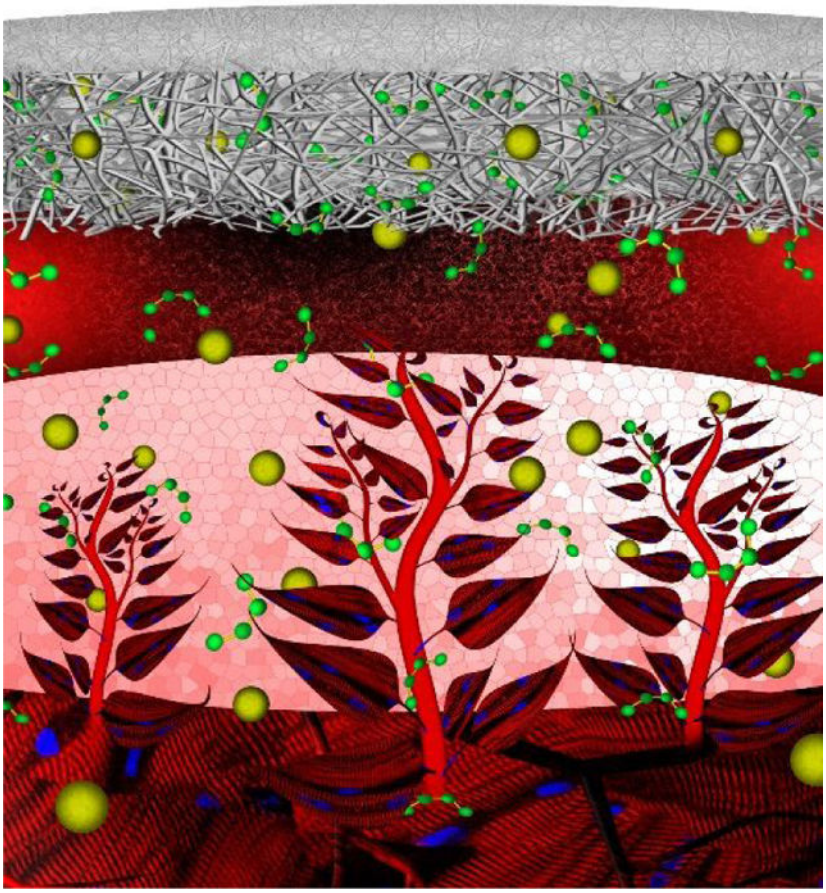

Figure description: Regeneration of human myocardial tissue using regenerative nanomedicine approaches.

1. INTRODUCTION

1.1. Cardiovascular Diseases

Cardiovascular diseases (CVDs) are by far the leading cause of death in the world, accounting for 17.7 million deaths annually.[1] An array of structural and/or functional disorders that damage ventricular blood filling (diastole) or outflow (systole) can result in heart failure (HF).[2] As a multifactorial clinical syndrome with many etiologies, accurate assessment of the magnitude of HF has been challenging due to the lack of dependable population-based estimates of the incidence, pervasiveness, and prognosis.[2–4] Data from the National Health and Nutrition Examination Survey (NHANES) between 2011–2014 showed that approximately 6.5 million Americans from age 20 or older had HF.[5] This study estimated that HF prevalence will increase by 46% from 2012 to 2030, by which time more than 8 million individuals will be suffering from HF in the United States (1 in every 33 adults).[5]

Ischemic cardiomyopathy (ICM) is a condition with high morbidity and mortality, in which the systolic and diastolic capacities have deteriorated as a result of ischemic heart disease.

ICM is defined as left ventricular (LV) dysfunction with one or more of the following: i) a history of prior myocardial infarction (MI) or revascularization; ii) >75% stenosis in the left main or the left anterior descending coronary artery; and iii) >75% stenosis in at least two coronary arteries.[6] The incidence of ICM has been growing mainly due to the overall longer human lifespan, resulting in increasing numbers of patients with persistent impaired LV dysfunction.[6]

ICM encompasses a variety of pathophysiologies and clinical presentations. Patients surviving an acute MI, even if not complicated by HF at the first stage, later require hospitalization as a consequence of the ensuing HF. This suggests that the decline in cardiac function is not only due to acute events but also the progressive nature of the disease.[7] Several clinical approaches and pre-clinical studies are used to prevent or delay the process of myocardial dysfunction. However, the high mortality rates of acute HF clearly indicate an urgent and continuing need for developing new therapeutic approaches to reduce death rates and improve patients' quality of life.

1.2. Clinical Challenges Associated with HF

The mortality rate for HF patients five years after diagnosis is ~50%[8]. The current clinical approaches (e.g., pharmaceuticals, cell therapy, surgical reconstruction, and implantable assist devices) have demonstrated only limited success in preventing the progress of HF. The main clinical challenges, which nanotechnology may help to overcome in the field of HF are listed below:

1.2.1. Robust Identification of HF Markers in the Blood.—Our blood plasma contains over 10,000 proteins but 99% of the protein mass in the plasma proteome is dominated by only 22 proteins.[9,10] This means that robust identification of the disease-specific proteins/biomarkers that have a very low or rare abundance in plasma is challenging with the current proteomics approaches. Therefore, one of the crucial clinical diagnostic challenge is to detect HF biomarkers without false-negative and/or false-positive errors.

1.2.2. Predicting Long Term Effects of Cardiac Injuries.—Identification and discrimination of the level of cardiac injury and its long-term effects on cardiac function are of great clinical interest. This is because, in some cases, myocardial infarction only causes subtle injuries with initially negligible signs of adverse effects on heart function.[11] In a fraction of these patients, in contrast to clinical expectations, substantial reductions in heart function are observed long term (e.g., as early as a couple of months) after initial treatment. Although identification of the patients at risk of further cardiac damage in longer time is of clinical interest, there is currently no effective diagnostic approach for robust identification of these subpopulations of patients.

1.2.3. Delivering Therapeutic Molecules and/or Cells into the Damaged Part of Myocardium.—Therapeutic molecules and/or cells must be delivered to the "stunned" myocardium, or the transient post-ischemic dysfunctional part of the heart tissue. The damaged cardiac cells in the stunned area have a unique capacity to retrieve their functions during the course of HF. Therefore, targeted delivery of therapeutic molecules and/or cells

enables clinicians to minimize the scar tissue and maximize heart functions. However, current clinical strategies provide only limited success in targeted delivery of the therapeutic biosystems.

1.2.4. Low Therapeutic Cell Retention and Engraftment in Myocardium.—The cell therapy approach has demonstrated great potential in retrieving cardiac tissue during HF. Theoretically, the therapeutic cells can integrate into the damaged cardiac cells and release their therapeutic paracrine factors to regenerate and heal the stunned part of myocardium. However, pre-clinical and clinical trials of cell therapy approaches thus far have found low retention and engraftment to the host cardiac tissue.[12–16]

1.2.5. Patient-Specific Mature and Functional Cardiomyocytes.—One of the main reasons for the low retention and engraftment of therapeutic cells is the role of immune system in cell rejection.[17–20] Development of patient specific cardiac cells is recognized as a useful strategy to overcome this problem. The patient-specific cardiac cells are mainly produced by differentiation of human pluripotent stem cells (hiPSCs). However, this process is plagued by the low maturity of the produced cells, which not only reduces their therapeutic efficacy and integration into the host tissue but also creates some serious side effects such as arrythmia.[16]

1.2.6. Robust Monitoring of Therapeutic Cells In Vivo.—Clinical monitoring of the therapeutic cells is very important to probe the fate of the cells.[21] The sensitivity and specificity of current clinical strategies are not good enough to monitor therapeutic cells over the course of treatment.

1.2.7. Reperfusion Injury.—Reperfusion injury is typified by vascular, myocardial, or electrophysiological dysfunction brought about by the return of bloodstream to ischemic tissue. When the stream of blood into cardiac myocytes is interrupted through the blocking of a coronary artery, a sequence of actions results in cellular injury and death. In the context of severe MI, a report posited that reperfusion injury is responsible for up to 50% of the final myocardial damage.[22]

1.3. Nanotechnology

Nanotechnology is an emerging and dynamic multidisciplinary field concerned with atomic and molecular structures that, at least in one dimension, lie within 0.1–100 nm range.[23] At a nanoscale system, the majority of the atoms are associated with the surface of the material. Given the dominance of the surface properties at this ultra-small dimension compared to the bulk characteristics, nanomaterials exhibit distinct mechanical, electrical, catalytic, thermal, magnetic, and imaging features that invite intriguing commercial, medical, and environmental applications.[24] For example, gold nanoparticles show surface plasmon resonance at the nanoscale, which is uncharacteristic of gold at the microscale.[25] This novel feature enables gold nanoparticles to be utilized in a wide range of applications such as chemical and biological sensing.[26] As another example, the paramagnetic characteristics of iron oxide compounds are transformed to superparamagnetic when the size of the iron oxide nanoparticles dips below 20 nm[23]. Changes in the shape and size of nanoparticles (i.e.,

alterations in their surface geometry) cause a shift in the electrical field density on the surface[27]. These alterations lead to a change in the oscillation frequency of the electrons, which in turn generates variations in cross-sections that affect optical properties including absorption and scattering. For example, the size-dependent energy difference between the ground and excited energy levels dictates the color and fluorescence emission of CdSe quantum dots[28]. One reason that such drastic changes in material properties accompany the transition from the micro to the nanoscale range is the dominance of surface properties over bulk properties in nanomaterials.

Owing to the distinct material characteristics, nanotechnology has experienced tremendous growth in research and development over the recent decades, leading to the emergence of various interdisciplinary branches of science such as nanomedicine, nanobiology, and nanobiotechnology.[29] Nanomedicine is defined by the US National Institutes of Health (NIH) as the application of nanotechnology in controlling biological systems, treatment, diagnosis, and monitoring of diseases.[30] Nanoparticles have been employed in many novel medical applications such as effective delivery of toxic biomolecules to targeted sites (e.g., cancerous tissue) without exposing healthy cells, sensitive and precise imaging to detect disease at very early stages, and crossing difficult barriers (e.g., the blood-brain barrier) to deliver imaging and therapeutic molecules to specific diseased tissues.[31,32]

Nanotechnologies also play a major role in the field of regenerative medicine, aiming at constructing tissues or organs to replace damaged body parts.[33] For instance, the simple introduction of cells into a diseased organ for tissue repair is now being augmented by seeding the cells onto engineered nanomaterial scaffolds with biological functionalization to further enhance the efficiency of cell transplants.[34] These nanostructured materials can provide an instructive template for cell growth, alignment, differentiation, and tissue architecture, and therefore facilitate the formation of functional tissue grafts. Through this method, a variety of tissues and organs could be formed using a wide range of synthetic or natural nano-biomaterials, in addition to the choice of the appropriate cell type.[35]

Among the various therapeutic advances, regenerative medicine and nanotechnologies have shown a considerable capacity to salvage or regenerate damaged heart tissue in animal models.[36] The superior characteristics of nano-biomaterials have shown great promise in developing engineered cardiovascular constructs for a variety of tissue engineering applications.[37,38] To develop efficient nanotech-based regenerative medicine platforms in humans, clinicians and engineers must achieve a greater common understanding of the problems, challenges, and opportunities in both fields.

In this review, our goal is to provide a comprehensive overview of the critical features of ischemic cardiovascular diseases, and emerging trends in the fields of cardiac nanotechnology, from the perspectives of both clinicians and bioengineers. We also discuss the potential application of nanotechnologies for addressing the challenges and limitations associated with the clinical application of current cardiac diagnostic and therapeutic approaches.

It is imperative to achieve a mechanistic understanding of the biological fate of nanotechnologies, their safety, and biological identities prior to their translation into clinical therapies, a gap that has prevented the successful commercialization of nanotechnologies in medical fields.[39] In addition to the clinical applications, we will discuss opportunities and challenges for the use of nanotechnologies in *in vitro* and *ex vivo* studies of cardiovascular disease, as there are also some concerns on the safety and biological fate of those technologies.

2. NANOTECHNOLOGY APPROACHES TO IDENTIFY HEART FAILURE BIOMARKERS

Early detection of cardiovascular disease increases the chance for successful treatment and potential cure, giving the patient a better prognosis, extended survival, and improved quality of life. As the processes of cardiac disease (e.g., formation of arthrosclerosis plaques) leave various proteins in blood plasma—even in their very early stages—one promising approach for early detection is molecular analysis of blood for such biomarkers. Advances in proteomic analyses offer researchers a new-found ability to detect the changes taking place in the initial stages of various diseases, including a powerful tool for identifying potential biomarkers for early detection via mass spectrometry.[40,41] However, thus far the sensitivity and specificity of such approaches are limited for early detection purposes due to the low levels of biomarkers in human plasma.[10,40,42]

Cardiac biomarkers, such as cardiac troponins (cTns), myoglobin (Myo), and creatinine kinase MB (CK-MB), are released into the bloodstream when the heart is damaged or stressed. Table 1 summarizes the important biomarkers and their detection assays/limitations. In many conditions such as acute MI, the levels of such biomarkers can inform a physician whether advanced imaging modalities or invasive procedures are warranted. For example, relaxation and contraction of a striated muscle occur through a set of proteins called cTn that control and regulate the calcium-mediated interaction of actin and myosin. A healthy subject is thought to have a plasma level of cTnI in the range of 0.1–0.2 ng/L because of the continuous myonecrosis during normal life[43]. Due to its high sensitivity and specificity, cTnI is an appropriate biomarker for identification of cardiac injury[44]. However, at least 30% of patients with severe coronary syndrome in the absence of elevated ST interval on their electrocardiogram also have undetectable troponin levels in clinical assay[45]. The precise detection of these biomarkers that have a low concentration in plasma is a big challenge in proteomics approaches, as almost 99% of plasma is occupied by highly abundant proteins; as a result, the precise detection of low abundance and rare proteins/biomarkers is tricky due to possible false-positive and/or false-negative results that can affect critical clinical decisions.[46] Thus, new high-sensitive troponin assays utilizing nanotechnology capable of precise detecting cTnI in the nanogram per liter range are urgently needed.

One strategy for recognition of low concentrations of cTnI is to use targeted nanoparticles that can specifically bind to the desired proteins (see Table 2 for details). The targeted nanoparticles are designed to specifically attach to the desired biomarkers due to their ability

to concentrate these proteins at their surfaces. For example, peptide- or antibody-conjugated nanoparticles and nanorods have been developed to robustly detect cTnI, myoglobin, and CK-MB in human plasma/serum with a much higher detection sensitivity (i.e., in the range of pg/ml) compared to the conventional detection strategies.[87–93]

Asides from circulating biomarkers, nanoparticles have been developed to target the sites of overexpressed biomarkers/receptors such as CD13 and collagen. For example, cyclic NGR peptides targeting quantum dots[94] and liposomes[95], which selectively bind to CD13, have been successfully developed and used for detection of myocardial angiogenesis.

One of the central obstacles in the applications of targeted nanoparticles is the formation of the biomolecular/protein corona (i.e., a layer of biomolecules which covers the surface of nanoparticles upon their interactions with biological fluids[98–100]), which can substantially reduce the sensitivity of this target-based strategy (Figure 1). The protein corona can shield the targeting species at the surface of the nanoparticle, which reduces the sensitivity of the detection approach and also causes false positive/negative outcomes. We hypothesized this concept in 2011[101], which was validated experimentally in 2013[102,103]. For example, it was shown that silica nanoparticles functionalized with transferrin, which were developed to target transferrin receptor, lost their targeting capacity after incubation with plasma.[102]

There are several proposed strategies to minimize the shielding effect of protein corona and increase the detection/targeting efficacy of nanoparticles. One strategy is to minimize protein adsorption using coatings, among which zwitterionic compounds have demonstrated a strong potential (Figure 2A). For example, corona-free gold nanoparticles can be created using a series of zwitterionic coatings.[104] Combining a zwitterionic coating and targeting ligands may improve detection/targeting efficacy of nanoparticles by reducing the shielding effects of the protein corona. For example, the development of silica nanoparticles conjugated with biotincysteine (as a targeting molecule and zwitterionic ligand, respectively) could minimize corona-induced mistargeting.[105]

Another strategy to minimize protective shielding by the biomolecular corona is to pre-coat nanoparticles and directly enroll unique plasma proteins consisting of essential targeting capabilities through protein-protein interactions (Figure 2B). For example, pre-coating silica nanoparticles with gamma-globulins was found to enrich the biomolecular corona with various types of opsonin proteins such as immunoglobulins.[106] Opsonin-enriched nanoparticles should be very effective in targeting macrophages that have Fc receptors. However, there was no significant enhancement of nanoparticle uptake by macrophages, although their corona was rich in opsonin proteins, highlighting the importance of attaching functional binding motifs to their cell receptors.[107] This strategy should be further evaluated by enhancing the exposure of targeted proteins with more readily available functional motifs for cell receptors or targeted biomarker to achieve the desired targeting/detection efficacy.

A very recent report revealed that the pre-adsorption of antibodies on the surface of nanoparticles can maintain targeting capacity of nanocarriers in the presence of the protein corona, whereas the targeting capacity of chemically conjugated antibodies was substantially reduced by the formation of protein corona (Figure 2C).[108]

3. DEVELOPMENT OF NANOTECHNOLOGIES TO PREDICT LONG-TERM EFFECTS OF HEART FAILURE ON CARDIAC INJURIES

The current clinical setting may benefit from the development of novel nanotechnologies that can provide more information on the disease/injury progress and therefore predict the risk of substantial reduction in cardiac functions caused by subtle initial ischemic injuries. Development of nanotechnologies for identification and discrimination of disease at different stages is of crucial importance for a wide range of diseases, including cancer, cardiac, and neurodegenerative diseases. To the best of our knowledge, no nanotechnology-based approach has been developed to monitor and predict cardiac disease progression. However, a new technique based on the combination of protein corona and sensor array technology was recently developed for the identification and discrimination of cancers at various stages with excellent sensitivity, specificity, and prediction accuracy (Figure 3 A and B).[110] This protein corona sensor array technique uses classification approaches to analyze the composition of protein corona at the surface of various nanoparticles and find their association with diseases. The use of cohort sample from healthy people who developed various types of cancers eight years after plasma collection revealed the efficacy of the platform even in the very early stages of cancers (Figure 3 C and D).[110]

The protein corona sensor array has been successfully used to discriminate between healthy individuals and patients with multiple sclerosis and Alzheimer's disease.[111] We therefore suggest that a similar technology may allow the identification, discrimination, and prediction of the cardiovascular disease and HF progression. If successful, the outcomes of the protein corona sensor array technology will help facilitate the management of cardiac patient care and treatment plans.

4. NANOTECHNOLOGIES FOR DELIVERY OF THERAPEUTIC MOLECULES INTO THE DAMAGED PART OF MYOCARDIUM

The main goal for an efficient and safe pharmacological treatment is the sustained and targeted delivery of biomolecules/drugs to the site of injury.[112,113] In this regard, targeted nanoparticles (using specific targeting moieties) have shown promise to efficiently deliver drugs to heart tissue. Well-defined biomarkers of MI, which can be used as potential targeting sites for nanoparticles, are presented in Figure 4. Table 3 summarizes representative examples of nanoplatforms developed to target damaged heart tissue and deliver biomolecules/drugs.

Angiotensin II type 1 (AT1) receptor is one of the targeting sites that are being used for HF treatment.[114] Development of nanoliposomes functionalized with ligands targeting the AT1 receptor demonstrated highly efficient attachment to cells expressing the AT1 receptor in the infarcted area.[115] Other biomolecules used for fabrication of targeted nanoparticles included matrix metalloproteinase (MMP) enzymes (MMP2 and MMP9). For example, MMP-responsive spherical micellar nanoparticles were able to retain and localize in the infarcted tissue of a rat model of MI.[116]

N-acetylglucosamine (GlcNAc) has a known high affinity for cardiomyocytes and tendency to be taken up by these cells. Therefore, conjugation of this sugar compound to the surface of nanoparticles may increase its uptake by cardiomyocytes. In a test of this hypothesis, p38-inhibiting SB239063-loaded polyketal nanoparticles were functionalized with GlcNAc and injected into a myocardial-infarction rat model. The outcomes revealed the accumulation of the nanoparticles in the myocardium resulted in substantially improved cardiac regeneration and function by salvaging the stunned cardiomyocytes.[117] Unregulated calcium signaling and abnormal calcium release worsened cardiac contractility disorders and arrhythmias in failing cardiac myocytes.[118,119] S100A1 protein and N-acetylglucosamine bound to and modulated the proteins involved in calcium regulation (e.g., SERCA2a, PLB, RyR2, and STIM1).[120,121] Expression levels of S100A1 in myocardial tissue seemed considerably down-regulated in end-stage HF. Intracoronary delivery of the human S100A1 gene by a first-generation adenovirus reduced the level (i.e., S100A1) in an established chronic HF rat model rescuing both contractile performance and Ca^{2+} cycling of the failing myocardium[122]. Maxwell et al.[123] demonstrated that GlcNAc nanoparticles carrying S100A1 protein modulate calcium signaling pathways and decrease irregular calcium release in failing cardiac cells. These bioactive nanoparticles efficiently delivered the therapeutics into the failing cardiac cells and provided an additional therapeutic impact through modification of proteins involved in signaling pathways.

Insulin-like growth factor-1 (IGF-1) improves cardiomyocyte survival after MI. Therefore, its safe delivery at high concentrations to infarcted areas of the heart may improve cardiac regeneration/function.[124–126] Chang et al.[127] employed this strategy to show that IGF-1-loaded PLGA/PEI nanoparticles considerably decreased both the left ventricular diastolic/systolic dimensions and the infarct size, as well as increased fractional shortening (FS) after injection into the border district of the infarcted part in a mouse model of MI.

Coenzyme Q10 (CoQ10) is a powerful endogenous antioxidant that has been extensively investigated for use in treatment of cardiovascular disease, particularly coronary artery disease and HF[128]. CoQ10-loaded liposomes administered to rabbits with an experimental MI were found to extend the intracellular delivery of CoQ10 and consequently reduce the portion of the permanently damaged myocardium[129].

In addition to drugs, nanotechnology can also deliver genes and RNA to improve cardiac functions by modifying the expression of cardiac genes and their consequent protein secretion.[137–141] Although viral and plasmid vectors are commonly used for gene transfection purposes, the *in vivo* results of these studies have not been replicated in humans.[142] For example, therapeutic genes delivered to heart tissue via intravenous injection of viral vectors cannot properly localize in the infarcted areas and are distributed to other organs.[143] To increase their efficacy, viral vectors encoding genes involved in heart regeneration are directly delivered to the damaged area through intramyocardial injection.[144] However, this administration route is invasive and may cause considerable adverse effects in patients with acute heart disease. Therefore, the development of alternative carriers for RNA delivery is of great interest. Nanoparticles are utilized for the safe and efficient delivery of genes and RNA to treat various diseases, including cardiovascular disease[138–141] (see examples in Table 4).

Vascular endothelial growth factor (VEGF) is known as a distinguished proangiogenic cytokine. VEGF has been found to significantly promote the neovascularization of patients' hearts. Therapeutic neovascularization was investigated in an ischemic rat model by using VEGF–dextran–PLGA microsphere-loaded fibrin gel[145].

Magnetic properties of nanoparticles can empower their targeting and therapeutic efficacy through the use of external magnetic force guidance.[112,152] For example, by using an external magnetic field, magnetic nanobeads containing adenoviral vectors (Ad)-encoded *hVEGF* gene (Ad*hVEGF*) were found to better reach the infarcted area in a mouse model of MI, promoting cardiac regeneration and function specifically through efficient *hVEGF* gene delivery.[148,153]

Combining magnetic and thermal-responsive polymeric nanoparticles creates a smart nanoplatform with the capacity to deliver drugs to targeted sites (Figure 5).[152] In such nanoplatforms, therapeutic biomolecules are loaded into the thermal-sensitive polymeric structure. Upon reaching the targeted site, magnetic nanoparticles are heated by an alternating an external magnetic field, breaking the chemical bonds in the thermo-sensitive polymeric carriers and therefore releasing the therapeutic biomolecules. It is noteworthy that the induced local heat by nanoparticles is strongly dependent on the nanoparticles' physiochemical properties.

The possibility of nanoparticles being targeted by the immune system is a significant barrier preventing the efficient delivery of therapeutics to the desired sites inside the heart. There are several approaches to develop nanoparticles with high blood residency times. One approach to enable nanoparticles to escape from immune system is to coat their surfaces with platelet membranes.[154,155] Another approach is to control the protein corona profile on the surface of nanoparticles in such a way as to minimize their possible interactions with the immune system (e.g., by minimizing the contribution of opsonin proteins in the corona composition[156]).[99,157,158] For example, the formed protein corona at the surface of liposomes was recently found to strongly control their interactions with peripheral blood mononuclear cells (PBMCs) involved in liposome removal from the bloodstream.[159] Pre-coating of liposomes with human plasma proteins has been shown to be an effective strategy to minimize liposome capture by circulating leukocytes, which in turn can enhance their blood residency time (Figure 6).[159]

5. CELL THERAPY: CHALLENGES AND OPPORTUNITIES

Cell therapy involves the transfer of therapeutic cells, such as bone marrow-derived mesenchymal stem cells and patient-specific cardiomyocytes obtained mainly through reprogramming of human cells to induced pluripotent cells (hiPSCs) that are differentiated to induced cardiomyocytes[160,161], to the myocardium to allow therapeutic myocardial regeneration and/or improvement in cardiac functions. It is important to note that cell therapy is still in its infancy and undergoing initial clinical trials, and is not currently widely available for clinical application. These therapeutic cells can release paracrine factors that can help stunned or hibernating cardiomyocytes in the peri-infarcted area of the heart recover and thus bring about cardiac salvage.[162–164] More specifically, the transplanted cells

assist in the generation of growth factors, cytokines, and other signaling molecules. These activities improve myocardial functionality through particular mechanisms such as improvement in myocardial perfusion owing to angiogenesis, prolongation of the survival of myocytes or other cells, and activation of progenitor cells within the myocardium that function as new cardiomyocytes.[165]

Apart from cardiac salvage, the therapeutic cells can also aggregate in the damaged tissue to help regenerate the myocardium.[166,167] Besides induced patient-specific cardiac cells, clinical studies have also investigated other appealing methods such as the utilization of skeletal myoblasts, bone marrow mononuclear cells, bone marrow progenitor cells, mesenchymal stem cells, and cardiac stem cells to treat patients with chronic HF. However, the proposed mechanisms underlying the benefits of cell therapy are still uncertain.[168] Some research suggests that the trans-differentiation of hematopoietic stem cells into cardiac myocytes is unattainable, despite the observation of a few cell fusion events. In addition, autologous skeletal myoblasts are capable of contraction but not of transdifferentiation into cardiomyocytes.[169–171]

A 2014 meta-analysis using an organized evaluation examined 23 arbitrary controlled trials of autologous adult bone marrow-derived stem cells in 1,255 participants who had chronic ischemic heart disease and HF.[172] This study found only low-quality evidence supporting benefit for mortality at a minimum period of 12 months based upon data from 8 trials with 494 participants. The low-quality evidence indicated that 12-month mortality was not significantly improved based upon data from 21 trials with 1,138 participants. Moderate-quality evidence for improvement in the LVEF and the NYHA functional class was found at less than 12 months and at 12 months or longer. Negative results were infrequent, and no long-term discouraging consequences were reported. An in-depth valuation of potential hazards associated with cellular cardiomyoplasty as a therapeutic modality was not possible due to the limitations of available clinical data.

With the research in myocardial reproduction focused mostly on cell-based cardiac repair, the cell therapy approach still faces several main limitations, including: i) insufficient cell retention and engraftment along with electromechanical coupling of therapeutic cells in heart tissue[12–16]; ii) difficulties in efficient conveyance of therapeutic cells to the injured part of myocardium and *in vivo* monitoring therapeutic cells using clinical MRI; iii) teratoma formation due to the existence of undifferentiated stem cells[149,173]; iv) difficulty in preparing mature patient-specific cardiomyocytes[17–20]; v) significant differences in structure and functionality between human hiPSC-derived cardiomyocytes and adult mature primary cardiomyocytes, in addition to the difficulty of aligning cells in culture[174]; and vi) risk of ventricular arrhythmia occurrence[16]. In this section, we provide information on nanotechnologies' potential to overcome the predetermined issues of cell therapy.

5.1. Development of Nano-Based Approaches to Enhance Therapeutic Cell Retention and Engraftment in Myocardial Tissue

Cell replacement in heart is one of the most common therapeutic approaches used to heal damaged tissue and restore heart function after heart failure. However, low cell engraftment and retention are the main limitations of cell transplantation because of washout by the

coronary vein.[175,176] The immune system plays an key role in reducing the retention of the transplanted therapeutic cell. Overall, some 95–99% of cells directly injected in myocardium are often lost before 80h.

Several types of nano-based approaches have been developed to overcome the predetermined low cell engraftment and retention issues. The first strategy is to enhance the effectiveness of therapeutic cell delivery is to safely magnetize therapeutic cells using magnetic nanoparticles, and deliver them to the distressed myocardium by applying an external magnetic field.[177] As these magnetic nanoparticles are also used as contrast agents and therefore detectable by magnetic resonance imaging, labeled cells can then be monitored using clinical MRI.[178,179] Enhancing the magnetic properties of therapeutic cells can substantially increase their targeting efficacy and monitoring sensitivity. One strategy to enhance their magnetization is by encapsulating a large number of magnetic nanoparticles in polymeric microparticles. For instance, iron oxide nanoparticles can be encapsulated in biodegradable poly(lactide-co-glycolide) microparticles (PLGA MPs), which are easily taken up by the therapeutic cells and could be retained for more than 10 days (Figure 7). The long-time residence of iron oxideloaded PLGA-MPs in the transplanted cells can substantially enhance signal intensity and other parameters (e.g., R_2 signal and r_2 relaxivity), consequently improving their detectability by MRI.[180]

The second strategy is to develop dual antibody-targeted nanoparticles that can be conjugated to the markers on the surface of both therapeutic cells and injured cardiac cells.[181] These types of nanoparticles can connect therapeutic cells to injured cells, facilitating their retention and improving their therapeutic efficacy. As an example, the use of anti-CD45- and anti-MLC-conjugated iron oxide nanoparticles was found to significantly improve the integration of therapeutic and damaged cells, which in turn substantially improved the heart function in a rat model of MI.

The third strategy to enhance therapeutic cells' engraftment and retention is developing nanotechnologies to reduce the triggered inflammatory responses after MI. For example, it is known that the extra infiltration and continuous localization of proinflammatory $Ly6C^{high}$ monocytes exacerbate the inflammatory response and extend the infarcted area.[182] The overexpression of receptor C-C chemokine receptor 2 (CCR2) enhances the $Ly6C^{high}$ infiltration and as such can be used as a suitable therapeutic target to suppress the inflammation response.[183] To this end, photoluminescent mesoporous silicon nanoparticles were developed as a nanocarrier for delivery of siCCR2 into $Ly6C^{high}$ monocytes. The siCCR2-loaded nanoparticles distribute siCCR2 into monocytes and therefore suppress the CCR2 gene, improving the life time/survival level and therapeutic efficacy of transplanted therapeutic cells.[184]

The fourth strategy is to create a microenvironment using nanofibrous materials to improve therapeutic cell retention. Self-assembling peptide nanofibers are a good example as they are liquid in acidic pH and can form a three-dimensional scaffold at physiological pH. By combining the therapeutic cells with these fibers, the fibers form a jelly microenvironment after injection to the myocardium that can preserve the therapeutic cells.[185] For example, it was demonstrated that myocardial injection of the combination of nanofibers and bone

marrow mononuclear cells led to longer retention time and survival for the therapeutic cells, which in turn improved both systolic and diastolic functions in a mature minipig model of MI.[186]

The fifth strategy is to entrap the therapeutic cells in nanostructured hydrogels and engraft the hydrogels to the surface of damaged heart tissue.[187,188] Compared to the direct cell injection strategies, the use of cellular patches protects the therapeutic cells against immune rejection. The attachment of these patches to the heart tissue can be performed using a variety of approaches, including conventional stitching[189] and advanced thermal integration with plasmonic nanoparticles[190]. For example, UV-vis thermal activation of the embedded gold nanoparticles in cellular patch demonstrated a promising capacity in patch integration to the myocardium tissue of rat hearts after infarction (Figure 8).[190]

The sixth strategy is to fabricate three-dimensional cardiac porous patches containing therapeutic cells.[187,188,191,192] This strategy enables therapeutic cells to release their paracrine factors to the damaged area of the heart while being protected from fast immune system removal (as the immune system has no access to the patches). As these patches are mainly made out of biopolymers[193–195], they have limited synchronized capacity with the embedded cells mainly due to their poor conductivity. The conductivity of the patches can be substantially enhanced by incorporation of conductive materials/polymers in the patch structure.[196] In one example, gold nanowires were incorporated in alginate patches to improve their conductivity. Studies revealed that the conductive patches could create thicker, better aligned tissues, and higher levels muscle contraction and electrical coupling proteins compared to the patches without nanowires.

5.2. Improving *In Vivo* Monitoring of Therapeutic Cells

Due to their unique capacity to serve as contrast agents, magnetic nanoparticles have been widely used to track the therapeutic cells *in vivo*. Among a wide range of magnetic nanoparticles, superparamagnetic iron oxide nanoparticles are the most commonly used nanoparticles for biomedical applications mainly due to their biocompatibility properties. Although the cell tracking using these nanoparticles demonstrated promising outcomes, recent findings also revealed that this cell labeling strategy may have a risk of producing false-positive signals through i) a newly discovered phenomenon known as "remagnetization"[197] and ii) NP excretion from the cells after cell death or exocytosis[198,199].

Remagnetization happens after labeling of stem cells with magnetic nanoparticles. The stem cells first degrade nanoparticles and then synthesize new magnetic nanoparticles using the released iron by degradation of the nanoparticles.[197] The magnetic nanoparticles can also be released through exocytosis process of the cells or cell death[200]. These processes may cause false-positive MRI signals that do not accurately indicate the viability and/or location of the stem cells. For example, through combinatory approaches (e.g., using both MRI and luminescence imaging) scientists revealed that MRI signals persisted in the heart muscle of animal models for weeks after disappearance of the stem cells.[199,201]

Two strategies were proposed to minimize the risk of the predetermined false-positive outcomes. The first strategy is to genetically modify the therapeutic cells to overexpress iron

compounds like ferritin. For example, mouse skeletal myoblasts were genetically manipulated to overexpress ferritin, and the engineered cells were then tracked with MRI up to three weeks after transplantation.[202] The second strategy is the label therapeutic cells with live contrast agents (i.e., magnetotactic bacteria). Recent findings revealed that the signal from the therapeutic cells labeled with a live contrast agent was cleared within one week of cell death, whereas the labeled cells with the iron oxide nanoparticles persisted over two weeks after cell death (Figure 9).[203]

5. 3. Nanotechnology-Based Approaches for Minimizing Teratoma Formation

One major problem with using therapeutic cells in cardiac regeneration is the risk of teratoma formation.[204,205] The risk of teratoma formation usually comes from the existence of undifferentiated stem cells (e.g., iPSCs) in the therapeutic cells. Therefore, to ensure the clinical safety of transplanted cells, it is essential to develop new generation of sensors that can detect undifferentiated cells with high specificity and sensitivity. To that end, targeted nanoparticles were developed to identify specific cell types in cell mixtures.[206,207] For example, targeted Raman-tagged gold nanoparticles were developed to be attached to the specific receptors on the surface of iPSCs, including antigen-5 (SSEA-5) and TRA-1–60.[208] The NP could specifically identify undifferentiated iPSCs through their specific receptors with high sensitivity (~0.0001%).

The same strategy can be used to remove traces of undifferentiated stem cells in the therapeutic cells using magnetic nanoparticles. The cells labelled with magnetic nanoparticles can be fully removed from the therapeutic cell mixture using well-defined magnetic separation approaches such as the magnetic-activated cell sorting (MACS)[209] system.

5.4. Development of Nano-Based Approaches to Improve Maturity and Alignment of hiPSC-Derived Cardiac Cells

Growing evidence points to substrates mechanical and morphological characteristics having a unique capacity to direct stem cell differentiation and maturation.[210–214] Substrates that mimic the shape and/or tissue stiffness of adult mature cardiomyocytes are shown to have a profound effect on inducing maturation into hiPSC-derived cardiomyocytes.[215,216] For example, polyacrylamide substrates can be made with physiological stiffness and two-dimensional shape of adult cardiomyocytes (created through Matrigel micropatterns) to improve the maturation of immature hiPSC-derived cardiomyocytes (see Figure 10 for details).[215]

Building nanopatterned substrates that mimic the 3D shape of mature cardiomyocytes may provide additional opportunities not only for improving reproducibility of the differentiated cardiomyocytes through the chemically defined approach, but also enhancing the maturation and alignment of immature differentiated cardiomyocytes.[216] The bioinspired substrates may also have the capacity to induce physical differentiation of hiPSCs toward mature cardiomyocytes without chemical growth factors. This work builds on the recently presented proof-of-concept data supporting the capacity of cell-imprinted substrates to direct differentiation of stem cells toward mature cells[214,217–220] and early versions of the

substrates with cardiomyocyte shapes. Abadi et al.[216] developed bioengineered substrates to generate mature cardiomyocytes from hiPSCs, using a combination of photolithography and the reflow process (Figure 11A) to create cylindrical micropatterns and cell-imprinted primary human mature cardiomyocytes for formation of submicron-level cell-surface asperities on substrates made of polydimethylsiloxane (PDMS). They found that micropatterned substrates could effectively produce aligned, mature, and functional cardiomyocytes (Figure 11B).

These strategies of maturation, along with others[221–223] (e.g., long-term culturing), may reduce the risk of cardiac arrhythmia (i.e., abnormal rate and rhythm of heartbeat), by improving the low maturity and efficacy of therapeutic cells by aligning, integrating, and synchronizing them with the host cardiac cells.[224,225]

6. NANOTECHNOLOGY-BASED APPROACHES TO REDUCE OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION

The production of reactive oxygen species (ROS) is a significant side effect in reperfusion injury. The ROS including superoxide anion, hydrogen peroxide (H_2O_2), and hydroxyl radical are highly reactive compounds, and therefore capable of oxidizing the proteins, nucleic acids, and lipids. The ROS, formed as a natural by-product compounds in the process of the aerobic metabolism, are primarily derived from oxygen molecules. In association with multiple cellular signaling, ROS perform an important role as secondary messengers in ordinary conditions. Consequently, appropriate antioxidants are adapted in the process to control and restrain the ROS levels in the range of picomolar. However, ROS are also produced by several processes/pathways involving the myocardium and/or infiltrating inflammatory cells[226–228]. The pathological mechanisms in cardiac I/R injury are responsible for overproduction of such compounds.[228–230] Oxidative stress is induced in tissues/cells after myocardial reperfusion injury. Myoglobin and hemoglobin, which are known as non-enzymatic source of ROS, increase after myocardial reperfusion injury.[231] The enzymatic ROS, produced after myocardial reperfusion injury, are produced by the enzymatic reduction of molecular oxygen to form H_2O_2 and/or superoxide. Xanthine oxidase, NADPH oxidase (Nox), mitochondria, cytochrome p450 and uncoupled nitric oxide synthase are the main sources of enzymatic ROS/RNS generated after myocardial reperfusion injury.[232–234] Myocardial reperfusion injury induces the overexpression of inducible NO synthases that triggers nitrosative stress and consequent heart damage.[235] After myocardial reperfusion injury, the metabolism of copper and iron is impaired and the excess copper/iron induce ROS formation.[236]

ROS can affect vital functions of cardiac cells, including their growth, metabolism, and proliferation through several pathways (e.g., damage to cell membranes and activation of apoptotic pathways).[237,238] Therefore, strategies that minimize ROS after reperfusion injury are clinically important and can diminish the deteriorative effects of reperfusion injury on the myocardium. Among various antioxidants, superoxide dismutase (SOD), glutathione (GSH), and glutathione peroxidase (GPx) can attenuate the damaging effects of ROS[239]. For instance, in transgenic mice whose SOD is overexpressed, the dimension of the infarct is

noticeably reduced. However, there are reports of antioxidants failing to prevent an injury or demonstrating an early protective effect in some studies, though this outcome decreased as the duration of reperfusion increased[240]. A promising approach to prevent, or at least minimize, the adverse effects of oxidative stress, calcium influx, cell membrane disruption, and mitochondrial dysfunction (see examples in Table 5) is utilization of nanoparticles for antioxidant delivery.

The generation of excess ROS exacerbates the pathogenesis of ischemic reperfusion injury. For instance, hydrogen peroxide (H_2O_2) triggers ischemic reperfusion through the induction of inflammation, cell apoptosis, and tissue damage.[241,242] H_2O_2-responsive nanoparticles/nanocarriers may be used as a new approach to diagnose and treat H_2O_2-induced ischemic reperfusion injury. It is noteworthy that a variety of stimuli-responsive nanoparticles have been used to deliver suitable drugs against reperfusion injury. For example, Lee et al.[243] developed (VA)-loaded copolyoxalate polymeric nanoparticles that responded only to high concentrations of H_2O_2. When exposed to high levels of H_2O_2, the polymeric nanoparticles released the vanillyl alcohol and reduced tissue impairment by preventing ROS overproduction, inflammation, and apoptosis. Various types of stimuli-responsive (e.g., pH and thermal) nanoparticles have the ability of transporting therapeutic agents to the site of ischemic reperfusion injury (Figure 12).[244–247]

ROS is known as the main cause of arterial stenosis. During inflammation, NOX enzyme family (component of NADPH oxidase enzyme) produces ROS (H_2O_2 and O_2^-).[250] Lysine-based nanoparticles can be used for delivery of siRNA specifically targeting NOX2 into damaged artery. For example, the delivery of effective concentration of NOX2-specific siRNA was found to suppress the expression of NOX2 and prevented neo-intimal hyperplasia after angioplasty.[251]

Some food-derived isolates have therapeutic advantages beside their natural usage in nutrition.[252] The application of nanotechnology in formulation of NP-food complex with nutritive and therapeutic benefits is an attractive strategy to prevent/treat the cardiovascular diseases. Curcumin is a typical type of nutraceuticals (food compounds with therapeutic properties) with cardioprotective effects.[253] It prevents the cardiac inflammation or oxidative stress which triggers I/R injury.[252,254,255] Nisin, a peptide used for treatment of cancer and bacterial infection, is another nutraceutical existing in some diets.[256] These nutritive compounds have demonstrated natural therapeutic benefits when they are encapsulated in PLGA nanoparticles. For instance, the formulated curcumin-Nisin Based Poly Lactic Acid nanoparticles showed cardioprotective effects by triggering the cascades involved in the antioxidant defense system or inhibition of inflammation.[257]

Oxidative stress has the capacity to alter the mitochondrial metabolism pathway toward glucose consumption and reduction of ATP generation,[258] mainly by interfering with ROS during the transportation of p53 to the mitochondria.[259–261] The development of nanocurcumin was shown to solve this effect[249] by impeding p53 transportation into mitochondria, which is accomplished through strengthening the mitochondrial membrane. The nanoparticles restored mitochondrial function/homeostasis and protected

cardiomyocytes from mitochondrial metabolic shift to glucose as a favorite substrate for creating energy.[249]

Mitochondrial dysfunction triggers cardiomyocyte apoptosis/necrosis and enhances HF.[262] Therefore, restoring mitochondrial function using therapeutic drugs can be an effective approach to minimize cardiomyopathy and HF. One of the main challenges of this approach is the delivery of therapeutics to cardiomyocytes' mitochondria.[262–265]

The mitochondrial permeability transition pore (mPTP) is opened in the in initiation of reperfusion injury to neutralize the mitochondrial oxidative stress.[266] It is well-recognized that the opened mPTP induces cardiomyocyte apoptosis/necrosis. Therefore, mPTP-opening inhibitors such as cyclosporine A (CsA) used as an immunosuppressive drug can be effective for reducing the HF progression.[267] Experiments revealed that the intravenous injection of CsA could not prevent HF in human patients.[263] This was because the therapeutic effects of CsA is only exerted when it reaches inner mitochondrial membrane of ischemic cardiomyocytes and binds to cyclophilin D.[268] To tackle this issue, nanoparticles have been recently developed for targeted delivery of mitoprotective agents to cardiac mitochondria, and the outcomes revealed their preferential penetration into the damaged myocardium. For example, PLGA nanoparticles loaded with CsA could accumulate in myocardium mitochondria and prevent mPTP-opening and, in turn, limit HF progression.[269]

7. DEVICE-BASED TREATMENT OF HEART FAILURE

There are several implant-based approaches, such as implantable cardioverter-defibrillator (ICD) therapy[270,271] and cardiac resynchronization therapy (CRT),[270,271] in clinical use to prevent death in patients with HF. Although nanotechnologies may have a promising role in enhancing the efficacy of these approaches while minimizing their side effects, their current use in the field is rather limited. CRT, for example, is an effective treatment for symptomatic HF patients with LV dyssynchrony. This therapy is currently recommended for advanced HF patients with NYHA class III or IV, severe systolic dysfunction (LV ejection fraction ≤35 percent), and intraventricular conduction delay (QRS >150 milliseconds).[270,271] A major problem of CRT-based approaches is the risk of thrombosis, specifically due to the implantation of internal foreign materials in in the coronary sinus that is next to the LV. Nanotechnology may greatly help miniaturize the implantable CRTs to reduce the risk of thrombosis as well as enhance their therapeutic efficacy.[272] In addition, new nanotechnology approaches may be able to enhance the sound receptors of the CRT to optimize the resynchronization process. Such miniaturized nano/micro sensors can be built into the tip of the leads[273] in direct contact with the wall of heart to enhance the sensitivity and therapeutic efficacy of the CRT approach.

Another significant challenge with the use of implantable devices that may be resolved by nanotechnology is the risk of corrosion and immune reactions to the foreign material. Miniaturization of the implant size can substantially reduce the interaction of the implant device with biological fluids, diminishing the risk of corrosion and unwanted immune reactions. Another potential role of nanotechnology in cardiac implants is the possibility of controlling the implant function with a wireless and long-lasting power system. A main

obstacle in making efficient wireless cardiac implants is the limitation of battery size.[274] The use of nanotechnology has already enhanced the effectiveness of a wide range of batteries by reducing their size.[275–278] Modification of these technologies to make highly biocompatible cardiac implantable materials will enable clinicians to use the wireless miniaturized implantable technology to delay or prevent HF.

8. POTENTIAL OF NANOTECHNOLOGY IN CARDIAC IMMUNO THERAPY

Nanomaterials possess immunomodulatory effects that may be used to promote and shape the humoral immune response in cardiovascular diseases[279]. This is relevant as both the innate and acquired immune systems may have an effect on cardiovascular illnesses like hypertension and HF. Reduced macrophage infiltration in the arterial wall has been correlated with an improvement of hypertensive disease in experimental models. Inflammation is known to be a significant contributor to the development of HF, especially in heart failure with preserved ejection fraction (HFpEF)[280]. The inflammatory response stimulates regenerative processes that then leads to a severe myocardial injury. Our knowledge about the fundamental mechanisms behind such adaptations is improving after recent investigations on humans and animals[281]. Furthermore, inflammation, depending on its amount, localization, and duration, may have both advantageous and disadvantageous effects. While excessive expression of tumor necrosis factor alpha (TNFα), a cytokine involved in the pathogenesis and progression of myocardial ischemia/reperfusion injury and HF[282], induces contractile dysfunction, hypertrophy, fibrosis and cell death, a lower TNFα concentration is protective. In chronic HF, activation of the immune system promotes the production and release of proinflammatory cytokines that constitute a key factor in the propagation and magnification of the immune response. Stimulation of cell division, proliferation, and differentiation can be induced using cytokines that engage cells to the area of inflammation. Hence, neutralization of improper inflammatory cytokines is emerging as an effective therapeutic approach under a variety of chronic inflammatory circumstances.

Immunomodulation therapy (IMT) is a type of immunotherapy that involves the removal of the patient's blood to be treated and re-administered via intramuscular injections.[283] The treatment is thought to boost immune cells' ability to activate immune modulators.[284] IMT is thought to involve the downregulation of proinflammatory cytokine levels along with upregulation of anti-inflammatory cytokines. Optimizing changes in the balance between proinflammatory and anti-inflammatory cytokines may prove more beneficial than the neutralization of single cytokine activities in treating conditions such as CHF[283]. Non-specific immunomodulation may also have a potential role for treating a large segment of the heart failure population by including patients with no history of MI. Although there is evidence on the benefits of IMT, its precise mechanisms remain to be established.

Nano-immunotherapy is a new and increasingly popular approach in nanomedicine with great potential for cancer treatments.[285,286] For instance, superparamagnetic iron oxide nanoparticles were found to change the functionality of tissue associated macrophages from M2 to M1 and therefore could be used to reduce cancer growth.[285] In the last few years, nanotherapeutics have been increasingly used to modulate immune responses in cardiovascular disease (Table 6). nanoparticles are a promising candidate to drive

macrophage polarization from M1 to M2 to repair infarcted area and survive injured cardiomyocytes. Polyurethane (PU) nanoparticles specifically were found to suppress the polarization toward M1 macrophage, reduce the production of inflammatory cytokines (TNF-α and IL-1β), and inhibit the activation of NF-κB and inflammasome signals.[287] They also induced the polarization of macrophage from M1 to M2 after subcutaneous implantation in rats. The PU nanoparticles functionalized with carboxyl group showed stronger inhibitory effects than those conjugated to the amine group. Therefore, PU NP is a potential candidate for modulation of immune response and nano-immunotherapy of heart-related diseases.

In contrast, polystyrene nanoparticles conjugated to carboxyl or amine functional group were found to specifically suppress M2 polarization and considerably reduce the expression of IL10, scavenger receptor CD163, and immune-inhibitory CD200R.[288] They did not affect the expression/release of proinflammatory cytokines produced by M1. The modified polystyrene nanoparticles can be used to impede cancer progression. Therefore, depending on their physicochemical properties (e. g., composition, charge, and functional groups), nanoparticles show different effects on macrophage polarization.

Despite considerable research efforts to advance stem cell therapy for heart disease and impressive progress in anti-inflammatory process, stem cell-based therapeutic approaches have several limitations in terms of cost and time of cell isolation and implantation adverse effects.[13,289,290] For example, the dendritic cells used for tuning the polarization of M1 to M2 macrophage affect whole systemic immune system.[291] M1 macrophages induce the proinflammatory pathway, while M2 macrophages trigger anti-inflammatory pathways and activate signaling cascades involved in cardiac repair.[292] The microenvironmental stimuli/conditions govern the polarization of macrophages into M1 and/or M2. Multiple biological factors/events must be coordinated to regulate the macrophage M1-M2 polarization balance. In some cases, M2 macrophage were found to accelerate the cardiac fibrosis and tumor growth, and therefore caution should be taken in driving macrophage polarization.[293–295] Nevertheless, the timely regulation of macrophage polarization has potential to be used as an effective strategy to develop cardiac regeneration and prevent cardiac fibrosis.

ROS is known as the main cause of M1 activation and subsequent inflammatory responses. 240,296 Therefore, antioxidants may be some of the best candidates to inhibit ROS-induced M1 activation. Nano-objects such as graphene oxides, which naturally act as an antioxidant and scavenge ROS, are promising choices to prevent M1 activation.[297] Graphene oxides functionalized with polyethylenimine (PEI) and folic acid-PEG were found to specifically target immune-stimulated macrophages, diminish ROS, and suppress the ROS-mediated inflammation.[298] In the next step, this modified graphene oxide was used for delivery of interleukin 4, which facilitates the macrophage polarization from M1 to M2. The loaded IL-4 plasmid DNA showed synergistic effect with this nanocarrier (GO-PEI/PEG) and improved macrophage polarization. The IL-4 plasmid DNA-loaded GO-PEI/PEG enhanced the macrophage polarization toward M2 and consequently restored the heart function in a mouse model of MI. Therefore, this complex has simultaneous cardiac-protective and cardiac-regenerative effects.

9. NANOTECHNOLOGY-BASED APPROACHES FOR ORGAN TRANSPLANATION

Patients who undergo organ transplantation must take medications that suppress innate immune cells such as myeloid cells for a long time (possibly the rest of their lives) to prevent organ rejection.[311] Unfortunately, immunosuppressive drugs also put patients at a higher risk of infection, cancer, and other diseases caused by T-cells inactivation.[312] To deal with these intractable issues with immune suppression, it is therefore imperative to develop smart therapeutics that specifically suppress myeloid cells without interfering with T-cell activation. The epigenetic modification of myeloid cells may be an effective approach to regulate the immune response. The mammalian target of rapamycin (mTOR) is a key signaling direction that can prevent trained immunity by affecting the epigenetic reprogramming in myeloid cells.[313] It is well-recognized that high-density lipoprotein (HDL) nanobiologics specifically direct the myeloid cells in hematopoietic organs.[314] Baraza et al.[315] used theses nanobiologics to deliver the mTORi inhibitor rapamycin and TRAF6i to myeloid cells. They showed that the combination of mTORi-HDL/TRAF6i-HDL simultaneously prevents trained immunity and CD40 costimulation, allowing safe organ transplantation without immunosuppression. They used this nano-immunotherapy approach for heart transplantation in mice and showed that 75% of mice that were given 3 injections of nano-immunotherapy, during a week after transplantation, accepted the transplantation and showed no rejection symptoms even after 100 days. By comparison, untreated animals that were used as controls rejected the transplanted heart in fewer than 10 days.

The recruitment of monocytes on grafts, in which they differentiated to macrophage, triggers the cascade of allograft rejection. Therefore, capturing the circulating monocytes and targeting macrophages localized on the grafts may reduce the transplantation-induced immune response that results in allograft rejection. Liposome-encapsulated clodronate specifically targeted circulating monocyte/macrophages was found to reduce macrophage localization on the graft and prevent allograft rejection.[316]

Ischemia reperfusion injury (IRI) is an unavoidable disorder occurring after organ transplantation that triggers inflammation responses mediating graft rejection. The IRI-induced immune response and autophagy activation in dendritic cells increase the expression of IL-6, an inflammatory cytokine. IL-6 in turn triggers the signaling cascades mediating the allograft rejection. Therefore, suppressing IL-6 may be an effective strategy to prevent allograft rejection. The anti-IL-6 antibody-loaded PLGA nanoparticles may allow the efficient local delivery and sustained release of anti-IL-6 antibody for blocking IL-6 produced by dendritic cells. Anti-IL-6 nanoparticles have been shown to suppress alloreactive T cells involved in rejection and consequently prevent organ rejection.[317]

Detection of parenchymal rejection in cardiac allografts is known a major clinical challenge. Currently, serial heart biopsy after transplantation, which is performed through invasive transvenous access, is used to detect immunomodulation or rejection in cardiac allograft.[318] This technique has profound adverse effects, and in some cases can induce arrhythmia, bleeding, or infections.[319] In addition, this technique is error-prone because the limitations in its sample size and place of sampling may lead to false-negative/positive results.

The majority of innate immune cells activated through inflammation and concentrated in myocardium are macrophages; as such, they can be targeted as an attractive biomarker to monitor the rejection of cardiac allograft.[320] nanoparticles have been successfully used to detect macrophages in the infarcted area. This strategy was also used to specifically sense the macrophages localized on the graft. It is well recognized that dextran-based nanoparticles are mainly taken up by immune cells and undergo insignificant uptake by other heart cells. In one study, dextran nanoparticles, which have a long circulation time, were tagged with the PET isotope copper-64 and used for monitoring transplant rejection via PET-CT imaging. PET imaging showed that nanoparticles specifically targeted the macrophages and accurately monitored the cardiac allograft rejection or survival.[321]

10. SAFETY OF NANOMEDICINE

Over the past decade, considerable research has focused on assessing the safety of nanomaterials and improving their physicochemical properties to minimize their possible side effects in various biomedical applications.[322,323] These efforts have already resulted in substantial progress in development of safe cancer[41,324] and cardiac[36,192] nanotechnologies. Examples of the successful and safe use of nanotechnologies in cardiac salvage and regeneration have been provided in this review; more comprehensive details on the potential applications of nanotechnology in imaging and treatment of atherosclerosis plaques are found in the Supporting Information (SI). In addition, well-developed nanotechnologies are now being tested in large animals to improve cardiac functions and demonstrate their potential clinical translation (Table 7).

Although the field of cardiac nanotechnology is developing exponentially, and intriguing reports of both *in vitro* and *in vivo* studies (using a wide range of small and large animals) are being communicated to the public and scientific communities, their successful clinical translation remains elusive.[39] The new field of nanomedicine has largely overlooked factors that are present in both the *in vitro* and *in vivo* microenvironment without fully understanding the nanobio interface, resulting in reduced precision of estimation of the nanoparticles' fate and safety in human subjects.[334] We and others have made extensive efforts to correct well-intentioned misinterpretations in the current literature, mainly through identifying and characterizing previously overlooked or unknown factors at the nanobio interface, including: (i) modifying existing assays to make them more suitable/legitimate for accurate evaluation of NP toxicity; (ii) optimizing *in vitro* protocols to better mimic actual *in vivo* conditions; and (iii) developing computational approaches to more accurately identify the underlying mechanisms of action.[100,334,335] We have recently reviewed the details of extensive efforts made by various scientists to address these issues to diminish the bench-to-clinic gap in numerous biomedical applications.[36,336] More specifically, we[39] and others[337] identified several important factors that need to be carefully considered and reported in nanomedicine studies to enable the medical community to create a robust nanomedicine library (Figure 13).

As cardiac nanotechnology is still in its infancy, resolving these missing factors in reports (which is one of the main lessons learned from cancer nanotechnology) can accelerate their clinical translation. In addition, we have reviewed[322,338–340] the current literature on the

toxicity of different types of nanoparticles in both *in vitro* and *in vivo* settings. Here, we provide additional information regarding the remaining potential adverse effects and safety warnings for the use of nanotechnology in cardiac diseases that should be carefully considered and resolved by both nanotechnology experts and clinicians.

Although nanotechnology has shown promise in reducing the side effects of ischemia and reperfusion, clinical translational experts should be aware of the crucial importance of the choice of *nanoparticle composition* and their specific *physicochemical* characteristics for this particular application (see Table 8 for more details). More specifically, the use of iron-based therapeutic nanoparticles for cardiac repair requires more consideration. This is because of recent findings that iron compounds, in the presence of ROS, can induce ferroptosis, a recently discovered form of programmed cell death associated with ischemic reperfusion injury.[341–344] The iron metabolism and/or Fenton reaction (i.e., a process that converts hydrogen peroxide into a hydroxyl free radical) results in an overproduction of ROS that induces regulated cell death.[345,346] In addition, the excessive iron is toxic to cardiac cells and in some cases can lead to cardiac dysfunction.[346] The overload of iron-based nanoparticles around the reperfused area is also shown to induce adverse LV remodeling.[346]

The capacity of nanoparticles to induce inflammation and oxidative stress is another important factor that should be carefully considered before using nanoparticles for cardiovascular disease. One reason is that the damaged cardiac tissue faces complex inflammatory processes, and the induction of additional oxidative stress or inflammation may impede the healing process. A few types of nanoparticles (e.g., single- and multi-walled carbon nanotubes, TiO_2, ZnO, and CeO_2) are shown to dysregulate autonomic reflexes via the induction of pulmonary inflammation.[94,347] Therefore, the potential cardiac side effects of these specific nanoparticles that induce oxidative stress and activate macrophages should be precisely monitored in cardiovascular systems, or a substitute nanoparticle with different physicochemical properties should be used instead for this application.[94,348–353]. For instance, it was shown that TiO_2 nanoparticles could induce myocarditis by exacerbating pulmonary and cardiac inflammation and aberrant expression of Th1/Th2-related cytokines after long exposure in mice.[354] The TiO_2 nanoparticles also demonstrated disrupted endothelium-dependent reactivity through the induction of ROS.[355]

Many of the organic nanoparticles (e.g., polymeric nanoparticles) fully degrade in the human body with no sign of long-term toxicities; however, for some inorganic nanoparticles, the evaluation of the potential long-term toxicity and their biological fates is essential for safety purposes. This important issue is not well understood and must be carefully studied in future research. Recent findings revealed that polymeric coating of gold nanoparticles could be degraded due to the proteolytic enzymes in the liver.[356] This shows that the physicochemical properties of such nanoparticles may change in the *in vivo* setting and therefore cause unwanted or unpredicted toxicity, immune activation, or aggregation. Such changes in physicochemical characteristics of nanoparticles add more complexity to the inflammatory responses of the host immune system, which may bring more adverse effects than expected for the HF process. For example, it is known that gold nanoparticles with specific physicochemical properties may change the conformation of fibrinogen proteins in their

corona layer, and therefore interact with integrin receptors and activate proinflammatory cytokine release pathways.[357] In addition, studies combining molecular dynamics and experimental approaches indicated that the bare gold metal surface, if made accessible to fibrinogen, can induce unfolding of this protein as well as inflammatory response.[358]

Another important factor that requires further investigation of long-term toxicity of some types of nanoparticles is the biological fate of degraded nanoparticles and their byproducts. For example, it was demonstrated that the release of the reactive metals that are used for synthesis of some types of nanoparticles has the capacity to reach cardiomyocytes and affect cardiac function by inducing oxidative stress and inflammation.[347,359] They can also dysregulate an autonomic CV reflex by inducing pulmonary inflammation.[347,359] For instance, the release of zinc ions from ZnO nanoparticles was shown to damage the coronary artery endothelial cells by triggering inflammation and oxidative stress.[360] Another example was found by the exposure of silica nanoparticles to lung tissue of male Wistar rats, which promoted vascular and cardiac inflammation.[361] In addition, intratracheal installation of silver nanoparticles was found to increase the circulating cytokine production and worsen the inflammation and cardiac I/R injury in rat models.[362]

Apart from the potential inflammatory effects of some nanoparticles, there is evidence that some types of nanoparticles affect thrombosis-induction. The physicochemical properties of these nanoparticles affect their contribution to thrombosis induction. For example, although polystyrene nanoparticles are recognized as safe nanomedicine products, their carboxyl-functionalized coating may increase the thrombosis risk.[363] Other examples are anatase-TiO_2 nanoparticles, carbon nanotubes, and silver nanoparticles. One of the central mechanisms behind the risk increase of thrombosis by nanoparticles is their capacity to activate platelets and enhance thrombus formation via induction of several thrombosis-associated genes and pathways such as thromboxane, MMP, and GPIIb/IIIa.[364–367]

11. SEXUAL INEQUALITY IN NANOTECHNOLOGY

Important sex differences exist in the epidemiology, symptomatology, pharmacology, and treatment of HF, which affect disease progression and outcomes after its onset.[379–383] These differences between men and women are related but not limited to variations in structure, function, and physiology of heart tissue even at the cellular level.[384–394] Sex-specific transcriptomic changes can be observed in patients with new-onset HF and during disease progression.[395] Understanding these changes could present an opportunity to advance the understanding of sex-specific cardiovascular disease pathophysiology.[396]

The observed sex-specific variations may result from sex steroid hormones, variations in gene dosing on sex chromosomes, gene regulatory networks, or genomic alterations in male and female genomes.[397–400] In cancer, such sex-specific variations in gene regulatory networks and genomic alterations have been demonstrated to cause substantial differences in occurrence, development, molecular phenotypes, and response to treatment.[397,401,402] Our team has been actively working on identifying physical and sex-dependent factors that occur at the interface between biology and nanoparticles to improve new strategies for personalized interventional, diagnostic, and therapeutic strategies that promote the

successful clinical adaptation of nanomedicine and cell therapy.[106,157,203,334,403–421] We have recently discovered the crucial role of cell-sex on the cellular capacity of nanoparticles (Figure 14 A).[403] To robustly compare the role of cell sex (i.e., using early stage male and female cells without the interference of sex-specific hormones), we chose human amniotic mesenchymal stem cells (hAMSCs) from the placenta's amniotic layer for both male and female fetuses. We noticed substantial differences in cytoskeleton structure, function, and paracrine factor release of hAMSCs for both sexes (Figure 14 B). These sex-specific variations may alter both the protein corona composition at the surface of nanoparticles and also their cellular uptakes and intracellular pathways. We also found that the cell sex markedly affects their reprograming capacity toward hiPSCs (Figure 14 C).

The role of cell sex on nanotechnology is scarcely investigated, with very few papers in the field.[403] The National Institutes of Health (NIH) is developing rigorous policies that require scientists to consider the effect of sex as a biological factor in the study design, analysis, and reporting of all basic and preclinical studies. As cardiac nanotechnology is still in its infancy, achieving mechanistic understanding of biochemical, structural, and functional cell sex differences and their effects on identifying the role of these sex-dependent differences on the protein corona composition and the corresponding cellular uptake and intracellular trafficking of nanoparticles can help facilitate the safe and efficient translation of cardiac nanotechnologies. In other words, obtaining deep information on the effects of cardiac cell sex on interactions between cells and therapeutic agents (e.g., drugs and nanoparticles) can markedly improve the safety and therapeutic efficacy of drugs/nanoparticles for HF, and provide important insights into sex-related individualized therapy.

12. CONCLUSIONS AND FUTURE PERSPECTIVES

Building strong bridges between clinicians and bioengineers/nanotechnology experts is essential for the field to direct the research strategies with careful plans, rather than through scattered reports, that can address the main unmet clinical needs. As described in this review, many of the potential applications of nanotechnologies in HF capable of saving many lives remain poorly understood. This is caused by the absence of efficient communications among experts in different fields. Effective communications and collaborations by scientists working in cardiac nanotechnology are imperative for achieving more accurate and precise prediction of the biological fate of nanomaterials, their safety, and therapeutic efficacy, all of which are instrumental in the ultimate goal of achieving successful clinical translation of nanotechnologies. At stake is the opportunity to use nanotechnology to improve the survival and quality of life of millions of people suffering from heart diseases, and in particular, ischemic cardiomyopathy.

New advances in simulation and data analysis can vastly improve both diagnostic and therapeutic cardiac nanotechnology approaches.[216,335] For example, the newly developed "virtual cell" simulation approach can greatly assist in virtual designing of substrates and probing cell-substrate interactions (at both cellular and molecular levels) to optimize physical, chemical, and mechanical properties of substrates that can induce desired cellular response.[335] These simulation approaches can substantially reduce the experimental costs

and consumed time by defining optimized conditions/characteristics for cardiology applications (e.g., substrates for cardiac cell maturation[217]).

The prevention and management of cardiovascular diseases increasingly depend on effective diagnostic testing. By enabling fast genotyping and biomarker measurement, point-of-care (POC) devices will provide individual patients with personalized treatments. Development of POC devices will involve multidisciplinary teams of technologists, biomarker scientists, health care providers, and clinical trialists to formulate needs assessments, design device and component technologies, conduct pilot testing, and perform rigorous prospective clinical trials. In the coming years, many efforts will be devoted at developing nanotechnologies for diagnostic imaging (e.g., using iron oxide nanoparticles). In this regard, nanoparticle-based molecular imaging agents will incorporate targeted agents to provide physicians with accurate structural and functional information and shed light into disease pathways.

Nanotechnology will have a deep impact on cardiovascular therapeutics by advancing the pharmacological treatments with respect to therapies currently on the market. Targeted drug delivery by nanoparticle-encapsulated drugs will circumvent many limitations of conventional therapies by increasing the effective drug concentration at the desired action site, and reducing systemic dosage and unwanted side effects. Safe and effective platforms for controlled and tailored drug delivery will significantly improve control of pharmacokinetics and bioavailability.

Another active field of research will be the development of nanoengineered materials for cardiac tissue regeneration. Nanomaterials will be consolidated as indispensable materials to tissue engineering applications for reproduction and healing of cardiac tissue. Nanomaterials, especially noble metal nanoparticles, will progressively contribute to maintain innovative opportunities to boost the conductivity of biomaterial scaffolds, whereas nanofiber scaffolds as biodegradable vascular grafts will decrease restenosis and make tissue or organ regeneration a reality.

The improved biomaterials compatible for injection are made of either synthetic or hydrated natural polymers. This composition reduces the wall stress and consequently leads to pathological dilative remodeling of the ventricle. Another advantage is a shielding atmosphere that helps promote retention and functionality of transplanted cells. Continuing advances in biomaterials will play a big role in many forms of cardiovascular therapeutics.

Lastly, a significant challenge for the future progress in cardiac nanotechnologies is the limited funding relative to other fields. For example, tremendous efforts and huge amounts of funding were dedicated to the successful development of cancer nanotechnology. Unlike cancer nanotechnology, cardiac nanotechnology has lagged in attaining traction over the last decade, with slower progress partly reflecting the far smaller investment committed to cardiac nanotechnology versus cancer nanotechnology. In the last few years, however, an expanding number of funding opportunities have led to more important innovations and high-quality publications in this area. However, progress in cardiovascular nanotechnology still faces several central issues (e.g., low *in vivo* therapeutic efficacy [422]) that can cause substantial misinterpretation of nanoparticles' biological readouts.[336,403] These issues

contributed to the failure of several clinical trials of potential nanotechnology products by leading companies; therefore fewer than expected nanotherapeutics are now on the market. As cardiac nanotechnology is still in its infancy, scientists should carefully consider lessons from the field of cancer nanotechnology, such as by applying optimal protocols to experimental setups and reporting the required essential information (e.g., nanoparticles' physicochemical properties, detailed information on the nano-bio interfaces and biological identity of nanoparticles, and full information on biological systems including cell passage numbers, cell sex, and cell types/origin)[39,403] in both reports and the nanoparticles' datasets.

ACKNOWLEDGMENTS

M.M. acknowledges support by IGNITE Award from the Connors Center for Women's Health & Gender Biology and Precision Health Medicine at Michigan State University.

Biographies

Mohammad Javad Hajipour obtained his Ph.D. in 2015 under supervision of Professor Morteza Mahmoudi on the development of personalized nanomedicine strategies. Currently, he is a postdoctoral fellow in Mahmoudi's lab at Michigan State University.

Mehdi Mehrani is an Assistant Professor of Cardiology at Tehran University of Medical Sciences since 2015. He is the head of Emergency department and Educational Development Office of Tehran Heart Center hospital. His interest is focused on acute cardiovascular care, especially myocardial infarction and its complications.

Seyed Hesameddin Abbasi is a Bernard Lown Scholar in cardiovascular health, at Harvard T.H. Chan School of Public Health, and a cardiovascular epidemiologist at Tehran Heart Center. He has been the author of more than 100 published papers in top tier journals including Lancet. His particular research is focused on development of novel innovations in reducing the burden of cardiovascular diseases, especially in heart failure and coronary artery disease.

Ahmad Amin is a cardiologist and the director of Heart Failure program at Rajaie Cardiovascular Medical and Research Center. He received his MD from Shiraz University of Medical Science and his fellowship in Heart Failure and Transplantation from Rajaie Cardiovascular, Medical and Research Center. He is also the president of the Iranian Society of Heart Failure.

Seyed Ebrahim Kassaian is an interventional cardiologist and Associate Professor of cardiology at Tehran Heart Center, Tehran University of Medical Sciences. Furthermore, he is a Bernard Lown Scholar in Cardiovascular Health, at Harvard T.H. Chan School of Public Health. He has been the author of more than 75 published papers in peer reviewed journals. His particular research interest is finding the best strategies to improve the medical care of patients with heart diseases.

Jessica Garbern is an instructor at Harvard Medical School, pediatric cardiologist at Boston Children's Hospital, and post-doctoral fellow in the Department of Stem Cell and

Regenerative Biology at Harvard University. She is interested in developing regenerative approaches to treat cardiovascular disease.

Giulio Caracciolo is an Associate Professor of Applied Physics at the Molecular Medicine Department of the Sapienza University of Rome. He co-authored more than 140 peer-reviewed publications and 2 patents. His research is focused on understanding the bio–nano interactions between drug delivery systems and biological media which represent a new paradigm in the field of pharmaceutics and nanomedicine.

Steven Zanganeh is a senior research scientist at Memorial Sloan Kettering Cancer Center. He has authored >45 papers (>1200 citations). His specific research interest is in immunoengineering with the main aim of translating cancer immunotherapy, nanomedicine, and molecular imaging science into technological solutions with potential societal impact in health care.

Mitra Chitsazan is a medical practitioner and received her degree from Iran University of Medical Sciences. Her current research, under supervision of Dr. Ahmad Amin, is focused on heart failure.

Haniyeh Aghaverdi is a medical doctor with extensive research expertise at Stanford School of Medicine and Brigham and Women's Hospital. She has authored 9 papers in top tier journals including ACS Nano, Trends in Biotechnologiy, and Advanced Functional Materials.

Seyed Mehdi Kamali Shahri received his Ph.D. from Pennsylvania State University (PSU) in the Energy and Chemical Engineering Departments focusing on surface science especially catalysis, adsorption, kinetic and thermodynamics of environmental issues. He joined the PSU in spring 2012 after completion of BS and MS degrees from Iran University of Science and Technology, Tehran, Iran.

Ali Akbar Ashkarran received his B.S. and M.S. both in physics from University of Mazandaran (2003) and University of Tehran (2005), respectively. He obtained his Ph.D. in Nanoscience and Nanotechnology from Sharif University of Technology in 2009, where he worked on environmental and biomedical applications of nanomaterials. He then worked as an assistant professor of physics and director of nanotechnology research laboratory at University of Mazandaran. He joined Harvard University in 2018. He is currently a research fellow in Professor Mahmoudi's lab at Michigan State University working on development of diagnostic approaches using human plasma.

Mohammad Raoufi is a faculty member in pharmacy department at Tehran University of Medical Sciences. He has authored >20 papers and holds>4 issued/pending US and International patents. His research focused in nanomedicine, nanofabrication and bio-interfaces. His is specialist on tissue engineering, porous material and biomaterial's characterization techniques.

Holly Bauser-Heaton is an interventional pediatric cardiologist and physician scientist at Sibley Heart Center at Children's Healthcare of Atlanta. She completed her MD, PhD in

2009 at Indiana University. Dr. Bauser-Heaton focused on signaling mechanisms of nitric oxide in hypoxic conditions and continues to investigate the role of NO in endothelial function. As a clinician, she completed her training at Stanford University and joined faculty of Sibley Heart Center in 2016. Pulmonary artery disease and its management is the focus for Dr. Heaton both in the clinical arena and the lab. She is interested in developing new procedures via transcatheter technique for individuals with pulmonary artery disease. Additionally, she has interest in utilizing 3D bioprinting to create pulmonary artery constructs that have the ability to keep up with a patient's somatic growth.

Jianyi "Jay" Zhang, M.D., Ph.D., F.A.H.A., is an international leader in myocardial bioenergetics, biomaterials, and stem cells for cardiac repair. He is tenured Professor of Medicine and of Engineering; T. Michael and Gillian Goodrich Endowed Chair of Engineering Leadership; and the Chair of the Department of Biomedical Engineering (BME) at the University of Alabama at Birmingham (UAB). The Zhang lab's active research areas involve cell therapy for myocardial repair using autologous, allogenic adult stem cells, or human pluripotent stem cell-derived cardiac cells, and large-animal models of severe left-ventricular dysfunction. Dr. Zhang's lab has been fabricating myocardial tissue patches to examine the mechanisms and the functional outcomes of myocardial contractile-, bioenergetic-, and gene/protein expression changes in hearts receiving different types of cell transplantation using tissue engineering and molecular biochemistry tools.

J Danny Muehlschlegel, MD, MMSc, FAHA is a cardiovascular anesthesiologist at Brigham and Women's Hospital, where he is also the Vice Chair of Research, the Director of Cardiac Anesthesia Research, and an Associate Professor of Anesthesia at Harvard Medical School. Danny is a physician-scientist with an active laboratory examining the impact of genetic variation upon adverse cardiovascular events and their significance on a functional level. He is the Principal Investigator of the TRANSCRIBE study (Transcriptomic Analysis of Left Ventricular Gene Expression), which aims to identify differential expression in human left ventricular myocardium upon exposure to ischemia, examine genetic variants that determine expression changes, and characterize these changes among different disease states.

Dr. Anna Moore has recently joined Michigan State University (MSU) the Professor of Radiology and Physiology at the Department of Radiology, College of Human Medicine. She is the Director of Precision Health Program and the Assistant Dean for Precision health at the College of Human Medicine. Prior to joining MSU, she worked for 27 years at Massachusetts General Hospital (MGH)/Harvard Medical School. Her research is aimed at developing molecular imaging theranostic agents for cancer imaging and therapy. Dr. Moore is a recipient of multiple grant awards from the NIH and other funding agencies and published her work in the most prestigious journals including Nature, Nature Medicine, Nature Biotechnology, PNAS and others.

Richard T. Lee is Professor of Stem Cell and Regenerative Biology at Harvard University and Professor of Medicine at Harvard Medical School. Dr. Lee is a graduate of Harvard College in Biochemical Sciences and received his M.D. from Cornell University Medical College. Dr. Lee completed both internal medicine residency and cardiology fellowship at Brigham and Women's Hospital in Boston. He is Leader of the Cardiovascular Program of

the Harvard Stem Cell Institute. He is a member of the Editorial Boards of the journals Circulation Research and Circulation. Dr. Lee's laboratory studies heart failure and metabolic diseases that accompany human aging, as these diseases are now major barriers to healthy aging. Dr. Lee also teaches undergraduate courses at Harvard College, where his laboratory is located. Dr. Lee has published over 250 peer-reviewed articles based on his research. Dr. Lee is an active clinician; he regularly treats both inpatients and outpatients as a clinical cardiologist at Brigham and Women's Hospital, and he served as Director of Noninvasive Cardiology at Brigham and Women's Hospital before opening his molecular biology laboratory. In addition, Dr. Lee has volunteered his time for general medical care to the homeless at a large Boston-area homeless shelter throughout his career.

Joseph C. Wu, MD, PhD is Director of the Stanford Cardiovascular Institute and Simon H. Stertzer, MD, Professor of Medicine (Cardiology) and Radiology at the Stanford School of Medicine. His lab works on biological mechanisms of patient-specific and disease-specific induced pluripotent stem cells (iPSCs). The main goals are to (i) understand basic cardiovascular disease mechanisms, (ii) accelerate drug discovery and screening, (iii) develop "clinical trial in a dish" concept, and (iv) implement precision cardiovascular medicine for prevention and treatment of patients.

Dr. Vahid Serpooshan completed his undergraduate studies in Materials Science at Sharif University and his PhD in tissue engineering at McGill University in Canada. Dr. Serpooshan worked for 7 years at Stanford University School of Medicine as Postdoctoral Fellow and Instructor at Stanford Cardiovascular Institute, working on developing a new generation of engineered cardiac patch to repair myocardial infarction (heart attack). In 2018, Dr. Serpooshan joined Emory University and Georgia Institute of Tech as an Assistant Professor of Biomedical Engineering and Pediatrics, where his multidisciplinary team is now working on a variety of 3D bioprinting-based tissue engineering projects.

Morteza Mahmoudi is an Assistant Professor at precision heath Program and Department of Radiology at Michigan State University. Prior coming to Michigan State University, he was an Assistant Professor at Brigham and Women's Hospital and Harvard Medical School. He has authored >190 papers (>17,400 citations) and holds>12 issued/pending US and International patents. He is among 2018 highly cited researchers in 2018 as reported by Clarivate Analytics. His specific research interest is in nanomedicine and regenerative medicine for the development of new nano-based platforms for prevention/treatment of life-threatening conditions such as cardiomyopathy, cancer, and neurodegenerative diseases. Beside his research in nanomedicine and regenerative medicine, Dr. Mahmoudi is also very active on social sciences with a focus on academic bullying. He is the founder and director of the Academic Parity Movement (www.paritymovement.org), a non-profit organization born out of a need for justice, and the protection of researchers' most basic human rights within academic institutions.

REFERENCES

(1). Dokainish H; Teo K; Zhu J; Roy A; AlHabib KF; ElSayed A; Palileo-Villaneuva L; Lopez-Jaramillo P; Karaye K; Yusoff K Global mortality variations in patients with heart failure: results

from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. Lancet Glob. Health 2017, 5, e665–e672. [PubMed: 28476564]

(2). Yancy CW; Jessup M; Bozkurt B; Butler J; Casey DE; Drazner MH; Fonarow GC; Geraci SA; Horwich T; Januzzi JL 2013 ACCF/AHA guideline for the management of heart failure. Circulation 2013, 128, e240–e327. [PubMed: 23741058]

(3). Briceno N; Perera D To Revascularise or Not To Revascularise, That Is the Question: the Diagnostic and Management Conundrum of Ischaemic Cardiomyopathy. Curr. Cardiol. Rep 2016, 18, 54–61. [PubMed: 27115418]

(4). Burch G; Giles T; Colcolough H Ischemic cardiomyopathy. Am. Heart J 1970, 79, 291–292. [PubMed: 5413167]

(5). Heidenreich PA; Albert NM; Allen LA; Bluemke DA; Butler J; Fonarow GC; Ikonomidis JS; Khavjou O; Konstam MA; Maddox TMet al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ. Heart. Fail 2013, 6, 606–619. [PubMed: 23616602]

(6). Felker GM; Shaw LK; O'Connor CM A standardized definition of ischemic cardiomyopathy for use in clinical research. J. Am. Coll. Cardiol 2002, 39, 210–218. [PubMed: 11788209]

(7). Torabi A; Cleland JG; Khan NK; Loh PH; Clark AL; Alamgir F; Caplin JL; Rigby AS; Goode K The timing of development and subsequent clinical course of heart failure after a myocardial infarction. Eur. Heart J 2008, 29, 859–870. [PubMed: 18353754]

(8). Ziaeian B; Fonarow GC Epidemiology and aetiology of heart failure. Nat. Rev. Cardiol 2016, 13, 368–378. [PubMed: 26935038]

(9). Anderson NL; Anderson NG The human plasma proteome: history, character, and diagnostic prospects. Mol. Cell. Proteomics 2002, 1, 845–867. [PubMed: 12488461]

(10). Hanash SM; Pitteri SJ; Faca VM Mining the plasma proteome for cancer biomarkers. Nature 2008, 452, 571–579. [PubMed: 18385731]

(11). Halliday BP; Wassall R; Lota AS; Khalique Z; Gregson J; Newsome S; Jackson R; Rahneva T; Wage R; Smith G Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet 2018, 393, 61–73. [PubMed: 30429050]

(12). Sanganalmath SK; Bolli R Cell therapy for heart failure: a comprehensive overview of experimental and clinical studies, current challenges, and future directions. Circ. Res 2013, 113, 810–834. [PubMed: 23989721]

(13). Segers VF; Lee RT Stem-cell therapy for cardiac disease. Nature 2008, 451, 937–942. [PubMed: 18288183]

(14). Laflamme MA; Murry CE Regenerating the heart. Nat. Biotechnol 2005, 23, 845–856. [PubMed: 16003373]

(15). Laflamme MA; Murry CE Heart regeneration. Nature 2011, 473, 326–335. [PubMed: 21593865]

(16). Chong JJ; Yang X; Don CW; Minami E; Liu Y-W; Weyers JJ; Mahoney WM; Van Biber B; Cook SM; Palpant NJ Human embryonic-stem-cell-derived cardiomyocytes regenerate non-human primate hearts. Nature 2014, 510, 273–277. [PubMed: 24776797]

(17). Nakamura Y; Miyagawa S; Yoshida S; Sasawatari S; Toyofuku T; Sawa Y Immunologic Impacts of Natural Killer Cell-Related Innate Immune Rejection Mediated by CD226 and NKG2D on the Engraftment of Syngeneic Cardiomyocyte Derived from Induced Pluripotent Stem Cell. Circulation 2018, 138, A11324–A11324.

(18). Liu X; Li W; Fu X; Xu Y The immunogenicity and immune tolerance of pluripotent stem cell derivatives. Front. Immunol 2017, 8, 645–650. [PubMed: 28626459]

(19). Bolli R; Ghafghazi S Stem cells: cell therapy for cardiac repair: what is needed to move forward? Nat. Rev. Cardiol 2017, 14, 257–258. [PubMed: 28361979]

(20). Menasché P Cell therapy trials for heart regeneration—lessons learned and future directions. Nat. Rev. Cardiol 2018, 15, 659–671. [PubMed: 29743563]

(21). Santoso MR; Yang PC Magnetic nanoparticles for targeting and imaging of stem cells in myocardial infarction. Stem Cells Int 2016, 4198790. [PubMed: 27127519]

(22). Hausenloy DJ; Bøtker HE; Condorelli G; Ferdinandy P; Garcia-Dorado D; Heusch G; Lecour S; Van Laake LW; Madonna R; Ruiz-Meana M Translating cardioprotection for patient benefit:

position paper from the Working Group of Cellular Biology of the Heart of the European Society of Cardiology. Cardiovasc. Drug Rec 2013, 98, 7–27.

(23). Kim BY; Rutka JT; Chan WC Nanomedicine. N. Engl. J. Med 2010, 363, 2434–2443. [PubMed: 21158659]

(24). Hubbell JA; Chilkoti A Chemistry. Nanomaterials for drug delivery. Science 2012, 337, 303–305. [PubMed: 22822138]

(25). Nishijima Y; Rosa L; Juodkazis S Surface plasmon resonances in periodic and random patterns of gold nano-disks for broadband light harvesting. Opt. Express 2012, 20, 11466–11477. [PubMed: 22565766]

(26). Saha K; Agasti SS; Kim C; Li X; Rotello VM Gold nanoparticles in chemical and biological sensing. Chem. Rev 2012, 112, 2739–2779. [PubMed: 22295941]

(27). Wei Q; Xiong F; Tan S; Huang L; Lan EH; Dunn B; Mai L Porous One-Dimensional Nanomaterials: Design, Fabrication and Applications in Electrochemical Energy Storage. Adv. Mater 2017, 29, 1602300.

(28). Dekaliuk MO; Viagin O; Malyukin YV; Demchenko AP Fluorescent carbon nanomaterials: “quantum dots” or nanoclusters? Phys. Chem. Chem. Phys 2014, 16, 16075–16084. [PubMed: 24965696]

(29). Barry NP; Sadler PJ Challenges for metals in medicine: how nanotechnology may help to shape the future. ACS Nano 2013, 7, 5654–5659. [PubMed: 23837396]

(30). Pelaz B; Alexiou C; Alvarez-Puebla RA; Alves F; Andrews AM; Ashraf S; Balogh LP; Ballerini L; Bestetti A; Brendel Cet al. Diverse Applications of Nanomedicine. ACS Nano 2017, 11, 2313–2381. [PubMed: 28290206]

(31). Mahmoudi M; Hosseinkhani H; Hosseinkhani M; Boutry S; Simchi A; Journeay WS; Subramani K; Laurent S Magnetic resonance imaging tracking of stem cells in vivo using iron oxide nanoparticles as a tool for the advancement of clinical regenerative medicine. Chem. Rev 2011, 111, 253–280. [PubMed: 21077606]

(32). Krol S; Macrez R; Docagne F; Defer G; Laurent S; Rahman M; Hajipour MJ; Kehoe PG; Mahmoudi M Therapeutic benefits from nanoparticles: the potential significance of nanoscience in diseases with compromise to the blood brain barrier. Chem. Rev 2012, 113, 1877–1903. [PubMed: 23157552]

(33). Pina S; Oliveira JM; Reis RL Natural-based nanocomposites for bone tissue engineering and regenerative medicine: a review. Adv. Mater 2015, 27, 1143. [PubMed: 25580589]

(34). Schnaider L; Brahmachari S; Schmidt NW; Mensa B; Shaham-Niv S; Bychenko D; Adler-Abramovich L; Shimon LJW; Kolusheva S; DeGrado WFet al. Self-assembling dipeptide antibacterial nanostructures with membrane disrupting activity. Nat. Commun 2017, 8, 1365. [PubMed: 29118336]

(35). Tibbitt MW; Rodell CB; Burdick JA; Anseth KS Progress in material design for biomedical applications. P. Natl. Acad. Sci. USA 2015, 112, 14444–14451.

(36). Mahmoudi M; Yu M; Serpooshan V; Wu JC; Langer R; Lee RT; Karp JM; Farokhzad OC Multiscale technologies for treatment of ischemic cardiomyopathy. Nat. Nanotechnol 2017, 12, 845–855. [PubMed: 28875984]

(37). Amezcua R; Shirolkar A; Fraze C; Stout DA Nanomaterials for Cardiac Myocyte Tissue Engineering. Nanomaterials (Basel) 2016, 6, 133.

(38). Zhang B; Xiao Y; Hsieh A; Thavandiran N; Radisic M Micro- and nanotechnology in cardiovascular tissue engineering. Nanotechnology 2011, 22, 494003–494012. [PubMed: 22101261]

(39). Mahmoudi M Debugging Nano-Bio Interfaces: Systematic Strategies to Accelerate Clinical Translation of Nanotechnologies. Trends Biotechnol 2018, 36, 755–769. [PubMed: 29559165]

(40). Wulfkuhle JD; Liotta LA; Petricoin EF Proteomic applications for the early detection of cancer. Nat. Rev. Cancer 2003, 3, 267–275. [PubMed: 12671665]

(41). Ferrari M Cancer nanotechnology: opportunities and challenges. Nat. Rev. Cancer 2005, 5, 161–171. [PubMed: 15738981]

(42). Tan HT; Low J; Lim SG; Chung M Serum autoantibodies as biomarkers for early cancer detection. FEBS Journal 2009, 276, 6880–6904. [PubMed: 19860826]

(43). Daubert MA; Jeremias A The utility of troponin measurement to detect myocardial infarction: review of the current findings. Vasc. Health Risk Manag 2010, 6, 691–699. [PubMed: 20859540]

(44). Babuin L; Jaffe AS Troponin: the biomarker of choice for the detection of cardiac injury. Cmaj 2005, 173, 1191–1202. [PubMed: 16275971]

(45). Bonaca M; Scirica B; Sabatine M; Dalby A; Spinar J; Murphy SA; Jarolim P; Braunwald E; Morrow DA Prospective evaluation of the prognostic implications of improved assay performance with a sensitive assay for cardiac troponin I. J. Am. Coll. Cardiol 2010, 55, 2118–2124. [PubMed: 20447535]

(46). Tu C; Rudnick PA; Martinez MY; Cheek KL; Stein SE; Slebos RJ; Liebler DC Depletion of abundant plasma proteins and limitations of plasma proteomics. J. Proteome Res, 2010, 9, 4982–4991. [PubMed: 20677825]

(47). Collinson P; Hadcocks L; Foo Y; Rosalki S; Stubbs P; Morgan S; O'Donnell J Cardiac troponins in patients with renal dysfunction. Ann. Clin. Biochem 1998, 35, 380–386. [PubMed: 9635103]

(48). Aartsen WM; Pelsers MMAL; Hermens WT; Glatz JFC; Daemen MJAP; Smits JFM Heart fatty acid binding protein and cardiac troponin T plasma concentrations as markers for myocardial infarction after coronary artery ligation in mice. Pflüg. Arch, 2000, 439, 416–422..

(49). End C; Seliger SL; deFilippi CR Interpreting cardiac troponin results from highly sensitive assays in patients with chronic kidney disease: acute coronary syndromes and beyond. Coronary Artery Dis 2013, 24, 720–723.

(50). Apple FS; Smith SW; Pearce LA; Ler R; Murakami MM Use of the Centaur TnI-Ultra assay for detection of myocardial infarction and adverse events in patients presenting with symptoms suggestive of acute coronary syndrome. Clin. Chem 2008, 54, 723–728. [PubMed: 18238833]

(51). Giannitsis E; Kurz K; Hallermayer K; Jarausch J; Jaffe AS; Katus HA Analytical validation of a high-sensitivity cardiac troponin T assay. Clin. Chem 2010, 56, 254–261. [PubMed: 19959623]

(52). Twerenbold R; Jaffe A; Reichlin T; Reiter M; Mueller C High-sensitive troponin T measurements: what do we gain and what are the challenges? Eur. Heart J 2012, 33, 579–586. [PubMed: 22267244]

(53). Members NWG; Apple FS; Jesse RL; Newby LK; Wu AH; Christenson RH National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical issues for biochemical markers of acute coronary syndromes. Circulation 2007, 115, e352–e355. [PubMed: 17384332]

(54). Twerenbold R; Jaeger C; Rubini Gimenez M; Wildi K; Reichlin T; Nestelberger T; Boeddinghaus J; Grimm K; Puelacher C; Moehring B Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction. Eur. Heart J 2016, 37, 3324–3332. [PubMed: 27357358]

(55). Chenevier-Gobeaux C; Bonnefoy-Cudraz É; Charpentier S; Dehoux M; Lefevre G; Meune C; Ray P; SFBC S High-sensitivity cardiac troponin assays: answers to frequently asked questions. Arch. Cardiovasc. Dis 2015, 108, 132–149. [PubMed: 25669958]

(56). Sherwood MW; Kristin Newby L High-sensitivity troponin assays: evidence, indications, and reasonable use. J. Am. Heart Assoc 2014, 3, e000403. [PubMed: 24470520]

(57). Herman DS; Kavsak PA; Greene DN Variability and Error in Cardiac Troponin TestingAn ACLPS Critical Review. Am. J. Clin. Pathol 2017, 148, 281–295. [PubMed: 28967956]

(58). Wu W-Y; Bian Z-P; Wang W; Zhu J-J PDMS gold nanoparticle composite film-based silver enhanced colorimetric detection of cardiac troponin I. Sens. Actuators B 2010, 147, 298–303.

(59). Cho I-H; Paek E-H; Kim Y-K; Kim J-H; Paek S-H Chemiluminometric enzyme-linked immunosorbent assays (ELISA)-on-a-chip biosensor based on cross-flow chromatography. Anal. Chim. Acta 2009, 632, 247–255. [PubMed: 19110101]

(60). Bhatnagar D; Kumar V; Kumar A; Kaur I Graphene quantum dots FRET based sensor for early detection of heart attack in human. Biosens. Bioelectron 2016, 79, 495–499. [PubMed: 26748366]

(61). Dorraj GS; Rassaee MJ; Latifi AM; Pishgoo B; Tavallaei M Selection of DNA aptamers against Human Cardiac Troponin I for colorimetric sensor based dot blot application. J. Biotechnol 2015, 208, 80–86. [PubMed: 26003883]

(62). Kwon Y-C; Kim M-G; Kim E-M; Shin Y-B; Lee S-K; Lee SD; Cho M-J; Ro H-S Development of a surface plasmon resonance-based immunosensor for the rapid detection of cardiac troponin I. Biotechnol. Lett 2011, 33, 921–927. [PubMed: 21207113]

(63). Eveness J; Kiely J; Hawkins P; Wraith P; Luxton R Evaluation of paramagnetic particles for use in a resonant coil magnetometer based magneto-immunoassay. Sens. Actuators B 2009, 139, 538–542.

(64). Zhou F; Lu M; Wang W; Bian Z-P; Zhang J-R; Zhu J-J Electrochemical immunosensor for simultaneous detection of dual cardiac markers based on a poly (dimethylsiloxane)-gold nanoparticles composite microfluidic chip: a proof of principle. Clin. Chem 2010, 56, 1701–1707. [PubMed: 20852134]

(65). Periyakaruppan A; Gandhiraman RP; Meyyappan M; Koehne JE Label-free detection of cardiac troponin-I using carbon nanofiber based nanoelectrode arrays. Anal. Chem 2013, 85, 3858–3863. [PubMed: 23384128]

(66). Kiely J; Hawkins P; Wraith P; Luxton R Paramagnetic particle detection for use with an immunoassay based biosensor. IET Sci. Meas. Technol 2007, 1, 270–275.

(67). Vuori J; Syrjälä H; Väänänen H Myoglobin/carbonic anhydrase III ratio: highly specific and sensitive early indicator for myocardial damage in acute myocardial infarction. Clin. Chem 1996, 42, 107–109. [PubMed: 8565206]

(68). Zhang B; Zhang Y; Liang W; Cui B; Li J; Yu X; Huang L Nanogold-penetrated poly (amidoamine) dendrimer for enzyme-free electrochemical immunoassay of cardiac biomarker using cathodic stripping voltammetric method. Anal. Chim. Acta 2016, 904, 51–57. [PubMed: 26724762]

(69). Lewandrowski K; Chen A; Januzzi J Cardiac markers for myocardial infarction: a brief review. Pathol. Patterns Rev 2002, 118, S93–S99.

(70). McCullough PA; Nowak RM; Foreback C; Tokarski G; Tomlanovich MC; Khoury NE; Weaver WD; Sandberg KR; McCord J Performance of multiple cardiac biomarkers measured in the emergency department in patients with chronic kidney disease and chest pain. Acad. Emerg. Med 2002, 9, 1389–1396. [PubMed: 12460842]

(71). Adeel M; Rahman MM; Lee J-J Label-free aptasensor for the detection of cardiac biomarker myoglobin based on gold nanoparticles decorated boron nitride nanosheets. Biosens. Bioelectron 2019, 126, 143–150. [PubMed: 30399516]

(72). Zhang G; Liu Z; Wang L; Guo Y Electrochemical aptasensor for myoglobin-specific recognition based on porphyrin functionalized graphene-conjugated gold nanocomposites. Sensors 2016, 16, 1803–1814.

(73). Darain F; Yager P; Gan KL; Tjin SC On-chip detection of myoglobin based on fluorescence. Biosens. Bioelectron 2009, 24, 1744–1750. [PubMed: 18945609]

(74). Mishra SK; Kumar D; Biradar AM Electrochemical impedance spectroscopy characterization of mercaptopropionic acid capped ZnS nanocrystal based bioelectrode for the detection of the cardiac biomarker—myoglobin. Bioelectrochemistry 2012, 88, 118–126. [PubMed: 22922532]

(75). Wang Y; Sun H; Li R; Ke P; Zhu H; Guo H; Liu M; Sun H An immunomagnetic separation based fluorescence immunoassay for rapid myoglobin quantification in human blood. Anal. Methods 2016, 8, 7324–7330.

(76). Gnedenko OV; Mezentsev YV; Molnar AA; Lisitsa AV; Ivanov AS; Archakov AI Highly sensitive detection of human cardiac myoglobin using a reverse sandwich immunoassay with a gold nanoparticle-enhanced surface plasmon resonance biosensor. Anal. Chim. Acta 2013, 759, 105–109. [PubMed: 23260683]

(77). Panteghini M Enzyme and muscle diseases. Curr. Opin. Rheumatol 1995, 7, 469–474. [PubMed: 8579966]

(78). Marin MM; Teichman SL Use of rapid serial sampling of creatine kinase MB for very early detection of myocardial infarction in patients with acute chest pain. Am. Heart J 1992, 123, 354–361. [PubMed: 1736570]

(79). Hedges J The role of CK-MB in chest pain decision-making. Am. J. Emerg. Med 1995, 12, 101–106.

(80). Chon H; Lee S; Yoon S-Y; Lee EK; Chang S-I; Choo J SERS-based competitive immunoassay of troponin I and CK-MB markers for early diagnosis of acute myocardial infarction. Chem. Commun 2014, 50, 1058–1060.

(81). Herling TW; O'Connell DJ; Bauer MC; Persson J; Weininger U; Knowles TP; Linse S A microfluidic platform for real-time detection and quantification of protein-ligand interactions. Biophys. J 2016, 110, 1957–1966. [PubMed: 27166804]

(82). Nahavandi S; Baratchi S; Soffe R; Tang S-Y; Nahavandi S; Mitchell A; Khoshmanesh K Microfluidic platforms for biomarker analysis. Lab Chip 2014, 14, 1496–1514. [PubMed: 24663505]

(83). Säfsten P In Epitope Mapping Protocols; Springer, 2009.

(84). Wolfson D; Lindberg E; Su L; Farber SJ; Dubin SB Three rapid immunoassays for the determination of creatine kinase MB: an analytical, clinical, and interpretive evaluation. Am. Heart J 1991, 122, 958–964. [PubMed: 1927882]

(85). Piran U; Kohn DW; Uretsky LS; Bernier D; Barlow EH; Niswander CA; Stastny M Immunochemiluminometric assay of creatine kinase MB with a monoclonal antibody to the MB isoenzyme. Clin. Chem 1987, 33, 1517–1520. [PubMed: 3304711]

(86). Costa TN; Strunz CMC; Nicolau JC; Gutierrez PS Comparison of MB fraction of creatine kinase mass and troponin I serum levels with necropsy findings in acute myocardial infarction. Am. J. Cardiol 2008, 101, 311–314. [PubMed: 18237591]

(87). Wang R; Zuo S; Wu D; Zhang J; Zhu W; Becker KH; Fang J Microplasma-Assisted Synthesis of Colloidal Gold Nanoparticles and Their Use in the Detection of Cardiac Troponin I (cTn-I). Plasma Processes Polym 2015, 12, 380–391.

(88). Haes AJ; Duyne RPV Preliminary studies and potential applications of localized surface plasmon resonance spectroscopy in medical diagnostics. Expert Rev. Mol. Diagn 2004, 4, 527–537. [PubMed: 15225100]

(89). Tadepalli S; Kuang Z; Jiang Q; Liu K-K; Fisher MA; Morrissey JJ; Kharasch ED; Slocik JM; Naik RR; Singamaneni S Peptide functionalized gold nanorods for the sensitive detection of a cardiac biomarker using plasmonic paper devices. Sci. Rep 2015, 5, 16206. [PubMed: 26552720]

(90). Tang L; Casas J Quantification of cardiac biomarkers using label-free and multiplexed gold nanorod bioprobes for myocardial infarction diagnosis. Biosens. Bioelectron 2014, 61, 70–75. [PubMed: 24858675]

(91). Lee I; Luo X; Huang J; Cui XT; Yun M Detection of cardiac biomarkers using single polyaniline nanowire-based conductometric biosensors. Biosensors 2012, 2, 205–220. [PubMed: 25585711]

(92). Aydin S; Ugur K; Aydin S; Sahin İ; Yardim M Biomarkers in acute myocardial infarction: current perspectives. Vasc. Health. Risk. Manag 2019, 15, 1–10. [PubMed: 30697054]

(93). Aslan K; Grell TA Rapid and sensitive detection of troponin I in human whole blood samples by using silver nanoparticle films and microwave heating. Clin. Chem 2011, 57, 746–752. [PubMed: 21398602]

(94). Oostendorp M; Douma K; Wagenaar A; Slenter JM; Hackeng TM; van Zandvoort MA; Post MJ; Backes WH Molecular magnetic resonance imaging of myocardial angiogenesis after acute myocardial infarction. Circulation 2010, 121, 775–783. [PubMed: 20124125]

(95). Sanders H; Strijkers G; Mulder W; Huinink H; Erich S; Adan O; Sommerdijk NA; Merkx M; Nicolay K Morphology, binding behavior and MR-properties of paramagnetic collagen-binding liposomes. Contrast Media Mol. Imaging 2009, 4, 81–88. [PubMed: 19191276]

(96). Keliher EJ; Ye Y-X; Wojtkiewicz GR; Aguirre AD; Tricot B; Senders ML; Groenen H; Fay F; Perez-Medina C; Calcagno C Polyglucose nanoparticles with renal elimination and macrophage avidity facilitate PET imaging in ischaemic heart disease. Nat. Commun 2017, 8, 14064. [PubMed: 28091604]

(97). Ruiz-Esparza GU; Segura-Ibarra V; Cordero-Reyes AM; Youker KA; Serda RE; Cruz-Solbes AS; Amione-Guerra J; Yokoi K; Kirui DK; Cara FE A specifically designed nanoconstruct associates, internalizes, traffics in cardiovascular cells, and accumulates in failing myocardium: a new strategy for heart failure diagnostics and therapeutics. Eur. J. Heart Fail 2016, 18, 169–178. [PubMed: 26749465]

(98). Bertrand N; Grenier P; Mahmoudi M; Lima EM; Appel EA; Dormont F; Lim J; Karnik R; Langer R; Farokhzad OC Mechanistic understanding of in vivo protein corona formation on polymeric nanoparticles and impact on pharmacokinetics. Nat. Commun 2017, 8, 777. [PubMed: 28974673]

(99). Monopoli MP; Åberg C; Salvati A; Dawson KA Biomolecular coronas provide the biological identity of nanosized materials. Nat. Nanotechnol 2012, 7, 779–786. [PubMed: 23212421]

(100). Mahmoudi M; Lynch I; Ejtehadi MR; Monopoli MP; Bombelli FB; Laurent S Protein–nanoparticle interactions: opportunities and challenges. Chem. Rev 2011, 111, 5610–5637. [PubMed: 21688848]

(101). Laurent S; Mahmoudi M Superparamagnetic iron oxide nanoparticles: promises for diagnosis and treatment of cancer. Int. J. Mol. Epidemiol. Genet 2011, 2, 367–390. [PubMed: 22199999]

(102). Salvati A; Pitek AS; Monopoli MP; Prapainop K; Bombelli FB; Hristov DR; Kelly PM; Åberg C; Mahon E; Dawson KA Transferrin-functionalized nanoparticles lose their targeting capabilities when a biomolecule corona adsorbs on the surface. Nat. Nanotechnol 2013, 8, 137–143. [PubMed: 23334168]

(103). Mirshafiee V; Mahmoudi M; Lou K; Cheng J; Kraft ML Protein corona significantly reduces active targeting yield. Chem. Commun 2013, 49, 2557–2559.

(104). Moyano DF; Saha K; Prakash G; Yan B; Kong H; Yazdani M; Rotello VM Fabrication of corona-free nanoparticles with tunable hydrophobicity. ACS nano 2014, 8, 6748–6755. [PubMed: 24971670]

(105). Safavi-Sohi R; Maghari S; Raoufi M; Jalali SA; Hajipour MJ; Ghassempour A; Mahmoudi M Bypassing protein corona issue on active targeting: zwitterionic coatings dictate specific interactions of targeting moieties and cell receptors. ACS Appl. Mater. Interfaces 2016, 8, 22808–22818. [PubMed: 27526263]

(106). Mirshafiee V; Kim R; Park S; Mahmoudi M; Kraft ML Impact of protein pre-coating on the protein corona composition and nanoparticle cellular uptake. Biomaterials 2016, 75, 295–304. [PubMed: 26513421]

(107). Kelly PM; Åberg C; Polo E; O'Connell A; Cookman J; Fallon J; Krpetić Ž; Dawson KA Mapping protein binding sites on the biomolecular corona of nanoparticles. Nat. Nanotechnol 2015, 10, 472–479. [PubMed: 25822932]

(108). Tonigold M; Simon J; Estupiñán D; Kokkinopoulou M; Reinholz J; Kintzel U; Kaltbeitzel A; Renz P; Domogalla MP; Steinbrink K Pre-adsorption of antibodies enables targeting of nanocarriers despite a biomolecular corona. Nat. Nanotechnol 2018, 13, 862–869. [PubMed: 29915272]

(109). Mahmoudi M Antibody orientation determines corona mistargeting capability. Nat. Nanotechnol 2018, 13, 775–776. [PubMed: 29915270]

(110). Caracciolo G; Safavi-Sohi R; Malekzadeh R; Poustchi H; Vasighi M; Chiozzi RZ; Capriotti AL; Laganà A; Hajipour M; Di Domenico M; Di Carlo A; Caputo D; Aghaverdi H; Papi M; Palmieri V; Santoni A; Palchetti S; Digiacomo L; Pozzi D; Suslick KS; Mahmoudi M Disease-specific protein corona sensor arrays may have disease detection capacity. Nanoscale Horiz 2019, 4, 1063–1067.

(111). Hajipour MJ; Ghasemi F; Aghaverdi H; Raoufi M; Linne U; Atyabi F; Nabipour I; Azhdarzadeh M; Derakhshankhah H; Lotfabadi A Sensing of Alzheimer's disease and multiple sclerosis using nano-bio interfaces. J. Alzheimers Dis 2017, 59, 1187–1202. [PubMed: 28759965]

(112). Mahmoudi M; Sant S; Wang B; Laurent S; Sen T Superparamagnetic iron oxide nanoparticles (SPIONs): development, surface modification and applications in chemotherapy. Adv. Drug Delivery Rev 2011, 63, 24–46.

(113). Langer R Drug delivery and targeting. Nature 1998, 392, 5–10. [PubMed: 9579855]

(114). Molavi B; Chen J; Mehta JL Cardioprotective effects of rosiglitazone are associated with selective overexpression of type 2 angiotensin receptors and inhibition of p42/44 MAPK. Am J. Physiol. Heart Circ. Physiol 2006, 291, H687–H693. [PubMed: 16582019]

(115). Dvir T; Bauer M; Schroeder A; Tsui JH; Anderson DG; Langer R; Liao R; Kohane DS Nanoparticles targeting the infarcted heart. Nano lett 2011, 11, 4411–4414. [PubMed: 21899318]

(116). Nguyen MM; Carlini AS; Chien MP; Sonnenberg S; Luo C; Braden RL; Osborn KG; Li Y; Gianneschi NC; Christman KL Enzyme-Responsive Nanoparticles for Targeted Accumulation and Prolonged Retention in Heart Tissue after Myocardial Infarction. Adv. Mater 2015, 27, 5547. [PubMed: 26305446]

(117). Gray WD; Che P; Brown M; Ning X; Murthy N; Davis ME N-acetylglucosamine conjugated to nanoparticles enhances myocyte uptake and improves delivery of a small molecule p38 inhibitor for post-infarct healing. J. Cardiovasc. Transl. Res 2011, 4, 631–643. [PubMed: 21833815]

(118). Pogwizd SM; Schlotthauer K; Li L; Yuan W; Bers DM Arrhythmogenesis and contractile dysfunction in heart failure. Circ. Res 2001, 88, 1159–1167. [PubMed: 11397782]

(119). Pieske B; Maier LS; Bers DM; Hasenfuss G Ca2+ handling and sarcoplasmic reticulum Ca2+ content in isolated failing and nonfailing human myocardium. Circ. Res 1999, 85, 38–46. [PubMed: 10400909]

(120). Most P; Bernotat J; Ehlermann P; Pleger ST; Reppel M; Börries M; Niroomand F; Pieske B; Janssen PM; Eschenhagen T S100A1: a regulator of myocardial contractility. Proc. Natl. Acad. Sci. USA 2001, 98, 13889–13894. [PubMed: 11717446]

(121). Most P; Remppis A; Pleger ST; Löffler E; Ehlermann P; Bernotat J; Kleuss C; Heierhorst J; Ruiz P; Witt H Transgenic overexpression of the Ca2+-binding protein S100A1 in the heart leads to increased in vivo myocardial contractile performance. J. Biol. Chem 2003, 278, 33809–33817. [PubMed: 12777394]

(122). Most P; Pleger ST; Völkers M; Heidt B; Boerries M; Weichenhan D; Löffler E; Janssen PM; Eckhart AD; Martini J Cardiac adenoviral S100A1 gene delivery rescues failing myocardium. J. Clin. Invest 2004, 114, 1550–1563. [PubMed: 15578088]

(123). Maxwell JT; Somasuntharam I; Gray WD; Shen M; Singer JM; Wang B; Saafir T; Crawford BH; Jiang R; Murthy N Bioactive nanoparticles improve calcium handling in failing cardiac myocytes. Nanomedicine 2015, 10, 3343–3357. [PubMed: 26223412]

(124). Wang L; Ma W; Markovich R; Chen J-W; Wang PH Regulation of cardiomyocyte apoptotic signaling by insulin-like growth factor I. Circ. Res 1998, 83, 516–522. [PubMed: 9734474]

(125). Reiss K; Cheng W; Ferber A; Kajstura J; Li P; Li B; Olivetti G; Homcy CJ; Baserga R; Anversa P Overexpression of insulin-like growth factor-1 in the heart is coupled with myocyte proliferation in transgenic mice. Proc. Natl. Acad. Sci. USA 1996, 93, 8630–8635. [PubMed: 8710922]

(126). Duerr RL; Huang S; Miraliakbar HR; Clark R; Chien KR; Ross J Jr Insulin-like growth factor-1 enhances ventricular hypertrophy and function during the onset of experimental cardiac failure. J. Clin. Invest 1995, 95, 619. [PubMed: 7860746]

(127). Chang M-Y; Yang Y-J; Chang C-H; Tang AC; Liao W-Y; Cheng F-Y; Yeh C-S; Lai JJ; Stayton PS; Hsieh PC Functionalized nanoparticles provide early cardioprotection after acute myocardial infarction. J. Controlled Release 2013, 170, 287–294.

(128). Sarter B Coenzyme Q10 and cardiovascular disease: a review. J. Cardiovasc. Nurs 2002, 16, 9–20.

(129). Verma DD; Hartner WC; Thakkar V; Levchenko TS; Torchilin VP Protective effect of coenzyme Q10-loaded liposomes on the myocardium in rabbits with an acute experimental myocardial infarction. Pharm. Res 2007, 24, 2131–2137. [PubMed: 17657597]

(130). Takahama H; Minamino T; Asanuma H; Fujita M; Asai T; Wakeno M; Sasaki H; Kikuchi H; Hashimoto K; Oku N Prolonged targeting of ischemic/reperfused myocardium by liposomal adenosine augments cardioprotection in rats. J. Am. Coll. Cardiol 2009, 53, 709–717. [PubMed: 19232905]

(131). Scott RC; Rosano JM; Ivanov Z; Wang B; Chong PL-G; Issekutz AC; Crabbe DL; Kiani MF Targeting VEGF-encapsulated immunoliposomes to MI heart improves vascularity and cardiac function. FASEB J 2009, 23, 3361–3367. [PubMed: 19535683]

(132). Getts DR; Terry RL; Getts MT; Deffrasnes C; Müller M; van Vreden C; Ashhurst TM; Chami B; McCarthy D; Wu H Therapeutic inflammatory monocyte modulation using immune-modifying microparticles. Sci. Transl. Med 2014, 6, 219ra217–219ra217.

(133). Harel-Adar T; Mordechai TB; Amsalem Y; Feinberg MS; Leor J; Cohen S Modulation of cardiac macrophages by phosphatidylserine-presenting liposomes improves infarct repair. P. Natl. Acad. Sci. USA 2011, 108, 1827–1832.

(134). Nagaoka K; Matoba T; Mao Y; Nakano Y; Ikeda G; Egusa S; Tokutome M; Nagahama R; Nakano K; Sunagawa K A new therapeutic modality for acute myocardial infarction: nanoparticle-mediated delivery of pitavastatin induces cardioprotection from ischemiareperfusion injury via activation of PI3K/Akt pathway and anti-inflammation in a rat model. PloS One 2015, 10, e0132451. [PubMed: 26167913]

(135). Peña B; Bosi S; Aguado BA; Borin D; Farnsworth NL; Dobrinskikh E; Rowland TJ; Martinelli V; Jeong M; Taylor MR Injectable Carbon Nanotube-Functionalized Reverse Thermal Gel Promotes Cardiomyocytes Survival and Maturation. ACS Appl. Mater. Interfaces 2017, 9, 31645–31656. [PubMed: 28895403]

(136). Chen HH; Yuan H; Cho H; Feng Y; Ngoy S; Kumar AT; Liao R; Chao W; Josephson L; Sosnovik DE Theranostic Nucleic Acid Binding Nanoprobe Exerts Anti-inflammatory and Cytoprotective Effects in Ischemic Injury. Theranostics 2017, 7, 814–825. [PubMed: 28382156]

(137). Ylä-Herttuala S; Martin JF Cardiovascular gene therapy. Lancet 2000, 355, 213–222. [PubMed: 10675133]

(138). Whitehead KA; Langer R; Anderson DG Knocking down barriers: advances in siRNA delivery. Nat. Rev. Drug Discovery 2009, 8, 129–138. [PubMed: 19180106]

(139). Lee J-S; Green JJ; Love KT; Sunshine J; Langer R; Anderson DG Gold, poly (β-amino ester) nanoparticles for small interfering RNA delivery. Nano Lett 2009, 9, 2402–2406. [PubMed: 19422265]

(140). Howard KA; Rahbek UL; Liu X; Damgaard CK; Glud SZ; Andersen MØ; Hovgaard MB; Schmitz A; Nyengaard JR; Besenbacher F RNA interference in vitro and in vivo using a chitosan/siRNA nanoparticle system. Mol. Ther 2006, 14, 476–484. [PubMed: 16829204]

(141). Shu D; Shu Y; Haque F; Abdelmawla S; Guo P Thermodynamically stable RNA three-way junction for constructing multifunctional nanoparticles for delivery of therapeutics. Nat. Nanotechnol 2011, 6, 658–667. [PubMed: 21909084]

(142). Thomas CE; Ehrhardt A; Kay MA Progress and problems with the use of viral vectors for gene therapy. Nat. Rev. Genet 2003, 4, 346–358. [PubMed: 12728277]

(143). Hofmann A; Wenzel D; Becher UM; Freitag DF; Klein AM; Eberbeck D; Schulte M; Zimmermann K; Bergemann C; Gleich B Combined targeting of lentiviral vectors and positioning of transduced cells by magnetic nanoparticles. P. Natl. Acad. Sci. USA 2009, 106, 44–49.

(144). Su H; Lu R; Kan YW Adeno-associated viral vector-mediated vascular endothelial growth factor gene transfer induces neovascular formation in ischemic heart. P. Natl. Acad. Sci. USA 2000, 97, 13801–13806.

(145). Zhang ZD; Xu YQ; Chen F; Luo JF; Liu CD Sustained delivery of vascular endothelial growth factor using a dextran/poly(lactic-co-glycolic acid)-combined microsphere system for therapeutic neovascularization. Heart Vessels 2019, 34, 167–176. [PubMed: 30043157]

(146). Turnbull IC; Eltoukhy AA; Fish KM; Nonnenmacher M; Ishikawa K; Chen J; Hajjar RJ; Anderson DG; Costa KD Myocardial delivery of lipidoid nanoparticle carrying modRNA induces rapid and transient expression. Mol. Ther 2016, 24, 66–75. [PubMed: 26471463]

(147). Leuschner F; Courties G; Dutta P; Mortensen LJ; Gorbatov R; Sena B; Novobrantseva TI; Borodovsky A; Fitzgerald K; Koteliansky V Silencing of CCR2 in myocarditis. Eur. Heart J 2014, 36, 1478–1488. [PubMed: 24950695]

(148). Zhang Y; Li W; Ou L; Wang W; Delyagina E; Lux C; Sorg H; Riehemann K; Steinhoff G; Ma N Targeted delivery of human VEGF gene via complexes of magnetic nanoparticleadenoviral vectors enhanced cardiac regeneration. Plos One 2012, 7, e39490. [PubMed: 22844395]

(149). Kheirolomoom A; Kim CW; Seo JW; Kumar S; Son DJ; Gagnon MKJ; Ingham ES; Ferrara KW; Jo H Multifunctional nanoparticles facilitate molecular targeting and miRNA delivery to inhibit atherosclerosis in ApoE–/–mice. ACS Nano 2015, 9, 8885–8897. [PubMed: 26308181]

(150). Paul A; Hasan A; Kindi HA; Gaharwar AK; Rao VT; Nikkhah M; Shin SR; Krafft D; Dokmeci MR; Shum-Tim D Injectable graphene oxide/hydrogel-based angiogenic gene delivery system for vasculogenesis and cardiac repair. ACS Nano 2014, 8, 8050–8062. [PubMed: 24988275]

(151). Paul A; Binsalamah ZM; Khan AA; Abbasia S; Elias CB; Shum-Tim D; Prakash S A nanobiohybrid complex of recombinant baculovirus and Tat/DNA nanoparticles for delivery of Ang-1 transgene in myocardial infarction therapy. Biomaterials 2011, 32, 8304–8318. [PubMed: 21840594]

(152). Laurent S; Dutz S; Häfeli UO; Mahmoudi M Magnetic fluid hyperthermia: focus on superparamagnetic iron oxide nanoparticles. Adv. Colloid Interface Sci 2011, 166, 8–23. [PubMed: 21601820]

(153). Delyagina E; Li W; Ma N; Steinhoff G Magnetic targeting strategies in gene delivery. Nanomedicine 2011, 6, 1593–1604. [PubMed: 22077463]

(154). Modery-Pawlowski CL; Tian LL; Pan V; McCrae KR; Mitragotri S; Gupta AS Approaches to synthetic platelet analogs. Biomaterials 2013, 34, 526–541. [PubMed: 23092864]

(155). Hu C-MJ; Fang RH; Wang K-C; Luk BT; Thamphiwatana S; Dehaini D; Nguyen P; Angsantikul P; Wen CH; Kroll AV Nanoparticle biointerfacing by platelet membrane cloaking. Nature 2015, 526, 118–121. [PubMed: 26374997]

(156). Saha K; Rahimi M; Yazdani M; Kim ST; Moyano DF; Hou S; Das R; Mout R; Rezaee F; Mahmoudi M Regulation of macrophage recognition through the interplay of nanoparticle surface functionality and protein corona. ACS Nano 2016, 10, 4421–4430. [PubMed: 27040442]

(157). Caracciolo G; Farokhzad OC; Mahmoudi M Biological identity of nanoparticles in vivo: clinical implications of the protein corona. Trends Biotechnol 2017, 35, 257–264. [PubMed: 27663778]

(158). Mahmoudi M Debugging nano–bio interfaces: systematic strategies to accelerate clinical translation of nanotechnologies. Trends Biotechnol 2018, 36, 755–769. [PubMed: 29559165]

(159). Giulimondi F; Digiacomo L; Pozzi D; Palchetti S; Vulpis E; Capriotti AL; Chiozzi RZ; Laganà A; Amenitsch H; Masuelli Let al. Interplay of protein corona and immune cells controls blood residency of liposomes. Nat. Commun 2019, 10, 3686. [PubMed: 31417080]

(160). Moretti A; Bellin M; Welling A; Jung CB; Lam JT; Bott-Flügel L; Dorn T; Goedel A; Höhnke C; Hofmann F Patient-specific induced pluripotent stem-cell models for long-QT syndrome. N. Engl. J. Med 2010, 363, 1397–1409. [PubMed: 20660394]

(161). Sun N; Yazawa M; Liu J; Han L; Sanchez-Freire V; Abilez OJ; Navarrete EG; Hu S; Wang L; Lee A Patient-specific induced pluripotent stem cells as a model for familial dilated cardiomyopathy. Sci. Transl. Med 2012, 4, 130ra147–130ra147.

(162). Gnecchi M; Zhang Z; Ni A; Dzau VJ Paracrine mechanisms in adult stem cell signaling and therapy. Circ. Res 2008, 103, 1204–1219. [PubMed: 19028920]

(163). Gnecchi M; He H; Noiseux N; Liang OD; Zhang L; Morello F; Mu H; Melo LG; Pratt RE; Ingwall JS Evidence supporting paracrine hypothesis for Akt-modified mesenchymal stem cell-mediated cardiac protection and functional improvement. FASEB J 2006, 20, 661–669. [PubMed: 16581974]

(164). Tachibana A; Santoso MR; Mahmoudi M; Shukla P; Wang L; Bennett M; Goldstone AB; Wang M; Fukushi M; Ebert A Paracrine Effects of the Pluripotent Stem Cell-Derived Cardiac Myocytes Salvage the Injured Myocardium. Circ. Res 2017, 121, e22–e36. [PubMed: 28743804]

(165). Murry CE Cardiac aid to the injured but not the elderly? Nat. Med 2007, 13, 901–902. [PubMed: 17679999]

(166). Wang J-S; Shum-Tim D; Chedrawy E; Chiu RC-J The coronary delivery of marrow stromal cells for myocardial regeneration: pathophysiologic and therapeutic implications. J. Thorac. Cardiovasc. Surg 2001, 122, 699–705. [PubMed: 11581601]

(167). Orlic D; Kajstura J; Chimenti S; Jakoniuk I; Anderson SM; Li B; Pickel J; McKay R; Nadal-Ginard B; Bodine DM Bone marrow cells regenerate infarcted myocardium. Nature 2001, 410, 701–705. [PubMed: 11287958]

(168). Sanganalmath SK; Bolli R Cell therapy for heart failure. Cir. Res 2013, 113, 810–834.

(169). Murry CE; Soonpaa MH; Reinecke H; Nakajima H; Nakajima HO; Rubart M; Pasumarthi KB; Virag JI; Bartelmez SH; Poppa V Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. Nature 2004, 428, 664–668. [PubMed: 15034593]

(170). Nygren JM; Jovinge S; Breitbach M; Säwén P; Röll W; Hescheler J; Taneera J; Fleischmann BK; Jacobsen SEW Bone marrow-derived hematopoietic cells generate cardiomyocytes at a low frequency through cell fusion, but not transdifferentiation. Nat. Med 2004, 10, 494–501. [PubMed: 15107841]

(171). Murry CE; Field LJ; Menasché P Cell-based cardiac repair. Circulation 2005, 112, 3174–3183. [PubMed: 16286608]

(172). Fisher SA; Brunskill SJ; Doree C; Mathur A; Taggart DP; Martin-Rendon E Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. Cochrane Database Syst. Rev 2014, 4, CD007888.

(173). Nussbaum J; Minami E; Laflamme MA; Virag JA; Ware CB; Masino A; Muskheli V; Pabon L; Reinecke H; Murry CE Transplantation of undifferentiated murine embryonic stem cells in the heart: teratoma formation and immune response. FASEB J 2007, 21, 1345–1357. [PubMed: 17284483]

(174). Abadi PP; Garbern JC; Behzadi S; Hill MJ; Tresback JS; Heydari T; Ejtehadi MR; Ahmed N; Copley E; Aghaverdi H Engineering of Mature Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes Using Substrates with Multiscale Topography. Adv. Funct. Mater 2018, 28, 1707378.

(175). Teng CJ; Luo J; Chiu RC; Shum-Tim D Massive mechanical loss of microspheres with direct intramyocardial injection in the beating heart: implications for cellular cardiomyoplasty. J. Thorac. Cardiovasc. Surg 2006, 132, 628–632. [PubMed: 16935119]

(176). Terrovitis J; Lautamäki R; Bonios M; Fox J; Engles JM; Yu J; Leppo MK; Pomper MG; Wahl RL; Seidel J Noninvasive quantification and optimization of acute cell retention by in vivo positron emission tomography after intramyocardial cardiac-derived stem cell delivery. J. Am. Coll. Cardiol 2009, 54, 1619–1626. [PubMed: 19833262]

(177). Ottersbach A; Mykhaylyk O; Heidsieck A; Eberbeck D; Rieck S; Zimmermann K; Breitbach M; Engelbrecht B; Brügmann T; Hesse M Improved heart repair upon myocardial infarction: Combination of magnetic nanoparticles and tailored magnets strongly increases engraftment of myocytes. Biomaterials 2018, 155, 176–190. [PubMed: 29179133]

(178). Mahmoudi M; Hosseinkhani H; Hosseinkhani M; Boutry S; Simchi A; Journeay WS; Subramani K; Laurent S Magnetic resonance imaging tracking of stem cells in vivo using iron oxide nanoparticles as a tool for the advancement of clinical regenerative medicine. Chem. Rev 2011, 111, 253–280. [PubMed: 21077606]

(179). Mahmoudi M; Tachibana A; Goldstone AB; Woo YJ; Chakraborty P; Lee KR; Foote CS; Piecewicz S; Barrozo JC; Wakeel A Novel MRI contrast agent from magnetotactic bacteria enables in vivo tracking of iPSC-derived cardiomyocytes. Sci. Rep 2016, 6, 26960. [PubMed: 27264636]

(180). Xu C; Miranda-Nieves D; Ankrum JA; Matthiesen ME; Phillips JA; Roes I; Wojtkiewicz GR; Juneja V; Kultima JR; Zhao W Tracking mesenchymal stem cells with iron oxide nanoparticle loaded poly (lactide-co-glycolide) microparticles. Nano Lett 2012, 12, 4131–4139. [PubMed: 22769232]

(181). Cheng K; Shen D; Hensley MT; Middleton R; Sun B; Liu W; De Couto G; Marbán E Magnetic antibody-linked nanomatchmakers for therapeutic cell targeting. Nat. Commun 2014, 5, 4880. [PubMed: 25205020]

(182). Swirski FK; Nahrendorf M; Etzrodt M; Wildgruber M; Cortez-Retamozo V; Panizzi P; Figueiredo J-L; Kohler RH; Chudnovskiy A; Waterman P Identification of splenic reservoir monocytes and their deployment to inflammatory sites. Science 2009, 325, 612–616. [PubMed: 19644120]

(183). Jerath MR; Liu P; Struthers M; DeMartino JA; Peng R; Peterson LB; Cumiskey AM; Yang L; Rojas M; Patel DD Dual targeting of CCR2 and CX3CR1 in an arterial injury model of vascular inflammation. Thromb J 2010, 8, 14. [PubMed: 20836883]

(184). Lu W; Xie Z; Tang Y; Bai L; Yao Y; Fu C; Ma G Photoluminescent mesoporous silicon nanoparticles with siCCR2 improve the effects of mesenchymal stromal cell transplantation after acute myocardial infarction. Theranostics 2015, 5, 1068–1082. [PubMed: 26199646]

(185). Zhang S Fabrication of novel biomaterials through molecular self-assembly. Nat. Biotechnol 2003, 21, 1171–1178. [PubMed: 14520402]

(186). Lin Y-D; Yeh M-L; Yang Y-J; Tsai D-C; Chu T-Y; Shih Y-Y; Chang M-Y; Liu Y-W; Tang AC; Chen T-Y Intramyocardial peptide nanofiber injection improves postinfarction ventricular remodeling and efficacy of bone marrow cell therapy in pigs. Circulation 2010, 122, S132–S141. [PubMed: 20837904]

(187). Dvir T; Kedem A; Ruvinov E; Levy O; Freeman I; Landa N; Holbova R; Feinberg MS; Dror S; Etzion Y Prevascularization of cardiac patch on the omentum improves its therapeutic outcome. P. Natl. Acad. Sci. USA 2009, 106, 14990–14995.

(188). Zimmermann W-H; Melnychenko I; Wasmeier G; Didié M; Naito H; Nixdorff U; Hess A; Budinsky L; Brune K; Michaelis B Engineered heart tissue grafts improve systolic and diastolic function in infarcted rat hearts. Nat. Med 2006, 12, 452–458. [PubMed: 16582915]

(189). Wei K; Serpooshan V; Hurtado C; Diez-Cuñado M; Zhao M; Maruyama S; Zhu W; Fajardo G; Noseda M; Nakamura K Epicardial FSTL1 reconstitution regenerates the adult mammalian heart. Nature 2015, 525, 479–485. [PubMed: 26375005]

(190). Malki M; Fleischer S; Shapira A; Dvir T Gold nanorod-based engineered cardiac patch for suture-free engraftment by near IR. Nano Lett 2018, 18, 4069–4073. [PubMed: 29406721]

(191). Leor J; Aboulafia-Etzion S; Dar A; Shapiro L; Barbash IM; Battler A; Granot Y; Cohen S Bioengineered cardiac grafts: a new approach to repair the infarcted myocardium? Circulation 2000, 102, Iii-56–Iii-61. [PubMed: 11082363]

(192). Dvir T; Timko BP; Brigham MD; Naik SR; Karajanagi SS; Levy O; Jin H; Parker KK; Langer R; Kohane DS Nanowired three-dimensional cardiac patches. Nat. Nanotechnol 2011, 6, 720–725. [PubMed: 21946708]

(193). Dvir T; Benishti N; Shachar M; Cohen S A novel perfusion bioreactor providing a homogenous milieu for tissue regeneration. Tissue Eng 2006, 12, 2843–2852. [PubMed: 17518653]

(194). Dvir T; Tsur-Gang O; Cohen S “Designer” scaffolds for tissue engineering and regeneration. Isr. J. Chem 2005, 45, 487–494.

(195). Ye L; Chang Y-H; Xiong Q; Zhang P; Zhang L; Somasundaram P; Lepley M; Swingen C; Su L; Wendel JS Cardiac repair in a porcine model of acute myocardial infarction with human induced pluripotent stem cell-derived cardiovascular cells. Cell Stem Cell 2014, 15, 750–761. [PubMed: 25479750]

(196). Nezakati T; Seifalian A; Tan A; Seifalian AM Conductive polymers: opportunities and challenges in biomedical applications. Chem. Rev 2018, 118, 6766–6843. [PubMed: 29969244]

(197). Van de Walle A; Sangnier AP; Abou-Hassan A; Curcio A; Hémadi M; Menguy N; Lalatonne Y; Luciani N; Wilhelm C Biosynthesis of magnetic nanoparticles from nano-degradation products revealed in human stem cells. P. Natl. Acad. Sci. USA 2019, 116, 4044–4053.

(198). Amsalem Y; Mardor Y; Feinberg MS; Landa N; Miller L; Daniels D; Ocherashvilli A; Holbova R; Yosef O; Barbash IM Iron-oxide labeling and outcome of transplanted mesenchymal stem cells in the infarcted myocardium. Circulation 2007, 116, I-38–I-45. [PubMed: 17846324]

(199). Terrovitis J; Stuber M; Youssef A; Preece S; Leppo M; Kizana E SchÃ¤ r M, Gerstenblith G, Weiss RG, MarbÃi n E: Magnetic resonance imaging overestimates ferumoxide-labeled stem cell survival after transplantation in the heart. Circulation 2008, 117, 1555–1562. [PubMed: 18332264]

(200). Sakhtianchi R; Minchin RF; Lee K-B; Alkilany AM; Serpooshan V; Mahmoudi M Exocytosis of nanoparticles from cells: role in cellular retention and toxicity. Adv. Colloid Interface Sci 2013, 201, 18–29. [PubMed: 24200091]

(201). Chen IY; Greve JM; Gheysens O; Willmann JK; Rodriguez-Porcel M; Chu P; Sheikh AY; Faranesh AZ; Paulmurugan R; Yang PC Comparison of optical bioluminescence reporter gene and superparamagnetic iron oxide MR contrast agent as cell markers for noninvasive imaging of cardiac cell transplantation. Mol. Imaging. Biol 2009, 11, 178–187. [PubMed: 19034584]

(202). Naumova AV; Reinecke H; Yarnykh V; Deem J; Yuan C; Murry CE Ferritin overexpression for noninvasive magnetic resonance imaging–based tracking of stem cells transplanted into the heart. Mol. Imag 2010, 9, 201–210.

(203). Mahmoudi M; Tachibana A; Goldstone AB; Woo YJ; Chakraborty P; Lee KR; Foote CS; Piecewicz S; Barrozo JC; Wakeel A Novel MRI contrast agent from magnetotactic bacteria

enables in vivo tracking of iPSC-derived cardiomyocytes. Sci. Rep 2016, 6, 26960. [PubMed: 27264636]

(204). Hentze H; Soong PL; Wang ST; Phillips BW; Putti TC; Dunn NR Teratoma formation by human embryonic stem cells: evaluation of essential parameters for future safety studies. Stem Cell Res 2009, 2, 198–210. [PubMed: 19393593]

(205). Lee AS; Tang C; Cao F; Xie X; van der Bogt K; Hwang A; Connolly AJ; Robbins RC; Wu JC Effects of cell number on teratoma formation by human embryonic stem cells. Cell Cycle 2009, 8, 2608–2612. [PubMed: 19597339]

(206). Lane LA; Qian X; Nie S SERS nanoparticles in medicine: from label-free detection to spectroscopic tagging. Chem. Rev 2015, 115, 10489–10529. [PubMed: 26313254]

(207). Vo-Dinh T; Liu Y; Fales AM; Ngo H; Wang HN; Register JK; Yuan H; Norton SJ; Griffin GD SERS nanosensors and nanoreporters: golden opportunities in biomedical applications. Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol 2015, 7, 17–33. [PubMed: 25316579]

(208). Han J; Qian X; Wu Q; Jha R; Duan J; Yang Z; Maher KO; Nie S; Xu C Novel surface-enhanced Raman scattering-based assays for ultra-sensitive detection of human pluripotent stem cells. Biomaterials 2016, 105, 66–76. [PubMed: 27509304]

(209). Adams JD; Kim U; Soh HT Multitarget magnetic activated cell sorter. P. Natl. Acad. Sci. USA 2008, 105, 18165–18170.

(210). Engler AJ; Sen S; Sweeney HL; Discher DE Matrix elasticity directs stem cell lineage specification. Cell 2006, 126, 677–689. [PubMed: 16923388]

(211). Engler AJ; Griffin MA; Sen S; Bönnemann CG; Sweeney HL; Discher DE Myotubes differentiate optimally on substrates with tissue-like stiffness: pathological implications for soft or stiff microenvironments. J. Cell Biol 2004, 166, 877–887. [PubMed: 15364962]

(212). Saha K; Keung AJ; Irwin EF; Li Y; Little L; Schaffer DV; Healy KE Substrate modulus directs neural stem cell behavior. Biophys. J 2008, 95, 4426–4438. [PubMed: 18658232]

(213). Evans ND; Minelli C; Gentleman E; LaPointe V; Patankar SN; Kallivretaki M; Chen X; Roberts CJ; Stevens MM Substrate stiffness affects early differentiation events in embryonic stem cells. Eur. Cell Mater 2009, 18, 1–14. [PubMed: 19768669]

(214). Mahmoudi M; Bonakdar S; Shokrgozar MA; Aghaverdi H; Hartmann R; Pick A; Witte G; Parak WJ Cell-imprinted substrates direct the fate of stem cells. ACS Nano 2013, 7, 8379–8384. [PubMed: 24059979]

(215). Ribeiro AJ; Ang Y-S; Fu J-D; Rivas RN; Mohamed TM; Higgs GC; Srivastava D; Pruitt BL Contractility of single cardiomyocytes differentiated from pluripotent stem cells depends on physiological shape and substrate stiffness. P. Natl. Acad. Sci. USA 2015, 112, 12705–12710.

(216). Abadi PSS; Garbern JC; Bhzadi S; Hill MJ; Tresbeck JS; Heydari T; Ejtehadi MR; Ahmed N; Lee RT; Farokhzad OCet al. Engineering of Mature Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes using Substrates with Multi-Scale Topography. Adv. Func. Mater 2018, 28, 1707378.

(217). Bonakdar S; Mahmoudi M; Montazeri L; Taghipoor M; Bertsch A; Shokrgozar MA; Sharifi S; Majidi M; Mashinchian O; Hamrang Sekachaei Met al. Cell-Imprinted Substrates Modulate Differentiation, Redifferentiation, and Transdifferentiation. ACS Appl. Mater. Interfaces 2016, 8, 13777–13784. [PubMed: 27196338]

(218). Mashinchian O; Turner L-A; Dalby MJ; Laurent S; Shokrgozar MA; Bonakdar S; Imani M; Mahmoudi M Regulation of stem cell fate by nanomaterial substrates. Nanomedicine 2015, 10, 829–847. [PubMed: 25816883]

(219). Mashinchian O; Bonakdar S; Taghinejad H; Satarifard V; Heidari M; Majidi M; Sharifi S; Peirovi A; Saffar S; Taghinejad M Cell-Imprinted Substrates Act as an Artificial Niche for Skin Regeneration. ACS Appl. Mater. Interfaces 2014, 6, 13280–13292. [PubMed: 24967724]

(220). Moghaddam MM; Bonakdar S; Shariatpanahi MR; Shokrgozar MA; Faghihi S The effect of physical cues on the stem cell differentiation. Curr. Stem Cell Res. Ther 2019, 14, 268–277. [PubMed: 30588888]

(221). Veerman CC; Kosmidis G; Mummery CL; Casini S; Verkerk AO; Bellin M Immaturity of human stem-cell-derived cardiomyocytes in culture: fatal flaw or soluble problem? Stem Cells Dev 2015, 24, 1035–1052. [PubMed: 25583389]

(222). Nunes SS; Miklas JW; Liu J; Aschar-Sobbi R; Xiao Y; Zhang B; Jiang J; Massé S; Gagliardi M; Hsieh A Biowire: a platform for maturation of human pluripotent stem cell–derived cardiomyocytes. Nat. Methods 2013, 10, 781–787. [PubMed: 23793239]

(223). Lundy SD; Zhu W-Z; Regnier M; Laflamme MA Structural and functional maturation of cardiomyocytes derived from human pluripotent stem cells. Stem Cells Dev 2013, 22, 1991–2002. [PubMed: 23461462]

(224). Suzuki K; Fukushima S; Varela-Carver A; Coppen SR; Yamahara K; Felkin LE; Lee J; Barton PJ; Terracciano CM; Yacoub MH Response to letter regarding article,"Direct intramyocardial but not intracoronary injection of bone marrow cells induces ventricular arrhythmias in a rat chronic ischemic heart failure model". Circulation 2007, 116, e555.

(225). Chen H-SV; Kim C; Mercola M Electrophysiological challenges of cell-based myocardial repair. Circulation 2009, 120, 2496–2508. [PubMed: 20008740]

(226). Braunersreuther V; Jaquet V Reactive oxygen species in myocardial reperfusion injury: from physiopathology to therapeutic approaches. Current Pharm. Biotechnol 2012, 13, 97–114.

(227). Zhou T; Chuang C-C; Zuo L Molecular characterization of reactive oxygen species in myocardial ischemia-reperfusion injury. Biomed Res. Int 2015, 2015, 864946. [PubMed: 26509170]

(228). Granger DN; Kvietys PR Reperfusion injury and reactive oxygen species: the evolution of a concept. Redox Biol 2015, 6, 524–551. [PubMed: 26484802]

(229). Zhou T; Prather E; Garrison D; Zuo L Interplay between ROS and antioxidants during ischemia-reperfusion injuries in cardiac and skeletal muscle. Int. J. Mol. Sci 2018, 19, 417.

(230). Cadenas S ROS and redox signaling in myocardial ischemia-reperfusion injury and cardioprotection. Free Radic. Biol. Med 2018, 117, 76–89. [PubMed: 29373843]

(231). McLeod LL; Alayash AI Detection of a ferrylhemoglobin intermediate in an endothelial cell model after hypoxia-reoxygenation. Am. J. Physiol. Heart Circ. Physiol 1999, 277, H92–H99.

(232). Rodrigo R Oxidative stress and antioxidants: their role in human disease; Nova Science Publishers, Incorporated, 2009.

(233). Braunersreuther V; Montecucco F; Ashri M; Pelli G; Galan K; Frias M; Burger F; Quinderé ALG; Montessuit C; Krause K-H Role of NADPH oxidase isoforms NOX1, NOX2 and NOX4 in myocardial ischemia/reperfusion injury. J. Am. Coll. Cardiol 2013, 64, 99–107.

(234). Ferrari R The role of mitochondria in ischemic heart disease. J. Cardiovasc. Pharmacol 1996, 28, 1–10. [PubMed: 8797128]

(235). Darra E; Rungatscher A; de Prati AC; Podesser BK; Faggian G; Scarabelli T; Mazzucco A; Hallström S; Suzuki H Dual modulation of nitric oxide production in the heart during ischaemia/reperfusion injury and inflammation. Thromb. Haemost 2010, 104, 200–206. [PubMed: 20508903]

(236). Chevion M; Jiang Y; Har-El R; Berenshtein E; Uretzky G; Kitrossky N Copper and iron are mobilized following myocardial ischemia: possible predictive criteria for tissue injury. P. Natl. Acad. Sci. USA 1993, 90, 1102–1106.

(237). Takimoto E; Kass DA Role of oxidative stress in cardiac hypertrophy and remodeling. Hypertension 2007, 49, 241–248. [PubMed: 17190878]

(238). Giordano FJ Oxygen, oxidative stress, hypoxia, and heart failure. J. Clin. Invest 2005, 115, 500–508. [PubMed: 15765131]

(239). Poljsak B; Šuput D; Milisav I Achieving the balance between ROS and antioxidants: when to use the synthetic antioxidants. Oxid. Med. Cell. Longev 2013, 2013, 956792. [PubMed: 23738047]

(240). Hori M; Nishida K Oxidative stress and left ventricular remodelling after myocardial infarction. Cardiovasc. Res 2008, 81, 457–464. [PubMed: 19047340]

(241). Chang MC; Pralle A; Isacoff EY; Chang CJ A selective, cell-permeable optical probe for hydrogen peroxide in living cells. J. Am. Chem. Soc 2004, 126, 15392–15393. [PubMed: 15563161]

(242). Miller EW; Albers AE; Pralle A; Isacoff EY; Chang CJ Boronate-based fluorescent probes for imaging cellular hydrogen peroxide. J. Am. Chem. Soc 2005, 127, 16652–16659. [PubMed: 16305254]

(243). Lee D; Bae S; Hong D; Lim H; Yoon JH; Hwang O; Park S; Ke Q; Khang G; Kang PM H2O2-responsive molecularly engineered polymer nanoparticles as ischemia/reperfusion-targeted nanotherapeutic agents. Sci. Rep 2013, 3, 2233. [PubMed: 23868607]

(244). Bazban-Shotorbani S; Hasani-Sadrabadi MM; Karkhaneh A; Serpooshan V; Jacob KI; Moshaverinia A; Mahmoudi M Revisiting structure-property relationship of pH-responsive polymers for drug delivery applications. J. Controlled Release 2017, 253, 46–63.

(245). Stuart MAC; Huck WT; Genzer J; Müller M; Ober C; Stamm M; Sukhorukov GB; Szleifer I; Tsukruk VV; Urban M Emerging applications of stimuli-responsive polymer materials. Nat. Mater 2010, 9, 101–113. [PubMed: 20094081]

(246). Hoffman AS Stimuli-responsive polymers: Biomedical applications and challenges for clinical translation. Adv. Drug Delivery Rev 2013, 65, 10–16.

(247). Lu W; Le X; Zhang J; Huang Y; Chen T Supramolecular shape memory hydrogels: a new bridge between stimuli-responsive polymers and supramolecular chemistry. Chem. Soc. Rev 2017, 46, 1284–1294. [PubMed: 28138679]

(248). Xiong F; Wang H; Feng Y; Li Y; Hua X; Pang X; Zhang S; Song L; Zhang Y; Gu N Cardioprotective activity of iron oxide nanoparticles. Sci. Rep 2015, 5, 8579. [PubMed: 25716309]

(249). Nehra S; Bhardwaj V; Ganju L; Saraswat D Nanocurcumin prevents hypoxia induced stress in primary human ventricular cardiomyocytes by maintaining mitochondrial homeostasis. PloS One 2015, 10, e0139121. [PubMed: 26406246]

(250). Bedard K; Krause K-H The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. Physiol. Rev 2007, 87, 245–313. [PubMed: 17237347]

(251). Li J; Newburger PE; Gounis MJ; Dargon P; Zhang X; Messina LM Local arterial nanoparticle delivery of siRNA for NOX2 knockdown to prevent restenosis in an atherosclerotic rat model. Gene Ther 2010, 17, 1279–1287. [PubMed: 20485380]

(252). Gupta S; Chauhan D; Mehla K; Sood P; Nair A An overview of nutraceuticals: current scenario. J. Basic. Clin. Pharm 2010, 1, 55–62. [PubMed: 24825966]

(253). Fiorillo C; Becatti M; Pensalfini A; Cecchi C; Lanzilao L; Donzelli G; Nassi N; Giannini L; Borchi E; Nassi P Curcumin protects cardiac cells against ischemia-reperfusion injury: effects on oxidative stress, NF-κB, and JNK pathways. Free Radical Biol. Med 2008, 45, 839–846. [PubMed: 18638545]

(254). Morin D; Barthélémy S; Zini R; Labidalle S; Tillement J-P Curcumin induces the mitochondrial permeability transition pore mediated by membrane protein thiol oxidation. FEBS Lett 2001, 495, 131–136. [PubMed: 11322961]

(255). Manikandan P; Sumitra M; Aishwarya S; Manohar BM; Lokanadam B; Puvanakrishnan R Curcumin modulates free radical quenching in myocardial ischaemia in rats. Int. J. Biochem. Cell Biol 2004, 36, 1967–1980. [PubMed: 15203111]

(256). Joo NE; Ritchie K; Kamarajan P; Miao D; Kapila YL Nisin, an apoptogenic bacteriocin and food preservative, attenuates HNSCC tumorigenesis via CHAC 1. Cancer Med 2012, 1, 295–305. [PubMed: 23342279]

(257). Nabofa WE; Alashe OO; Oyeyemi OT; Attah AF; Oyagbemi AA; Omobowale TO; Adedapo AA; Alada AR Cardioprotective effects of curcumin-nisin based poly lactic acid nanoparticle on myocardial infarction in guinea pigs. Sci. Rep 2018, 8, 16649. [PubMed: 30413767]

(258). Gomez-Arroyo J; Mizuno S; Szczepanek K; Van Tassell B; Natarajan R; dos Remedios CG; Drake JI; Farkas L; Kraskauskas D; Wijesinghe DS Metabolic gene remodeling and mitochondrial dysfunction in failing right ventricular hypertrophy due to pulmonary arterial hypertension. Circ. Heart Fail 2012, 6, 136–144. [PubMed: 23152488]

(259). Marchenko ND; Zaika A; Moll UM Death signal-induced localization of p53 protein to mitochondria a potential role in apoptotic signaling. J. Biol. Chem 2000, 275, 16202–16212. [PubMed: 10821866]

(260). Mihara M; Erster S; Zaika A; Petrenko O; Chittenden T; Pancoska P; Moll UM p53 has a direct apoptogenic role at the mitochondria. Mol. Cell 2003, 11, 577–590. [PubMed: 12667443]

(261). Vaseva AV; Marchenko ND; Ji K; Tsirka SE; Holzmann S; Moll UM p53 opens the mitochondrial permeability transition pore to trigger necrosis. Cell 2012, 149, 1536–1548. [PubMed: 22726440]

(262). Ong S-B; Lu S; Katwadi K; Ismail NI; Kwek X-Y; Hausenloy DJ Nanoparticle delivery of mitoprotective agents to target ischemic heart disease. Future Cardiol 2017, 13, 195–198. [PubMed: 28569551]

(263). Cung T-T; Morel O; Cayla G; Rioufol G; Garcia-Dorado D; Angoulvant D; Bonnefoy-Cudraz E; Guérin P; Elbaz M; Delarche N Cyclosporine before PCI in patients with acute myocardial infarction. N. Engl. J. Med 2015, 373, 1021–1031. [PubMed: 26321103]

(264). Atar D; Arheden H; Berdeaux A; Bonnet J-L; Carlsson M; Clemmensen P; Cuvier V; Danchin N; Dubois-Randé J-L; Engblom H Effect of intravenous TRO40303 as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: MITOCARE study results. Eur. Heart J 2014, 36, 112–119. [PubMed: 25179768]

(265). Gibson CM; Giugliano RP; Kloner RA; Bode C; Tendera M; Janosi A; Merkely B; Godlewski J; Halaby R; Korjian S EMBRACE STEMI study: a Phase 2a trial to evaluate the safety, tolerability, and efficacy of intravenous MTP-131 on reperfusion injury in patients undergoing primary percutaneous coronary intervention. Eur. Heart J 2015, 37, 1296–1303. [PubMed: 26586786]

(266). Yellon DM; Hausenloy DJ Myocardial reperfusion injury. N. Engl. J. Med 2007, 357, 1121–1135. [PubMed: 17855673]

(267). Piot C; Croisille P; Staat P; Thibault H; Rioufol G; Mewton N; Elbelghiti R; Cung TT; Bonnefoy E; Angoulvant D Effect of cyclosporine on reperfusion injury in acute myocardial infarction. N. Engl. J. Med 2008, 359, 473–481. [PubMed: 18669426]

(268). Nakagawa T; Shimizu S; Watanabe T; Yamaguchi O; Otsu K; Yamagata H; Inohara H; Kubo T; Tsujimoto Y Cyclophilin D-dependent mitochondrial permeability transition regulates some necrotic but not apoptotic cell death. Nature 2005, 434, 652–658. [PubMed: 15800626]

(269). Ikeda G; Matoba T; Nakano Y; Nagaoka K; Ishikita A; Nakano K; Funamoto D; Sunagawa K; Egashira K Nanoparticle-mediated targeting of cyclosporine A enhances cardioprotection against ischemia-reperfusion injury through inhibition of mitochondrial permeability transition pore opening. Sci. Rep 2016, 6, 20467. [PubMed: 26861678]

(270). Ponikowski P; Voors AA; Anker SD; Bueno H; Cleland JG; Coats AJ; Falk V; González-Juanatey JR; Harjola V-P; Jankowska EA 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur. Heart J 2016, 37, 2129–2200. [PubMed: 27206819]

(271). Yancy CW; Jessup M; Bozkurt B; Butler J; Casey DE; Drazner MH; Fonarow GC; Geraci SA; Horwich T; Januzzi JL 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013, 128, 1810–1852. [PubMed: 23741057]

(272). Bussooa A; Neale S; Mercer J Future of Smart Cardiovascular Implants. Sensors 2018, 18, 2008.

(273). Tsai T-H; Tsai H-C; Wu T-K A CMOS micromachined capacitive tactile sensor with integrated readout circuits and compensation of process variations. IEEE Trans. Biomed. Circuits Syst 2014, 8, 608–616. [PubMed: 25314707]

(274). Ho JS; Kim S; Poon AS Midfield wireless powering for implantable systems. Proc. IEEE 2013, 101, 1369–1378.

(275). Lee SW; Yabuuchi N; Gallant BM; Chen S; Kim B-S; Hammond PT; Shao-Horn Y High-power lithium batteries from functionalized carbon-nanotube electrodes. Nat. Nanotechnol 2010, 5, 531–537. [PubMed: 20562872]

(276). Lin D; Liu Y; Cui Y Reviving the lithium metal anode for high-energy batteries. Nat. Nanotechnol 2017, 12, 194–206. [PubMed: 28265117]

(277). Zhang WM; Wu XL; Hu JS; Guo YG; Wan LJ Carbon coated Fe3O4 nanospindles as a superior anode material for lithium-ion batteries. Adv. Funct. Mater 2008, 18, 3941.

(278). Armand M; Tarascon J-M Building better batteries. Nature 2008, 451, 652–657. [PubMed: 18256660]

(279). Martín Giménez VM; Kassuha DE; Manucha W Nanomedicine applied to cardiovascular diseases: latest developments. Ther. Adv. Cardiovasc. Dis 2017, 11, 133–142. [PubMed: 28198204]

(280). Riehle C; Bauersachs J Key inflammatory mechanisms underlying heart failure. Herz 2019, 44, 96–106. [PubMed: 30715565]

(281). Tang J; Cui X; Caranasos TG; Hensley MT; Vandergriff AC; Hartanto Y; Shen D; Zhang H; Zhang J; Cheng K Heart repair using nanogel-encapsulated human cardiac stem cells in mice and pigs with myocardial infarction. ACS Nano 2017, 11, 9738–9749. [PubMed: 28929735]

(282). Kleinbongard P; Schulz R; Heusch G TNFα in myocardial ischemia/reperfusion, remodeling and heart failure. Heart Fail. Rev 2011, 16, 49–69. [PubMed: 20571888]

(283). Gullestad L; Aass H; Fjeld JG; Wikeby L; Andreassen AK; Ihlen H; Simonsen S; Kjekshus J; Nitter-Hauge S; Ueland T Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. Circulation 2001, 103, 220–225. [PubMed: 11208680]

(284). Mahmoudi M; Farokhzad OC Cancer immunotherapy: Wound-bound checkpoint blockade. Nat. Biomed. Eng 2017, 1, 0031.

(285). Zanganeh S; Hutter G; Spitler R; Lenkov O; Mahmoudi M; Shaw A; Pajarinen JS; Nejadnik H; Goodman S; Moseley Met al. Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues. Nat. Nanotechnol 2016, 11, 986–994. [PubMed: 27668795]

(286). Zanganeh S; Spitler R; Hutter G; Ho JQ; Pauliah M; Mahmoudi M Tumor-associated macrophages, nanomedicine and imaging: the axis of success in the future of cancer immunotherapy. Immunotherapy 2017, 9, 819–835. [PubMed: 28877626]

(287). Huang Y-J; Hung K-C; Hung H-S; Hsu S.-h. Modulation of macrophage phenotype by biodegradable polyurethane nanoparticles: possible relation between macrophage polarization and immune response of nanoparticles. ACS Appl. Mater. Interfaces 2018, 10, 19436–19448. [PubMed: 29775050]

(288). Fuchs A-K; Syrovets T; Haas KA; Loos C; Musyanovych A; Mailänder V; Landfester K; Simmet T Carboxyl-and amino-functionalized polystyrene nanoparticles differentially affect the polarization profile of M1 and M2 macrophage subsets. Biomaterials 2016, 85, 78–87. [PubMed: 26854393]

(289). Satessa G; Lenjisa J; Gebremariam E; Woldu M Stem cell therapy for myocardial infarction: challenges and prospects. J. Stem Cell Res. Ther 2015, 5, 1000270.

(290). Chang MG; Tung L; Sekar RB; Chang CY; Cysyk J; Dong P; Marbán E; Abraham MR Proarrhythmic potential of mesenchymal stem cell transplantation revealed in an in vitro coculture model. Circulation 2006, 113, 1832–1841. [PubMed: 16606790]

(291). Choo EH; Lee J-H; Park E-H; Park HE; Jung N-C; Kim T-H; Koh Y-S; Kim E; Seung K-B; Park C Infarcted myocardium-primed dendritic cells improve remodeling and cardiac function after myocardial infarction by modulating the regulatory T cell and macrophage polarization. Circulation 2017, 135, 1444–1457. [PubMed: 28174192]

(292). Mantovani A; Sica A; Sozzani S; Allavena P; Vecchi A; Locati M The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol 2004, 25, 677–686. [PubMed: 15530839]

(293). Bagnost T; Ma L; Da Silva RF; Rezakhaniha R; Houdayer C; Stergiopulos N; Andre C; Guillaume Y; Berthelot A; Demougeot C Cardiovascular effects of arginase inhibition in spontaneously hypertensive rats with fully developed hypertension. Cardiovasc. Res 2010, 87, 569–577. [PubMed: 20219858]

(294). Mantovani A; Sozzani S; Locati M; Allavena P; Sica A Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. Trends Immunol 2002, 23, 549–555. [PubMed: 12401408]

(295). Kim PJ; Mahmoudi M; Ge X; Matsuura Y; Toma I; Metzler S; Kooreman NG; Ramunas J; Holbrook C; McConnell MV Direct evaluation of myocardial viability and stem cell engraftment demonstrates salvage of the injured myocardium. Circ. Res 2015, 116, e40–e50. [PubMed: 25654979]

(296). Mittal M; Siddiqui MR; Tran K; Reddy SP; Malik AB Reactive oxygen species in inflammation and tissue injury. Antioxid. Redox Signaling 2014, 20, 1126–1167.

(297). Qiu Y; Wang Z; Owens AC; Kulaots I; Chen Y; Kane AB; Hurt RH Antioxidant chemistry of graphene-based materials and its role in oxidation protection technology. Nanoscale 2014, 6, 11744–11755. [PubMed: 25157875]

(298). Han J; Kim YS; Lim M-Y; Kim HY; Kong S; Kang M; Choo YW; Jun JH; Ryu S; Jeong H-y. Dual roles of graphene oxide to attenuate inflammation and elicit timely polarization of macrophage phenotypes for cardiac repair. ACS Nano 2018, 12, 1959–1977. [PubMed: 29397689]

(299). van der Valk FM; van Wijk DF; Lobatto ME; Verberne HJ; Storm G; Willems MC; Legemate DA; Nederveen AJ; Calcagno C; Mani Vet al. Prednisolone-containing liposomes accumulate in human atherosclerotic macrophages upon intravenous administration. Nanomedicine 2015, 11, 1039–1046. [PubMed: 25791806]

(300). van der Valk FM; Schulte DM; Meiler S; Tang J; Zheng KH; Van den Bossche J; Seijkens T; Laudes M; de Winther M; Lutgens Eet al. Liposomal prednisolone promotes macrophage lipotoxicity in experimental atherosclerosis. Nanomedicine 2016, 12, 1463–1470. [PubMed: 27015770]

(301). Dahlman JE; Barnes C; Khan O; Thiriot A; Jhunjunwala S; Shaw TE; Xing Y; Sager HB; Sahay G; Speciner Let al. In vivo endothelial siRNA delivery using polymeric nanoparticles with low molecular weight. Nat. Nanotechnol 2014, 9, 648–655. [PubMed: 24813696]

(302). Lewis DR; Petersen LK; York AW; Zablocki KR; Joseph LB; Kholodovych V; Prud'homme RK; Uhrich KE; Moghe PV Sugar-based amphiphilic nanoparticles arrest atherosclerosis in vivo. Proc. Natl. Acad. Sci. USA 2015, 112, 2693–2698. [PubMed: 25691739]

(303). Beldman TJ; Senders ML; Alaarg A; Perez-Medina C; Tang J; Zhao Y; Fay F; Deichmoller J; Born B; Desclos Eet al. Hyaluronan Nanoparticles Selectively Target Plaque-Associated Macrophages and Improve Plaque Stability in Atherosclerosis. ACS Nano 2017, 11, 5785–5799. [PubMed: 28463501]

(304). Nakashiro S; Matoba T; Umezu R; Koga J; Tokutome M; Katsuki S; Nakano K; Sunagawa K; Egashira K Pioglitazone-Incorporated Nanoparticles Prevent Plaque Destabilization and Rupture by Regulating Monocyte/Macrophage Differentiation in ApoE−/−Mice. Arterioscler. Thromb. Vasc. Biol 2016, 36, 491–500. [PubMed: 26821947]

(305). Courties G; Heidt T; Sebas M; Iwamoto Y; Jeon D; Truelove J; Tricot B; Wojtkiewicz G; Dutta P; Sager HBet al. In vivo silencing of the transcription factor IRF5 reprograms the macrophage phenotype and improves infarct healing. J. Am. Coll. Cardiol 2014, 63, 1556–1566. [PubMed: 24361318]

(306). Duivenvoorden R; Tang J; Cormode DP; Mieszawska AJ; Izquierdo-Garcia D; Ozcan C; Otten MJ; Zaidi N; Lobatto ME; van Rijs SMet al. A statin-loaded reconstituted high-density lipoprotein nanoparticle inhibits atherosclerotic plaque inflammation. Nat. Commun 2014, 5, 3065. [PubMed: 24445279]

(307). Zhang L; Wang Y; Xiao F; Wang S; Xing G; Li Y; Yin X; Lu K; Wei R; Fan Jet al. CKIP-1 regulates macrophage proliferation by inhibiting TRAF6-mediated Akt activation. Cell. Res 2014, 24, 742–761. [PubMed: 24777252]

(308). Katsuki S; Matoba T; Nakashiro S; Sato K; Koga J; Nakano K; Nakano Y; Egusa S; Sunagawa K; Egashira K Nanoparticle-mediated delivery of pitavastatin inhibits atherosclerotic plaque destabilization/rupture in mice by regulating the recruitment of inflammatory monocytes. Circulation 2014, 129, 896–906. [PubMed: 24305567]

(309). Davidson SM; Yellon DM Exosomes and cardioprotection - A critical analysis. Mol. Aspects Med 2018, 60, 104–114. [PubMed: 29122678]

(310). Wang Z; Li J; Cho J; Malik AB Prevention of vascular inflammation by nanoparticle targeting of adherent neutrophils. Nat. Nanotechnol 2014, 9, 204–210. [PubMed: 24561355]

(311). Gardiner KM; Tett SE; Staatz CE Multinational evaluation of mycophenolic acid, tacrolimus, cyclosporin, sirolimus, and everolimus utilization. Ann. Transplant 2016, 21, 1–11. [PubMed: 26729299]

(312). Gaston RS Chronic calcineurin inhibitor nephrotoxicity: reflections on an evolving paradigm. J. Am. Soc. Nephrol 2009, 4, 2029–2034.

(313). Cheng S-C; Quintin J; Cramer RA; Shepardson KM; Saeed S; Kumar V; Giamarellos-Bourboulis EJ; Martens JH; Rao NA; Aghajanirefah A mTOR-and HIF-1α–mediated aerobic glycolysis as metabolic basis for trained immunity. Science 2014, 345, 1250684. [PubMed: 25258083]

(314). Duivenvoorden R; Tang J; Cormode DP; Mieszawska AJ; Izquierdo-Garcia D; Ozcan C; Otten MJ; Zaidi N; Lobatto ME; Van Rijs SM A statin-loaded reconstituted high-density lipoprotein nanoparticle inhibits atherosclerotic plaque inflammation. Nat. Commun 2014, 5, 3065. [PubMed: 24445279]

(315). Braza MS; van Leent MM; Lameijer M; Sanchez-Gaytan BL; Arts RJ; Pérez-Medina C; Conde P; Garcia MR; Gonzalez-Perez M; Brahmachary M Inhibiting inflammation with Myeloid cell-specific nanobiologics promotes organ transplant acceptance. Immunity 2018, 49, 819–828.e6. [PubMed: 30413362]

(316). Wu YL; Ye Q; Eytan DF; Liu L; Rosario BL; Hitchens TK; Yeh F-C; Rooijen van N; Ho C Magnetic resonance imaging investigation of macrophages in acute cardiac allograft rejection after heart transplantation. Circ. Cardiovasc. Imaging 2013, 6, 965–973. [PubMed: 24097421]

(317). Solhjou Z; Uehara M; Bahmani B; Maarouf OH; Ichimura T; Brooks CR; Xu W; Yilmaz M; Elkhal A; Tullius SG Novel Application of Localized Nanodelivery of Anti–Interleukin-6 Protects Organ Transplant From Ischemia–Reperfusion Injuries. Am. J. Transplant 2017, 17, 2326–2337. [PubMed: 28296000]

(318). Miniati DN; Robbins RC Heart transplantation: a thirty-year perspective. Annu. Rev. Med 2002, 53, 189–205. [PubMed: 11818470]

(319). Gradek WQ; D'Amico C; Smith AL; Vega D; Book WM Routine surveillance endomyocardial biopsy continues to detect significant rejection late after heart transplantation. J. Heart Lung Transplant 2001, 20, 497–502. [PubMed: 11343975]

(320). Hancock WW; Thomson NM; Atkins RC Composition of interstitial cellular infiltrate identified by monoclonal antibodies in renal biopsies of rejecting human renal allografts. Transplantation 1983, 35, 458–463. [PubMed: 6342225]

(321). Ueno T; Dutta P; Keliher E; Leuschner F; Majmudar M; Marinelli B; Iwamoto Y; Figueiredo J-L; Christen T; Swirski FK Nanoparticle PET-CT detects rejection and immunomodulation in cardiac allografts. Circ. Cardiovasc. Imaging 2013, 6, 568–573. [PubMed: 23771986]

(322). Sharifi S; Behzadi S; Laurent S; Forrest ML; Stroeve P; Mahmoudi M Toxicity of nanomaterials. Chem. Soc. Rev 2012, 41, 2323–2343. [PubMed: 22170510]

(323). Auffan M; Rose J; Bottero J-Y; Lowry GV; Jolivet J-P; Wiesner MR Towards a definition of inorganic nanoparticles from an environmental, health and safety perspective. Nat. Nanotechnol 2009, 4, 634–641. [PubMed: 19809453]

(324). Bertrand N; Wu J; Xu X; Kamaly N; Farokhzad OC Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. Adv. Drug Delivery Rev 2014, 66, 2–25.

(325). Miragoli M; Ceriotti P; Iafisco M; Vacchiano M; Salvarani N; Alogna A; Carullo P; Ramirez-Rodríguez GB; Patrício T; Degli Esposti L Inhalation of peptide-loaded nanoparticles improves heart failure. Sci. Transl. Med 2018, 10, eaan6205. [PubMed: 29343624]

(326). Ichimura K; Matoba T; Nakano K; Tokutome M; Honda K; Koga J.-i.; Egashira K A translational study of a new therapeutic approach for acute myocardial infarction: nanoparticle-mediated delivery of pitavastatin into reperfused myocardium reduces ischemia-reperfusion injury in a preclinical porcine model. PloS One 2016, 11, e0162425. [PubMed: 27603665]

(327). Wen D; Xu J; Huan Y; Wei M; Zheng M Effects of Endothelial Progenitor Cells Used for Autograft Transplantation in Acute Myocardial Infarction Pig Model. Cardiovasc. Imaging Asia 2018, 2, 142–149.

(328). Gallet R; Dawkins J; Valle J; Simsolo E; De Couto G; Middleton R; Tseliou E; Luthringer D; Kreke M; Smith RR Exosomes secreted by cardiosphere-derived cells reduce scarring, attenuate adverse remodelling, and improve function in acute and chronic porcine myocardial infarction. Eur. Heart J 2016, 38, 201–211.

(329). Matuszak J; Baumgartner J; Zaloga J; Juenet M; Da Silva AE; Franke D; Almer G; Texier I; Faivre D; Metselaar JM Nanoparticles for intravascular applications: Physicochemical characterization and cytotoxicity testing. Nanomedicine 2016, 11, 597–616. [PubMed: 27003004]

(330). Liu Y; Sun L; Huan Y; Zhao H; Deng J Effects of basic fibroblast growth factor microspheres on angiogenesis in ischemic myocardium and cardiac function: analysis with dobutamine cardiovascular magnetic resonance tagging. Eur. J. Cardiothorac. Surg 2006, 30, 103–107. [PubMed: 16730451]

(331). Sakakibara Y; Tambara K; Sakaguchi G; Lu F; Yamamoto M; Nishimura K; Tabata Y; Komeda M Toward surgical angiogenesis using slow-released basic fibroblast growth factor. Eur. J. Cardiothorac. Surg 2003, 24, 105–112. [PubMed: 12853053]

(332). Marui A; Tabata Y; Kojima S; Yamamoto M; Tambara K; Nishina T; Saji Y; Inui K.-i.; Hashida T; Yokoyama S A novel approach to therapeutic angiogenesis for patients with critical limb ischemia by sustained release of basic fibroblast growth factor using biodegradable gelatin hydrogel. Circ. J 2007, 71, 1181–1186. [PubMed: 17652878]

(333). Smalling RW; Feld S; Ramanna N; Amirian J; Felli P; Vaughn WK; Swenson C; Janoff A Infarct salvage with liposomal prostaglandin E1 administered by intravenous bolus immediately before reperfusion in a canine infarction-reperfusion model. Circulation 1995, 92, 935–943. [PubMed: 7641377]

(334). Caracciolo G; Vali H; Moore A; Mahmoudi M Challenges in molecular diagnostic research in cancer nanotechnology. Nano Today, 2019, 27, 6–10.

(335). Heydari T; Heidari M; Mashinchian O; Wojcik M; Xu K; Dalby MJ; Mahmoudi M; Ejtehadi MR Development of a Virtual Cell Model to Predict Cell Response to Substrate Topography. ACS Nano 2017, 11, 9084–9092. [PubMed: 28742318]

(336). Zanganeh S; Spitler R; Erfanzadeh M; Alkilany AM; Mahmoudi M Protein corona: opportunities and challenges. Int. J. Biochem. Cell Biol 2016, 75, 143–147. [PubMed: 26783938]

(337). Faria M; Björnmalm M; Thurecht KJ; Kent SJ; Parton RG; Kavallaris M; Johnston AP; Gooding JJ; Corrie SR; Boyd BJ Minimum information reporting in bio–nano experimental literature. Nat. Nanotechnol 2018, 13, 777–785. [PubMed: 30190620]

(338). Mahmoudi M; Hofmann H; Rothen-Rutishauser B; Petri-Fink A Assessing the in vitro and in vivo toxicity of superparamagnetic iron oxide nanoparticles. Chem. Rev 2011, 112, 2323–2338. [PubMed: 22216932]

(339). Azhdarzadeh M; Saei AA; Sharifi S; Hajipour MJ; Alkilany AM; Sharifzadeh M; Ramazani F; Laurent S; Mashaghi A; Mahmoudi M Nanotoxicology: advances and pitfalls in research methodology. Nanomedicine 2015, 10, 2931–2952. [PubMed: 26370561]

(340). Saei AA; Yazdani M; Lohse SE; Bakhtiary Z; Serpooshan V; Ghavami M; Asadian M; Mashaghi S; Dreaden EC; Mashaghi A Nanoparticle surface functionality dictates cellular and systemic toxicity. Chem. Mater 2017, 29, 6578–6595.

(341). Dixon SJ; Lemberg KM; Lamprecht MR; Skouta R; Zaitsev EM; Gleason CE; Patel DN; Bauer AJ; Cantley AM; Yang WS Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 2012, 149, 1060–1072. [PubMed: 22632970]

(342). Xie Y; Hou W; Song X; Yu Y; Huang J; Sun X; Kang R; Tang D Ferroptosis: process and function. Cell Death Differ 2016, 23, 369–379. [PubMed: 26794443]

(343). Yang WS; Stockwell BR Ferroptosis: death by lipid peroxidation. Trends Cell Biol 2016, 26, 165–176. [PubMed: 26653790]

(344). Kim SE; Zhang L; Ma K; Riegman M; Chen F; Ingold I; Conrad M; Turker MZ; Gao M; Jiang X Ultrasmall nanoparticles induce ferroptosis in nutrient-deprived cancer cells and suppress tumour growth. Nat. Nanotechnol 2016, 11, 977–985. [PubMed: 27668796]

(345). Dixon SJ; Stockwell BR The role of iron and reactive oxygen species in cell death. Nat. Chem. Biol 2014, 10, 9–17. [PubMed: 24346035]

(346). Bulluck H; Rosmini S; Abdel-Gadir A; White SK; Bhuva AN; Treibel TA; Fontana M; Ramlall M; Hamarneh A; Sirker A Residual myocardial iron following intramyocardial hemorrhage during the convalescent phase of reperfused ST-segment–elevation myocardial infarction and adverse left ventricular remodeling. Circ. Cardiovasc. Imaging 2016, 9, e004940. [PubMed: 27894068]

(347). Donaldson K; Brown D; Clouter A; Duffin R; MacNee W; Renwick L; Tran L; Stone V The pulmonary toxicology of ultrafine particles. J. Aerosol Med 2002, 15, 213–220. [PubMed: 12184871]

(348). Cho W-S; Duffin R; Poland CA; Howie SE; MacNee W; Bradley M; Megson IL; Donaldson K Metal oxide nanoparticles induce unique inflammatory footprints in the lung: important implications for nanoparticle testing. Environ. Health Perspect 2010, 118, 1699–1706. [PubMed: 20729176]

(349). Bonner JC Nanoparticles as a potential cause of pleural and interstitial lung disease. Proc. Am. Thorac. Soc 2010, 7, 138–141. [PubMed: 20427587]

(350). Yazdi AS; Guarda G; Riteau N; Drexler SK; Tardivel A; Couillin I; Tschopp J Nanoparticles activate the NLR pyrin domain containing 3 (Nlrp3) inflammasome and cause pulmonary inflammation through release of IL-1α and IL-1β. P. Natl. Acad. Sci. USA 2010, 107, 19449–19454.

(351). Ma JY; Zhao H; Mercer RR; Barger M; Rao M; Meighan T; Schwegler-Berry D; Castranova V; Ma JK Cerium oxide nanoparticle-induced pulmonary inflammation and alveolar macrophage functional change in rats. Nanotoxicology 2011, 5, 312–325. [PubMed: 20925443]

(352). Horie M; Fukui H; Nishio K; Endoh S; Kato H; Fujita K; Miyauchi A; Nakamura A; Shichiri M; Ishida N Evaluation of acute oxidative stress induced by NiO nanoparticles in vivo and in vitro. J. Occup. Health 2011, 53, 64–74. [PubMed: 21233593]

(353). Wang X; Katwa P; Podila R; Chen P; Ke PC; Rao AM; Walters DM; Wingard CJ; Brown JM Multi-walled carbon nanotube instillation impairs pulmonary function in C57BL/6 mice. Part. Fibre Toxicol 2011, 8, 24. [PubMed: 21851604]

(354). Hong F; Wang L; Yu X; Zhou Y; Hong J; Sheng L Toxicological effect of TiO2 nanoparticle-induced myocarditis in mice. Nanoscale Res. Lett 2015, 10, 326.

(355). LeBlanc A; Moseley A; Chen B; Frazer D; Castranova V; Nurkiewicz T Nanoparticle inhalation impairs coronary microvascular reactivity via a local reactive oxygen species-dependent mechanism. Cardiovasc. Toxicol 2010, 10, 27–36. [PubMed: 20033351]

(356). Kreyling WG; Abdelmonem AM; Ali Z; Alves F; Geiser M; Haberl N; Hartmann R; Hirn S; De Aberasturi DJ; Kantner K In vivo integrity of polymer-coated gold nanoparticles. Nat. Nanotechnol 2015, 10, 619–623. [PubMed: 26076469]

(357). Deng ZJ; Liang M; Monteiro M; Toth I; Minchin RF Nanoparticle-induced unfolding of fibrinogen promotes Mac-1 receptor activation and inflammation. Nat. Nanotechnol 2011, 6, 39–44. [PubMed: 21170037]

(358). Kharazian B; Lohse SE; Ghasemi F; Raoufi M; Saei AA; Hashemi F; Farvadi F; Alimohamadi R; Jalali SA; Shokrgozar MA Bare surface of gold nanoparticle induces inflammation through unfolding of plasma fibrinogen. Sci. Rep 2018, 8, 12557. [PubMed: 30135553]

(359). Li J. J. e.; Muralikrishnan S; Ng C-T; Yung L-YL; Bay B-H Nanoparticle-induced pulmonary toxicity. Exp. Biol. Med 2010, 235, 1025–1033.

(360). Chuang K-J; Lee K-Y; Pan C-H; Lai C-H; Lin L-Y; Ho S-C; Ho K-F; Chuang H-C Effects of zinc oxide nanoparticles on human coronary artery endothelial cells. Food Chem. Toxicol 2016, 93, 138–144. [PubMed: 27185063]

(361). Downs TR; Crosby ME; Hu T; Kumar S; Sullivan A; Sarlo K; Reeder B; Lynch M; Wagner M; Mills T Silica nanoparticles administered at the maximum tolerated dose induce genotoxic effects through an inflammatory reaction while gold nanoparticles do not. Mutat Res. Genet. Toxicol. Environ. Mutagen 2012, 745, 38–50.

(362). Holland NA; Becak DP; Shannahan JH; Brown JM; Carratt S; Winkle L; Pinkerton KE; Wang CM; Munusamy P; Baer DR Cardiac ischemia reperfusion injury following instillation of 20 nm citrate-capped nanosilver. J. Nanomed. Nanotechnol 2015, 6, pii: 006. [PubMed: 26966636]

(363). Oslakovic C; Cedervall T; Linse S; Dahlbäck B Polystyrene nanoparticles affecting blood coagulation. Nanomed. Nanotechnol. Biol. Med 2012, 8, 981–986.

(364). Haberl N; Hirn S; Holzer M; Zuchtriegel G; Rehberg M; Krombach F Effects of acute systemic administration of TiO2, ZnO, SiO2, and Ag nanoparticles on hemodynamics, hemostasis and leukocyte recruitment. Nanotoxicology 2015, 9, 963–971. [PubMed: 25670207]

(365). Radomski A; Jurasz P; Alonso-Escolano D; Drews M; Morandi M; Malinski T; Radomski MW Nanoparticle-induced platelet aggregation and vascular thrombosis. Br. J. Pharmacol 2005, 146, 882–893. [PubMed: 16158070]

(366). Jun E-A; Lim K-M; Kim K; Bae O-N; Noh J-Y; Chung K-H; Chung J-H Silver nanoparticles enhance thrombus formation through increased platelet aggregation and procoagulant activity. Nanotoxicology 2011, 5, 157–167. [PubMed: 20822370]

(367). Nemmar A; Beegam S; Yuvaraju P; Yasin J; Tariq S; Attoub S; Ali BH Ultrasmall superparamagnetic iron oxide nanoparticles acutely promote thrombosis and cardiac oxidative stress and DNA damage in mice. Part. Fibre Toxicol 2016, 13, 22. [PubMed: 27138375]

(368). Wingard CJ; Walters DM; Cathey BL; Hilderbrand SC; Katwa P; Lin S; Ke PC; Podila R; Rao A; Lust RM Mast cells contribute to altered vascular reactivity and ischemiareperfusion injury following cerium oxide nanoparticle instillation. Nanotoxicology 2011, 5, 531–545. [PubMed: 21043986]

(369). Saber AT; Lamson JS; Jacobsen NR; Ravn-Haren G; Hougaard KS; Nyendi AN; Wahlberg P; Madsen AM; Jackson P; Wallin H Particle-induced pulmonary acute phase response correlates with neutrophil influx linking inhaled particles and cardiovascular risk. PLoS One 2013, 8, e69020. [PubMed: 23894396]

(370). Teeguarden JG; Webb-Robertson B-J; Waters KM; Murray AR; Kisin ER; Varnum SM; Jacobs JM; Pounds JG; Zanger RC; Shvedova AA Comparative proteomics and pulmonary toxicity of instilled single-walled carbon nanotubes, crocidolite asbestos, and ultrafine carbon black in mice. Toxicol. Sci 2010, 120, 123–135. [PubMed: 21135415]

(371). Li Z; Hulderman T; Salmen R; Chapman R; Leonard SS; Young S-H; Shvedova A; Luster MI; Simeonova PP Cardiovascular effects of pulmonary exposure to single-wall carbon nanotubes. Environ. Health Perspect 2007, 115, 377–382. [PubMed: 17431486]

(372). Mikkelsen L; Sheykhzade M; Jensen KA; Saber AT; Jacobsen NR; Vogel U; Wallin H; Loft S; Møller P Modest effect on plaque progression and vasodilatory function in atherosclerosis-prone mice exposed to nanosized TiO 2. Part. Fibre Toxicol 2011, 8, 32. [PubMed: 22074227]

(373). Nurkiewicz TR; Porter DW; Hubbs AF; Stone S; Chen BT; Frazer DG; Boegehold MA; Castranova V Pulmonary nanoparticle exposure disrupts systemic microvascular nitric oxide signaling. Toxicol. Sci 2009, 110, 191–203. [PubMed: 19270016]

(374). Thompson LC; Frasier CR; Sloan RC; Mann EE; Harrison BS; Brown JM; Brown DA; Wingard CJ Pulmonary instillation of multi-walled carbon nanotubes promotes coronary vasoconstriction and exacerbates injury in isolated hearts. Nanotoxicology 2014, 8, 38–49. [PubMed: 23102262]

(375). Urankar RN; Lust RM; Mann E; Katwa P; Wang X; Podila R; Hilderbrand SC; Harrison BS; Chen P; Ke PC Expansion of cardiac ischemia/reperfusion injury after instillation of three forms of multi-walled carbon nanotubes. Part. Fibre Toxicol 2012, 9, 38. [PubMed: 23072542]

(376). Stapleton PA; Minarchick VC; Cumpston AM; McKinney W; Chen BT; Sager TM; Frazer DG; Mercer RR; Scabilloni J; Andrew ME Impairment of coronary arteriolar endothelium-dependent dilation after multi-walled carbon nanotube inhalation: a time-course study. Int J Mol Sci 2012, 13, 13781–13803. [PubMed: 23203034]

(377). Kushida T; Saha K; Subramani C; Nandwana V; Rotello VM Effect of nano-scale curvature on the intrinsic blood coagulation system. Nanoscale 2014, 6, 14484–14487. [PubMed: 25341004]

(378). Dobrovolskaia MA; Patri AK; Simak J; Hall JB; Semberova J; De Paoli Lacerda SH; McNeil SE Nanoparticle size and surface charge determine effects of PAMAM dendrimers on human platelets in vitro. Mol. Pharmaceutics 2011, 9, 382–393.

(379). Strömberg A; Mårtensson J Gender differences in patients with heart failure. Eur. J. Cardiovasc. Nurs 2003, 2, 7–18. [PubMed: 14622644]

(380). Azad N; Kathiravelu A; Minoosepeher S; Hebert P; Fergusson D Gender differences in the etiology of heart failure: a systematic review. J. Geriatr. Cardiol 2011, 8, 15–23. [PubMed: 22783280]

(381). Mehta P; Cowie M Gender and heart failure: a population perspective. Heart 2006, 92, iii14–iii18. [PubMed: 16614262]

(382). Simon T; Mary-Krause M; Funck-Brentano C; Jaillon P Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). Circulation 2001, 103, 375–380. [PubMed: 11157688]

(383). Eisenberg E; Di Palo KE; Piña IL Sex differences in heart failure. Clin. Cardiol 2018, 41, 211–216. [PubMed: 29485677]

(384). Farrell SR; Ross JL; Howlett SE Sex differences in mechanisms of cardiac excitation-contraction coupling in rat ventricular myocytes. Am. J. Physiol. Heart. Circ. Physiol 2010, 299, H36–H45. [PubMed: 20453102]

(385). Keller KM; Howlett SE Sex differences in the biology and pathology of the aging heart. Can. J. Cardiol 2016, 32, 1065–1073. [PubMed: 27395082]

(386). Mallat Z; Fornes P; Costagliola R; Esposito B; Belmin J; Lecomte D; Tedgui A Age and gender effects on cardiomyocyte apoptosis in the normal human heart. J. Gerontol. A Biol. Sci. Med. Sci 2001, 56, M719–M723. [PubMed: 11682581]

(387). Bell JR; Curl CL; Harding TW; Petroff MV; Harrap SB; Delbridge LM Male and female hypertrophic rat cardiac myocyte functional responses to ischemic stress and β-adrenergic challenge are different. Biol. Sex Differ 2016, 7, 32. [PubMed: 27390618]

(388). Mendelsohn ME; Karas RH Molecular and cellular basis of cardiovascular gender differences. Science 2005, 308, 1583–1587. [PubMed: 15947175]

(389). Parks RJ; Ray G; Bienvenu LA; Rose RA; Howlett SE Sex differences in SR Ca2+ release in murine ventricular myocytes are regulated by the cAMP/PKA pathway. J. Mol. Cell. Cardiol 2014, 75, 162–173. [PubMed: 25066697]

(390). Sun J; Picht E; Ginsburg KS; Bers DM; Steenbergen C; Murphy E Hypercontractile female hearts exhibit increased S-nitrosylation of the L-type Ca2+ channel α1 subunit and reduced ischemia/reperfusion injury. Circ. Res 2006, 98, 403–411. [PubMed: 16397145]

(391). Donington JS; Colson YL Sex and gender differences in non-small cell lung cancer. Semin. Thorac. Cardiovasc. Surg 2011, 23, 137–145. [PubMed: 22041044]

(392). Carey MA; Card JW; Voltz JW; Arbes SJ Jr; Germolec DR; Korach KS; Zeldin DC It's all about sex: gender, lung development and lung disease. Trends Endocrinol. Metab 2007, 18, 308–313. [PubMed: 17764971]

(393). Siegiel R; Miller K; Jemal A Cancer Statistics, 2017. CA Cancer J. Clin 2017, 67, 7–30. [PubMed: 28055103]

(394). Kabir Z; Connolly GN; Clancy L Sex-differences in lung cancer cell-types? An epidemiologic study in Ireland. Ulster Med. J 2008, 77, 31–35. [PubMed: 18269115]

(395). Heidecker B; Lamirault G; Kasper EK; Wittstein IS; Champion HC; Breton E; Russell SD; Hall J; Kittleson MM; Baughman KL The gene expression profile of patients with new-onset heart failure reveals important gender-specific differences. Eur. Heart J 2009, 31, 1188–1196. [PubMed: 20031959]

(396). Stone G; Choi A; Oliva M; Gorham J; Heydarpour M; Seidman CE; Seidman JG; Aranki SF; Body SC; Carey VJ Sex differences in gene expression in response to ischemia in the human left ventricular myocardium. Hum. Mol. Genet 2019, 28, 1682–1693. [PubMed: 30649309]

(397). Arnold AP; Disteche CM Sexual Inequality in the Cancer Cell. Cancer Res 2018, 78, 5504–5505. [PubMed: 30275051]

(398). Bellott DW; Hughes JF; Skaletsky H; Brown LG; Pyntikova T; Cho T-J; Koutseva N; Zaghlul S; Graves T; Rock S Mammalian Y chromosomes retain widely expressed dosage-sensitive regulators. Nature 2014, 508, 494–499. [PubMed: 24759411]

(399). Veitia RA; Veyrunes F; Bottani S; Birchler JA X chromosome inactivation and active X upregulation in therian mammals: facts, questions, and hypotheses. J. Mol. Cell Biol 2015, 7, 2–11. [PubMed: 25564545]

(400). Disteche CM Dosage compensation of the sex chromosomes and autosomes. Semin. Cell Dev. Biol 2016, 56, 9–18. [PubMed: 27112542]

(401). Lopes-Ramos CM; Kuijjer ML; Ogino S; Fuchs CS; DeMeo DL; Glass K; Quackenbush J Gene regulatory network analysis identifies sex-linked differences in colon cancer drug metabolism processes. Cancer Res 2018, 78, 5538–5547. [PubMed: 30275053]

(402). Li CH; Haider S; Shiah Y-J; Thai K; Boutros PC Sex differences in cancer driver genes and biomarkers. Cancer Res 2018, 78, 5527–5537. [PubMed: 30275052]

(403). Serpooshan V; Sheibani S; Pushparaj P; Wojcik M; Jang AY; Santoso MR; Jang JH; Huang H; Safavi-Sohi R; Haghjoo Net al. Effect of Cell Sex on Uptake of Nanoparticles: The Overlooked Factor at the Nanobio Interface. ACS Nano 2018, 12, 2253–2266. [PubMed: 29536733]

(404). Mahmoudi M; Laurent S; Shokrgozar MA; Hosseinkhani M Toxicity evaluations of superparamagnetic iron oxide nanoparticles: cell “vision” versus physicochemical properties of nanoparticles. ACS Nano 2011, 5, 7263–7276. [PubMed: 21838310]

(405). Mahmoudi M; Simchi A; Imani M; Shokrgozar MA; Milani AS; Häfeli UO; Stroeve P A new approach for the in vitro identification of the cytotoxicity of superparamagnetic iron oxide nanoparticles. Colloids Surf. B 2010, 75, 300–309.

(406). Mahmoudi M; Abdelmonem AM; Behzadi S; Clement JH; Dutz S; Ejtehadi MR; Hartmann R; Kantner K; Linne U; Maffre P Temperature: the “ignored” factor at the nanobio interface. ACS Nano 2013, 7, 6555–6562. [PubMed: 23808533]

(407). Laurent S; Burtea C; Thirifays C; Häfeli UO; Mahmoudi M Crucial ignored parameters on nanotoxicology: the importance of toxicity assay modifications and “cell vision”. PloS One 2012, 7, e29997. [PubMed: 22253854]

(408). Mahmoudi M; Shokrgozar MA; Sardari S; Moghadam MK; Vali H; Laurent S; Stroeve P Irreversible changes in protein conformation due to interaction with superparamagnetic iron oxide nanoparticles. Nanoscale 2011, 3, 1127–1138. [PubMed: 21210042]

(409). Mahmoudi M; Saeedi-Eslami SN; Shokrgozar MA; Azadmanesh K; Hassanlou M; Kalhor HR; Burtea C; Rothen-Rutishauser B; Laurent S; Sheibani S Cell “vision”: complementary factor of protein corona in nanotoxicology. Nanoscale 2012, 4, 5461–5468. [PubMed: 22842341]

(410). Hajipour MJ; Laurent S; Aghaie A; Rezaee F; Mahmoudi M Personalized protein coronas: a “key” factor at the nanobiointerface. Biomater. Sci 2014, 2, 1210–1221.

(411). Mahmoudi M; Lohse SE; Murphy CJ; Fathizadeh A; Montazeri A; Suslick KS Variation of protein corona composition of gold nanoparticles following plasmonic heating. Nano lett 2013, 14, 6–12. [PubMed: 24328336]

(412). Amiri H; Bordonali L; Lascialfari A; Wan S; Monopoli MP; Lynch I; Laurent S; Mahmoudi M Protein corona affects the relaxivity and MRI contrast efficiency of magnetic nanoparticles. Nanoscale 2013, 5, 8656–8665. [PubMed: 23896964]

(413). Hajipour MJ; Raheb J; Akhavan O; Arjmand S; Mashinchian O; Rahman M; Abdolahad M; Serpooshan V; Laurent S; Mahmoudi M Personalized disease-specific protein corona influences the therapeutic impact of graphene oxide. Nanoscale 2015, 7, 8978–8994. [PubMed: 25920546]

(414). Behzadi S; Serpooshan V; Sakhtianchi R; Müller B; Landfester K; Crespy D; Mahmoudi M Protein corona change the drug release profile of nanocarriers: the “overlooked” factor at the nanobio interface. Colloids Surf. B 2014, 123, 143–149.

(415). Rauch J; Kolch W; Mahmoudi M Cell type-specific activation of AKT and ERK signaling pathways by small negatively-charged magnetic nanoparticles. Sci. Rep 2012, 2, 868. [PubMed: 23162692]

(416). Mirshafiee V; Kim R; Mahmoudi M; Kraft ML The importance of selecting a proper biological milieu for protein corona analysis in vitro: Human plasma versus human serum. Int. J. Biochem. Cell Biol 2016, 75, 188–195. [PubMed: 26643610]

(417). Corbo C; Molinaro R; Tabatabaei M; Farokhzad OC; Mahmoudi M Personalized protein corona on nanoparticles and its clinical implications. Biomater. Sci 2017, 5, 378–387. [PubMed: 28133653]

(418). Tachibana A; Santoso MR; Mahmoudi M; Shukla P; Wang L; Bennett M; Goldstone AB; Wang M; Fukushi M; Ebert AD Paracrine effects of the pluripotent stem cell-derived cardiac myocytes salvage the injured myocardium. Circ. Res 2017, 121, e22–e36. [PubMed: 28743804]

(419). Tavakol M; Montazeri A; Naghdabadi R; Hajipour MJ; Zanganeh S; Caracciolo G; Mahmoudi M Disease-related metabolites affect protein-nanoparticle interactions. Nanoscale 2018, 10, 7108–7115. [PubMed: 29616243]

(420). Behzadi S; Vatan NM; Lema K; Nwaobasi D; Zenkov I; Abadi PP; Khan DA; Corbo C; Aghaverdi H; Farokhzad OC Flat Cell Culturing Surface May Cause Misinterpretation of Cellular Uptake of Nanoparticles. Adv. Biosyst 2018, 2, 1800046.

(421). Wilhelm S; Tavares AJ; Dai Q; Ohta S; Audet J; Dvorak HF; Chan WC Analysis of nanoparticle delivery to tumours. Nat. Rev. Mater 2016, 1, 16014.

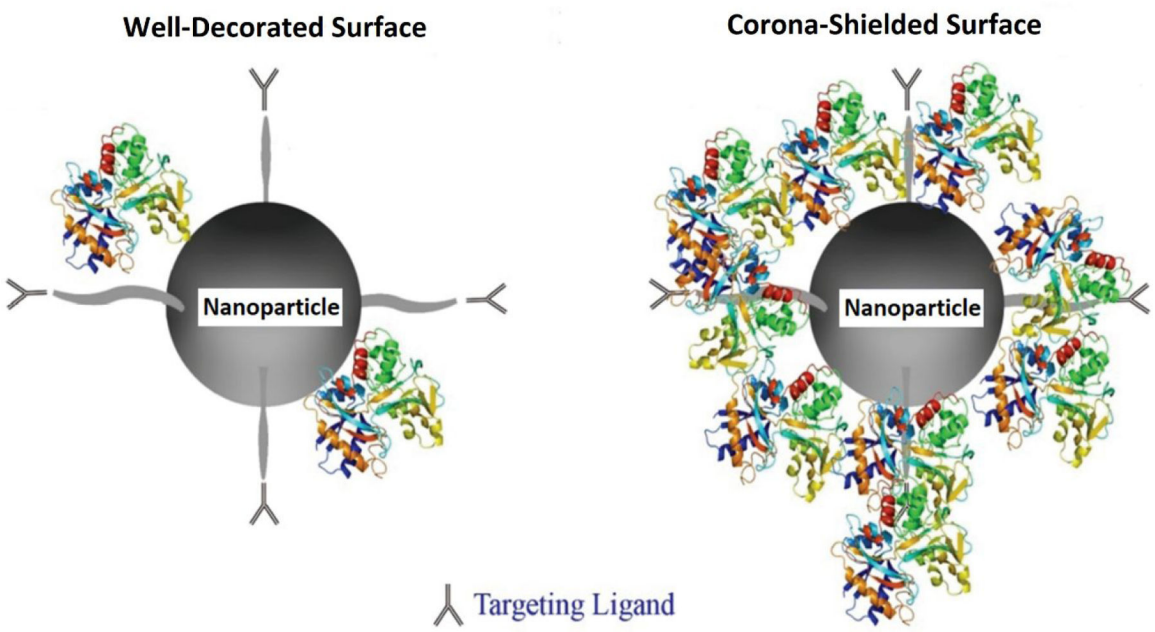

Figure 1.

Scheme showing the shielding effect of protein corona on targeted nanoparticles according to their characteristics. Figures are reproduced from the reference[101]; copyright [2011] e-Century Publishing Corporation.

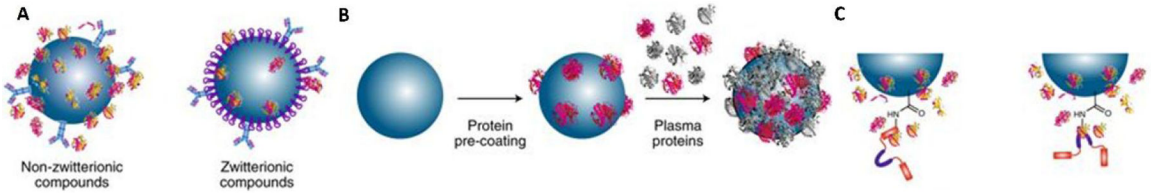

Figure 2.

Schematic showing the proposed strategies to minimize the shielding effects of the biomolecular/protein corona through (A) use of specific coatings to diminish biomolecular attachment to the surface of nanoparticles, (B) pre-coating, and (C) pre-adsorption of targeting species, rather than chemical conjugation, to the surface of nanoparticles. Figures are reproduced from the reference[109]; copyright [2018] Nature Publishing Group.

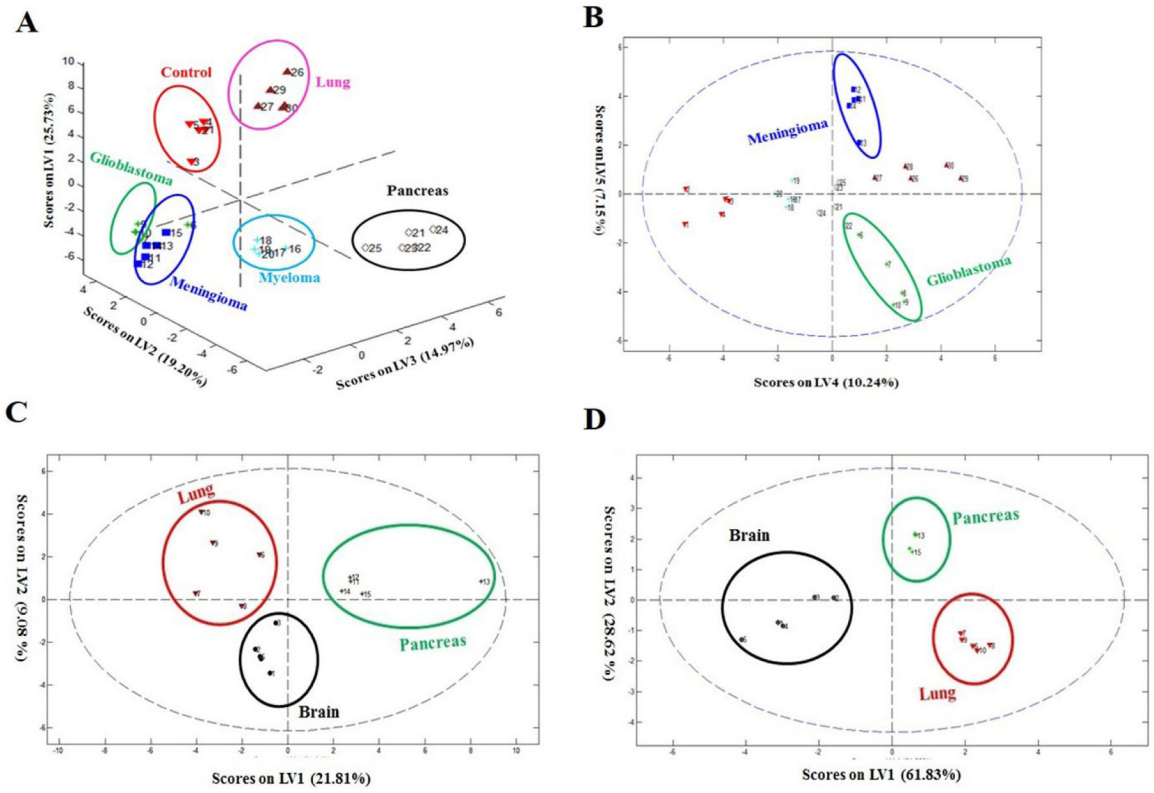

Figure 3.

Using protein corona sensor array for identification and discrimination of cancers at various stages. (A) Outcomes of the supervised classifier projecting cancers into the subspace created by the 1st, 2nd, and 3rd latent variables of the classifier. (B) Two types of brain cancers were discriminated in 4th and 5th latent variables of the model. (C), (D) Successful classification of cancers in plasma samples from healthy individuals who developed lung, brain, and pancreatic cancers eight years after plasma collections in the 1st and 2nd latent variables of the two developed models. Figures are reproduced from the reference[110]; copyright [2019] The Royal Society of Chemistry.

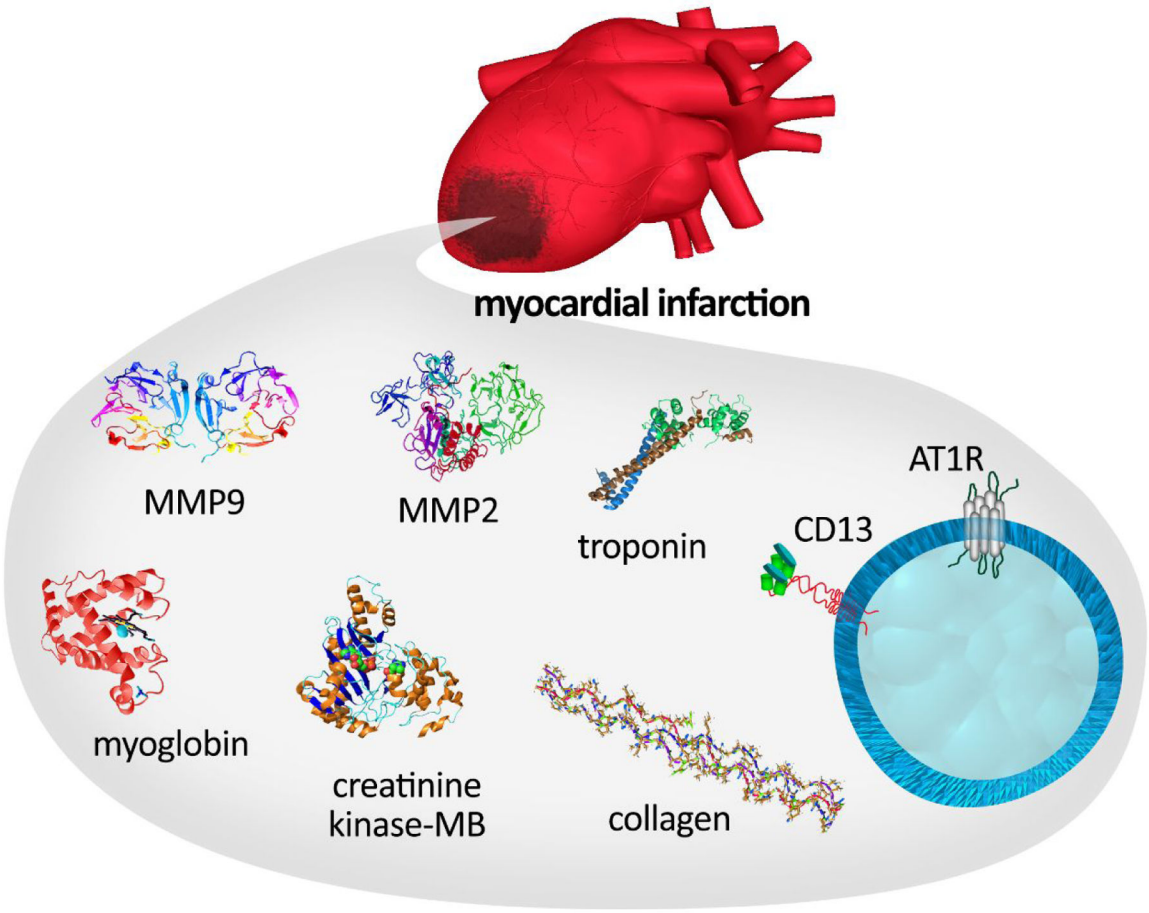

Figure 4.
Schematic representation of myocardial infarction–specific biomarkers

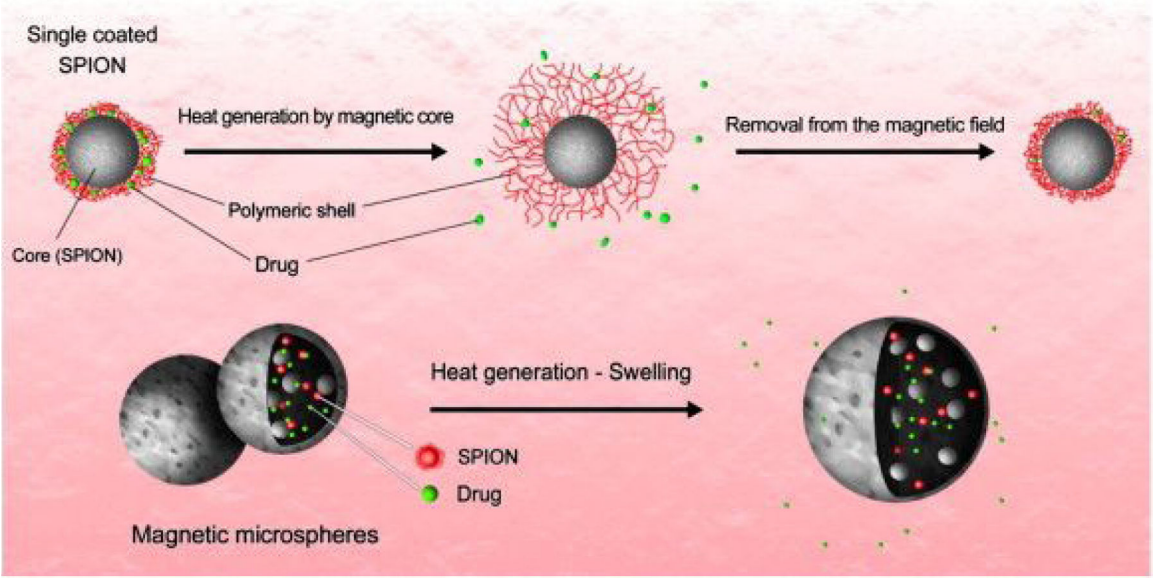

Figure 5.

Development of thermo-responsive polymeric nanoplatforms with embedded superparamagnetic iron oxide nanoparticles. The superparamagnetic iron oxide nanoparticles can be heated using an external magnetic field, which activates the thermo-responsive polymeric carrier to release the payload. Figure is reproduced from reference[152]; copyright [2011] Elsevier.

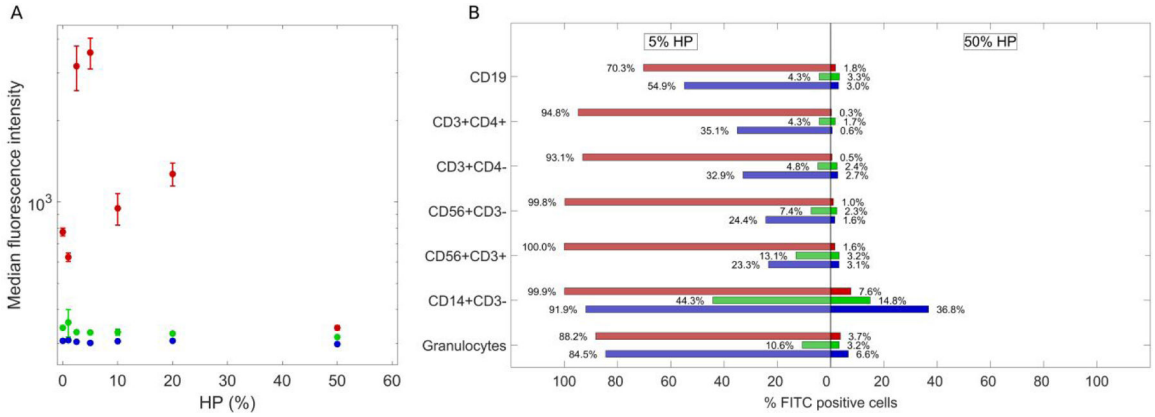

Figure 6.

Flow cytometry results demonstrating the uptake of protein corona coated liposomes [with positive (red), neutral (green) and negative (blue) surface charges], after incubation with various concentrations of human plasma (HP), by human monocyte THP-1 cells. (B) Uptake of various corona coated liposomes by distinct leukocyte subpopulations. Figures are reproduced from the reference[159]; copyright [2019] Nature Publishing Group.

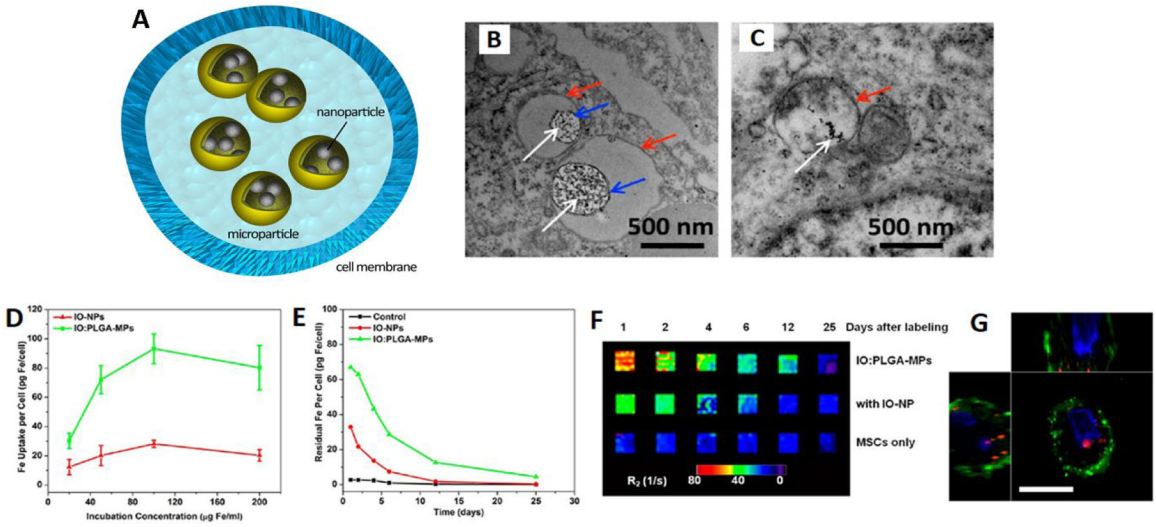

Figure 7.

(A) Schematic showing high-density and safe loading of iron oxide nanoparticles in therapeutic cells using biodegradable poly(lactide-co-glycolide) microparticles. Transmission electron microscopy images of the labeled cells with (B) magnetic nanoparticles embedded in microcapsules (PLGA-MPs) and (C) magnetic nanoparticles alone (IO-NPs) are shown. White, blue, and red arrows show the locations of IO-NPs, PLGA-MPs, and membrane of intracellular compartment, respectively. The results demonstrate the superior role of microparticles in (D) labeling the cells at various times (according to the cellular iron content) and (E) maintenance of the loaded iron ions in the cells. (F) R2-weighted MR images of equivalent numbers of labeled and unlabeled cells show the higher magnetization of microparticle-labeled cells over nanoparticles alone. (G) Fluorescent confocal image of the labeled cells with microparticles (18 days after labeling) (Green: cell membrane; Blue: nucleus Red: microparticles); scale bar is 10 μm. Figures B and G were reproduced from ref[180]; copyright [2012] American Chemical Society.

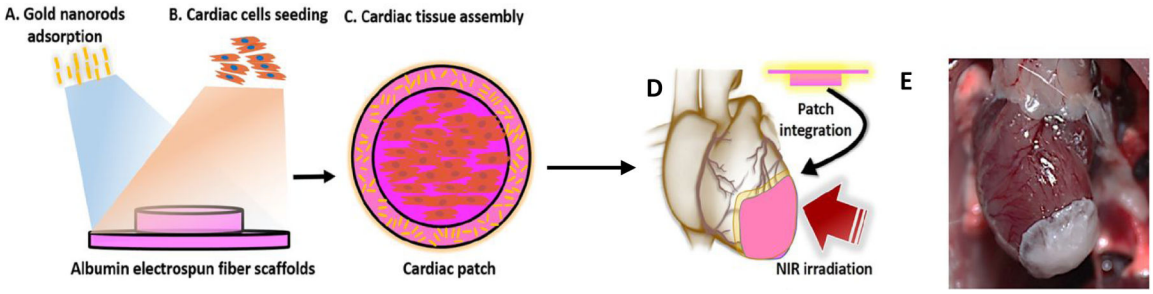

Figure 8.

(A) Gold nanorods adsorption to albumin electrospun fiber scaffolds. (B) Cardiac cells are seeded within the nanocomposite scaffolds to form the (C) cardiac patch. (D) Mechanism of cardiac patch integration. (E) The cardiac patch after integration with the rat heart. Figures are reproduced from the reference[190]; copyright [2018] American Chemical Society.

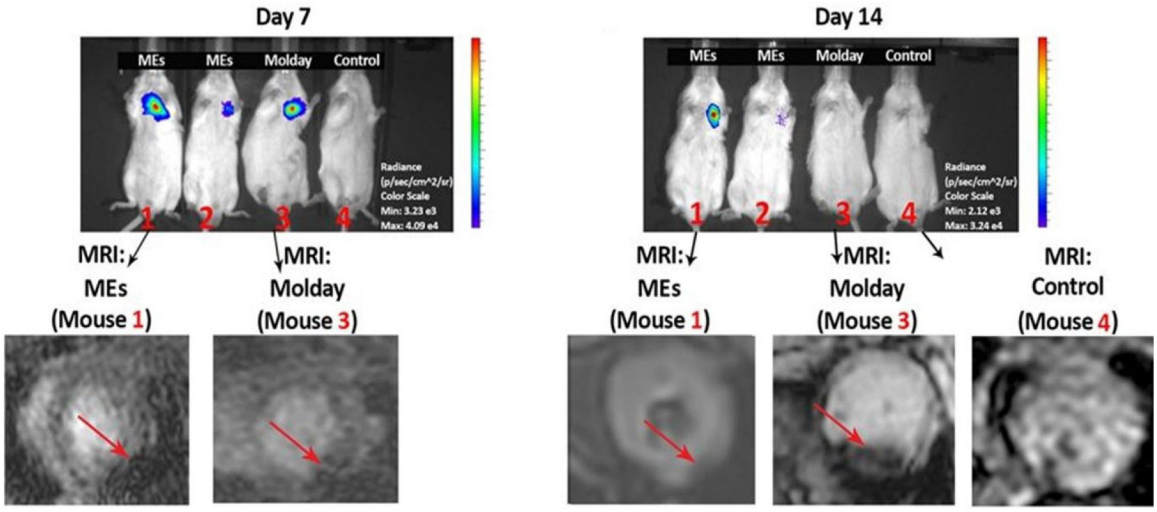

Figure 9:

Bioluminescence and magnetic resonance images of the mice injected with therapeutic cells, labelled with a live contrast agent (ME) or synthetic iron oxide nanoparticles (Molday). Arrows show the signal from the injected cells; two weeks after therapeutic cell injection, the arrows show the persisted signal in Molday-labeled cells, whereas the absence of bioluminescence signal confirmed the absence of live therapeutic cells in the area. Figures are reproduced from the reference[203]; copyright [2016] Nature Publishing Group.

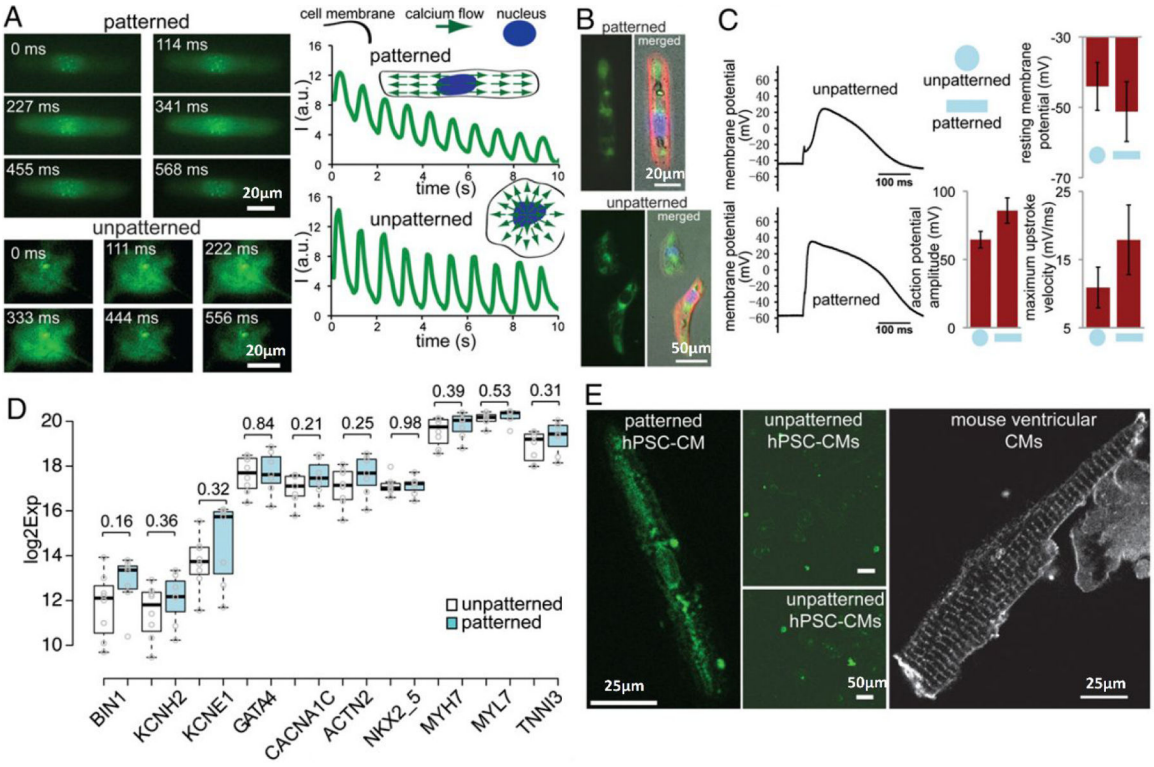

Figure 10.

Substrates with the physiological stiffness and two-dimensional shape of cardiomyocytes show a unique capacity in inducing maturation in hiPSC-derived cardiomyocytes. The cultured hiPSC-derived cardiomyocytes on the patterned substrates demonstrated isotropic (A) calcium flow (green) and (B) mitochondria distribution (green) compared to unpatterned substrates. (C) Variation of patch-clamp recordings (left) and action potential amplitude (right) of the cells cultured on patterned and unpatterned substrates. (D) Single-cell gene expression outcomes show an excellent ability of patterned substrates to induce gene maturation. (E) Directed distribution of t-tubule–like structures along the cell membrane of the cultured immature cells on patterned and unpatterned substrates. Figures are reproduced from the reference[215]; copyright [2015] National Academy of Sciences.

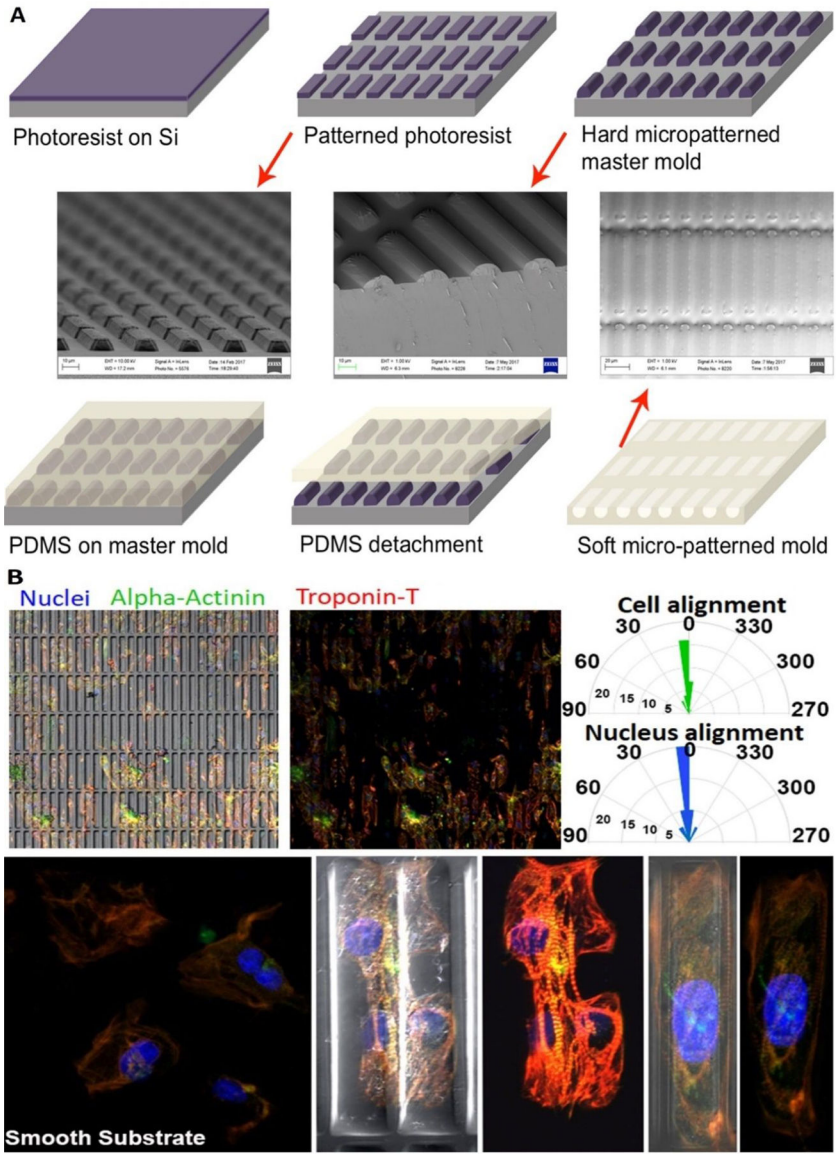

Figure 11.

(A) Scheme showing the preparation of patterned substrates based on the 3D-cardiomyocytes' shapes (cylindrical), and the scanning electron microscopy images showing the formation of patterned substrates. (B) Confocal images of the culture (at day 14) of the immature hiPSC-derived cardiomyocytes on the aligned patterned substrates with the shape of mature cardiomyocytes at different magnifications. As can be clearly seen in these images and the analyzed cell- and nucleus-alignment pies, the cultured cells on the patterned substrate induced the shape of cardiomyocytes and their nuclei (ellipsoidal shape) to the cultured cells in an aligned format; the cultured cells on the smooth substrate at the same age are presented for comparison (lower left panel). Figures are reproduced from reference[216]; copyright [2018] Wiley-VCH.

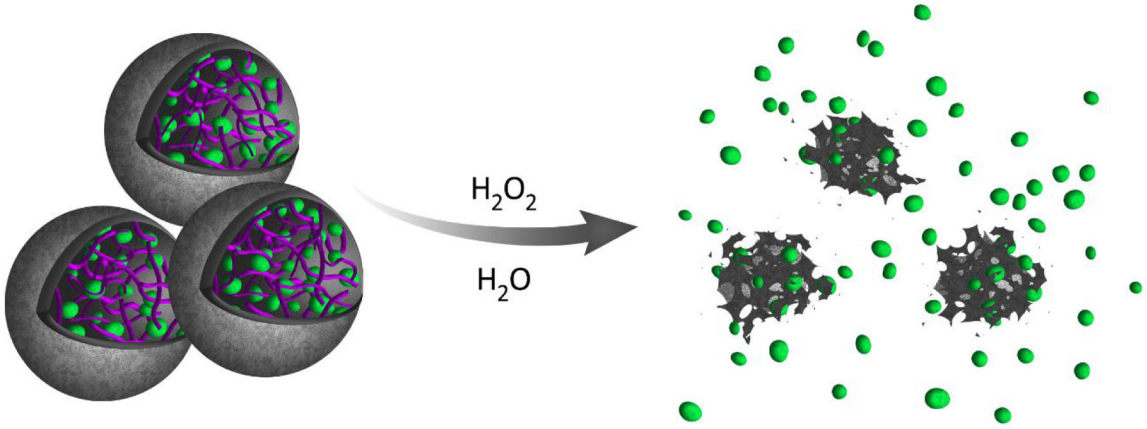

Figure 12.

Schematic showing examples of stimuli-responsive nanoparticles: the capacity of H_2O_2-responsive copolyoxalate polymeric nanoparticles to release their loaded drug (vanillyl alcohol; green dots) upon exposure to H_2O_2.

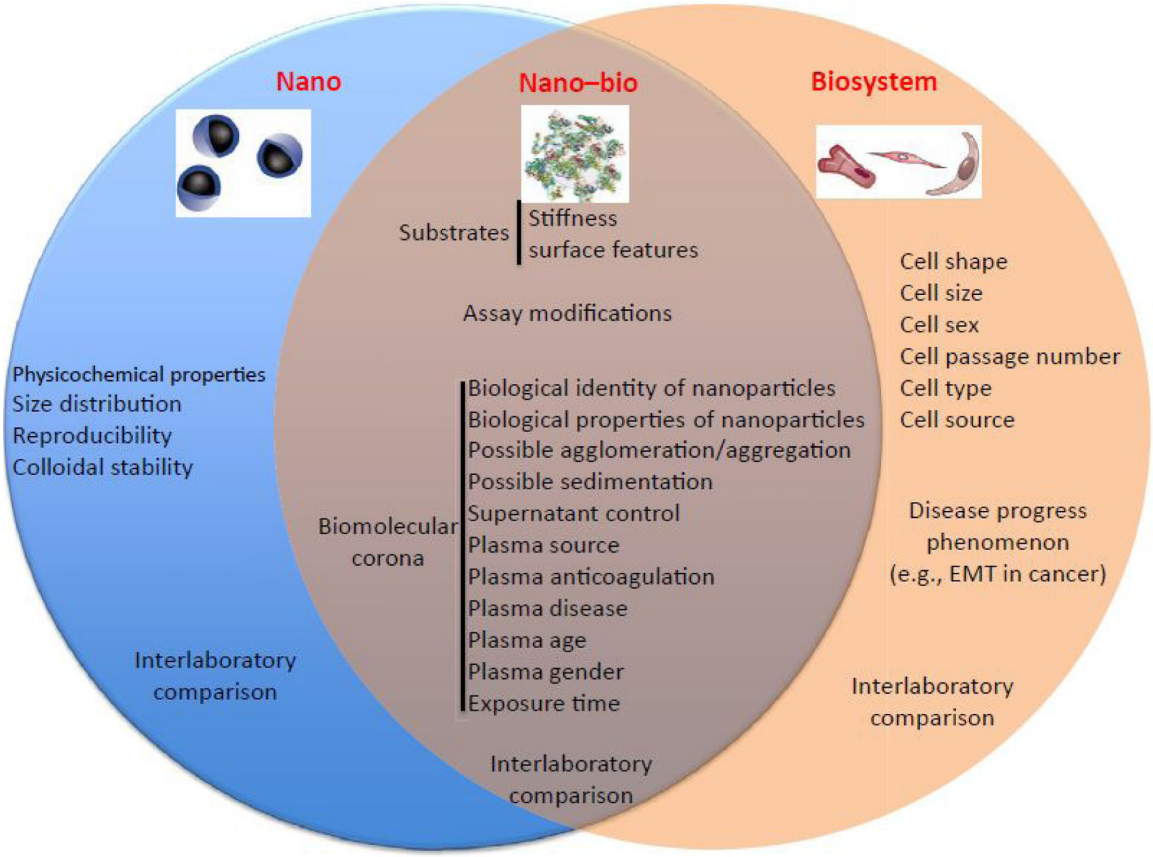

Figure 13:

The minimum set of required information and experimental setups that should be mentioned in nanomedicine related reports to achieve robust and reliable nanomedicine readouts. The figure was reproduced from the reference[39]; copyright [2018] Cell Press.

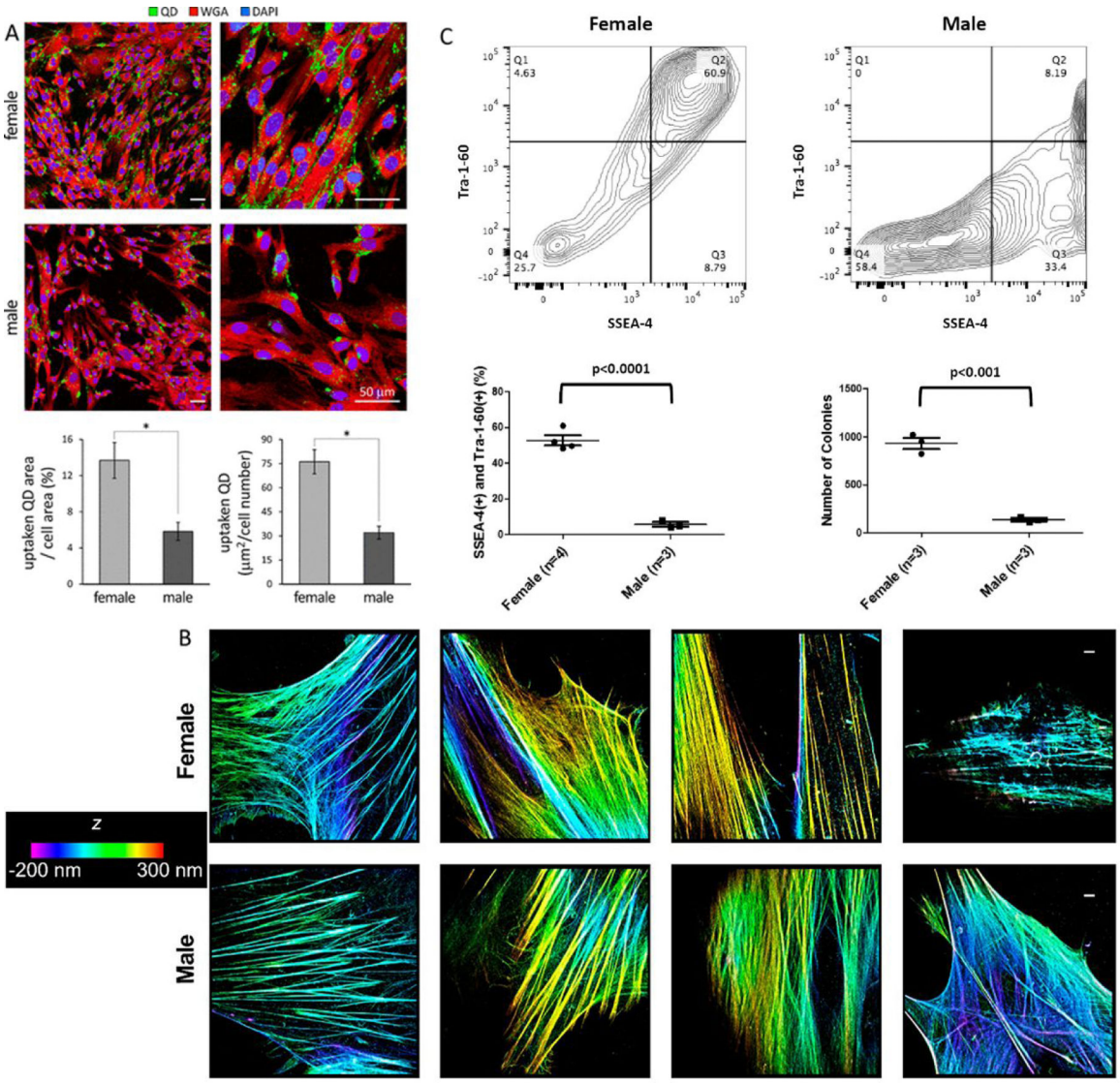

Figure 14.

(A) Variation of model nanoparticle (i.e., QDs) uptake in female and male human amniotic mesenchymal stem cells. (B) Differences in organization, distribution, and morphology of actin filaments/bundles in the cytoplasm of the male and female cells using super-resolution microscopy (scale bar: 1 μm). (C) Flow cytometry analysis demonstrating differences of reprogramming efficiency of male and female human amniotic mesenchymal stem cells (top panels) toward human pluripotent stem cells and the number of the reprogrammed colonies in culture (bottom panels). Figures are reproduced from the reference[403]; copyright [2018] American Chemical Society.

Table 1:

Summary of the detection limitations of the cardiac biomarkers.

Biomarker	Clinical limits for detection	Advanced technology that may address current limitations	Time of detection	Normal range value	Ref
Cardiac Troponin	- cTn assay is more expensive than other assays used to measure cardiac enzymes. -Both cTnT and cTnI are elevated in renal failure. - Increasing cTn assay sensitivity can help detect minimal concentrations of troponin in healthy cases and hence reduce the specificity. -Mild hs-cTn elevation can result from the following disorders: renal failure, pulmonary embolism, stroke, arrythmias, heart failure, takotsubo cardiomyopathy, sepsis, hypertensive crisis, hyper/hypotension, drug toxicity, hypothyroidism, myo/pericarditis, Rhabdomyolysis, traumatic injury, and stress-induced cardiomyopathy. -The challenges associated with hs-cTn include: heterogeneity and post-translational modification of cTn, sample/preparation/stability nonspecific to etiology of myocyte death, varying analytical sensitivity, nonreproducible false elevations, equipment calibration, and lack of reportable range and consensus standardization for performing and interpretation. -At least two measurements of cTn at three time points (0, 3 and 6h) are required to confirm MI.	Colorimetric sensors-poly-(dimethylsiloxane) (PDMS)-gold composite film-based biosensor -ELISA-on-a-chip (EOC) biosensor Optical sensors Paramagnetic-based sensors -A fluorescence resonance energy transfer (FRET) based biosensor -Aptasensor platform (Aptamer Au NP-based assay) Surface plasmon resonance (SPR)-based sensor -Gold films modified by monoclonal anti-cTnI antibody -fiber optic based SPR sensor Electrochemical-based sensor -Au nanoparticles poly (dimethylsiloxane) (PDMS) composite microfluidic -nanoelectrode arrays composed of vertically aligned carbon nanofiber Paramagnetic immune assay Microfluid immunosensor chip	10–40 min (Depending on analytical approach)	Normal: < 0.04 ng/mL Elevated above the 99th percentile of a healthy population: 0.04 – 0.39 ng/mL Probable myocardial infarction: ≥ 0.40 ng/mL	47–66
Myoglobin	- As myoglobin is the earliest sensitive biomarker that exists in skeletal and cardiac muscle, myoglobin elevation in blood is not specific to cardiac damage. - Serum myoglobin elevation may result from AMI, renal failure, intramuscular injection, strenuous exercise, skeletal muscle, and neuromuscular disorders, and after numerous intakes of toxins or drugs intake. - Measurement of myoglobin and cardiac-specific marker (troponin I), or skeletal-specific marker (carbonic anhydrase Ill) on serial samples is required to differentiate between myocardial and skeletal muscle damage.	Aptasensor platform - (Aptamer-Functionalized Black Phosphorus Sensing Platform) - Gold nanoparticles decorated on boron nitride nanosheets (Au nanoparticles/BNNSs) - Meso-tetra (4-carboxyphenyl) porphyrin-functionalized graphene-conjugated gold nanoparticles (TCPP-Gr/Au nanoparticles) Microfluidic immunosensor chip -Immobilization of anti-myoglobin antibody on a polystyrene substrate Electrochemical immunosensor on metal nanoparticles-3-Mercaptopropionic acid (MPA) capped ZnS nanocrystals functionalized with anti-myoglobin (Ab-Mb) Electrochemical Impedance Immunosensor - Graphene quantum dots modified electrode was functionalized with anti-myoglobin antibodies Fluorescence immunoassay - Magnetic and fluorescence nanoparticles (MNP@SiO2@BSA@Au) Surface plasmon resonance biosensor	10–40 min Depending on analytical approach	The normal range is 30 to 90 ng/mL	67–76
Creatinine kinase MB	CK-MB is not specific to cardiac disorders and its elevation may be related to skeletal muscle lesion. Due to its early pattern (3 to 5 h after infarction), CK-MB is only used to	Surface-enhanced Raman scattering (SERS)-based immunoassay Surface plasmon resonance-based sensors Chemiluminescence	15–30 min depending on analytical approach	Normal reference values for serum CK-MB range from 3 to	77–86

Biomarker	Clinical limits for detection	Advanced technology that may address current limitations	Time of detection	Normal range value	Ref
	detect early MI. It is not suitable to detect late MI (decrease after 48–72 h). It must be used as supplement to clinical decision-making.	Electro Chemiluminescence Fluorescence-based sensors Microfluid immunosensor chip		5% (percentage of total CK) or 5 to 25 IU/L.	

Table 2.

Nanotechnology-based strategies for diagnosis of MI.

Nanoparticle	Sensing/imaging target	Ligand	Ref
Gold nanorod	Concentration of troponin I in blood	The human troponin I binding peptide (-FYSHSFHENWPS-) and anti-cTnI antibody	89
		Antibodies specific to cTnI and myoglobin	90
single site-specific polyalanine (PANI) nanowire	Troponin I, myoglobin and creatinine kinase-MB	Antibodies specific to cTnI, myoglobin, and creatinine kinase-MB	91
Quantum dots	CD13	Cyclic NGR peptides	94
Liposome	Collagen	CNA35 Collagen-specific binding protein	95
^{18}F-Macroflor	Macrophage	Macroflor particle concentrated in cardiac plaque macrophage	96
Mesoporous silicon vectors	Failing myocardium	MSV preferentially accumulated in failing myocardium	97
porphyrin-functionalized graphene-conjugated gold nanoparticles	Myoglobin	Myoglobin binding aptamer	72

Table 3.

Nanotechnology-based strategies for treatment of MI.

Nanoparticle	Mechanism of action	Loaded drug/surface modification	Model of use/Animal	Administration route	Ref
mesoporous silicon vector	Accumulation in infarcted area through EPR effect	-	*In vivo;* male C57BL/6 mice	Intravenous injection	97
PEGylated liposome	Modified liposome attached to cells expressing AT1	Surface modification: Peptide specific to AT1	*In vivo;* C57/BL6 female mice	Intravenous injection	115
Micelle	Nanoparticles were responsive to matrix metalloproteinase enzymes	-	*In vivo;* Rat MI model	Intravenous injection	116
N-acetyl glucosamine (GlcNAc)	Regulation of calcium signaling pathway	Loaded drug: S100A1 protein	*In vitro*	-	123
Polyketal	Induction of cardiomyocytes growth and survival	Loaded drug: p38 inhibitor SB239063 Surface modification: N-acetyl-glucosamine (GlcNAc)	*In vivo;* adult male Sprague-Dawley rats	Intramyocardial injection	117
PLGA/PEI	Activation of Akt phosphorylation	Loaded drug: Insulin-like growth factor (IGF)-1	*In vivo;* Mice	Intramyocardial injection	127
Liposome	- Reduction of oxidative stress and cell death. - Induction of ischemic cell growth and survival	Loaded drug: Coenzyme Q10	*In vivo;* Rat	Intracoronary injection	129
PEGylated liposomal adenosine	Reduction of infarct size	Loaded drug: Adenosine triphosphate (ATP)	*In vivo;* Rat	Intravenous injection	130
Liposome	Improvement of fractional shortening and systolic function	Loaded drug: VEGF Surface modification: Anti-selectin ligand	*In vivo;* Rat		131
Polystyrene, Microdiamond and PLGA	Reduction of inflammatory monocyte	-	C57BL/6 mice with myocardial infarction	Intravenous injection	132
phosphatidylserine (PS)-presenting liposomes	Suppression of inflammation	Phosphatidyl serine	Rat model of acute MI	Intravenous injection	133
PLGA NP incorporating FITC	Activation of PI3K/Akt Pathway. Suppression of inflammation.	Pitavastatin	Rat IR model	Intravenous injection	134
Reverse thermal gel (RTG) functionalized with CNTs (RTG-CNT)	Promotion of survival, proliferation and function of cardiomyocytes	Reverse thermal gel (RTG)	*In vitro*	-	135
Thiazole orange conjugated dextran	Suppression of inflammation	-	*In vivo*; Mice model of myocardial I/R	Intravenous injection	136

Table 4.

Nanotechnologies for delivery of genes and RNAs.

Nanoparticle	Loaded gene/ RNAs	Application	Mechanism of action	Model of use/ Animal	Administration route	Remarks	Ref
Lipid	Green fluorescent protein modified mRNA	mRNA delivery to infarcted myocardium for repair and treatment of myocardial infarction	Transient overexpression of modified mRNA in the infarcted area	*In vivo;* Adult male Sprague-Dawley rats and female Yorkshire pigs	Myocardial injection	-	146
	Small interfering RNA for CCR2 (siCCR2)	siRNA delivery for myocarditis therapy	- Suppression of CCR2 expression - Prevention of leucocyte production in spleen and bone marrow - Promotion of left ventricular function - Prevention of CD11b+ production	*In vivo;* A/J mice with myocarditis	Intravenous injection	-	147
Magnetic nanobeads (MNBs)	Adenoviral vectors (Ad)-encoded *hVEGF* gene	Ad_{hVEGF} delivery to ischemic area for treatment of acute myocardial infarction	The MNBs loaded with Ad_{hvEGF} promoted heart regeneration, left ventricular function and arterial density	*In vivo;* Lewis rats with acute myocardial infarction	Intravenous injection	The MNBs loaded with Ad_{hVEGF} were guided to ischemic area *via* external magnetic field	148
Cationic lipoparticles	Anti-miR-721	Anti-miR-721 delivery for treatment of atherosclerosis	- Silencing miR-721 and MMP - Overexpression of TIMP3 and RECK genes	*In vivo;* Atherosclerotic mice ($ApoE^{-/-}$ mice)	Intravenous injection	Anti-miR-721 loaded cationic lipoparticles showed no suppressive effect in other organs	149
Polyethyleneimine graphene oxide/DNA_{VEFG} encapsulated in low-modulus methacrylated gelatin (GelMA) hydrogel	DNA_{VEFG}	DNA_{VEFG} delivery for treatment of myocardial infarction	Improving cardiac function via enhancing cell growth, survival, contractility and angiogenesis	*In vivo;* Lewis rats with myocardial infarction	Intramyocardial injection	This platform prolonged gene retention time in lesion site with no sign of toxicity and inflammation	150
Tat peptide/DNA nanoparticle and recombinant Baculovirus (Bac)	Angiopoietin-1 (Ang-1) transgene	Delivery of angiopoietin-1 (Ang-1) transgene for treatment of myocardial infarction	- Promoting cardiac function and regeneration - Enhancing ejection fraction - Increasing left ventricular thickness	*In vivo;* acute MI rat model	Intramyocardial injection		151

Table 5.

Example of nanoparticles with anti-oxidation activity.

Nanoparticle	Application	Mechanism of action	*In-vitro/In-vivo*	Remarks	Ref
Copolyoxalate polymeric loaded with vanillyl alcohol (VA)	Targeted delivery of vanillyl alcohol to ischemic reperfusion injury site	Prevention of H_2O_2-induced immune response and apoptosis; prevention of ROS overproduction	*In vivo;* hind-limb ischemic reperfusion and liver ischemic reperfusion models of mice	The nanoparticles release vanillyl alcohol upon exposure to H_20_2	243
2, 3-dimercaptosuccinic acid modified iron oxide	Heart protection from ischemic damage	- Prevention of calcium influx, oxidative stress and membrane disruption. - Heart regeneration and cardiac cell survival	*In vivo;* rat coronary artery ligature (CAL) model	-	248
Nano-sized curcumin	Prevention of hypoxia-induced cardiomyocyte damage	Prevention of mitochondrial dysfunction and oxidative stress	*In vitro*	The nanoparticles prevented mitochondrial metabolism changes	249

Table 6:

Summary of nano-immunotherapy systems in cardiovascular disease.

Nanoparticle	Application	Major Effector Cells	References
Liposome nanoparticles	Atherosclerotic disease	Macrophages	299 300
7C1-C14PEG2000 nanoparticles	Reduce monocyte transendothelial migration through siRNA delivery	Monocytes	301
Amphiphilic macromolecules-based nanoparticles	Arrest atherosclerosis *in vivo*	Macrophages	302
Hyaluronan nanoparticles	Probe atherosclerosis-associated inflammation	Macrophages	303
PLGA nanoparticle system	Prevent plaque destabilization and rupture	Monocytes/Macrophages	304
Lipidoid nanoparticles	Suppression of IRF5 level	Macrophages	305
HDL nanoparticles	Delivery of simvastatin to plaque	Macrophages	306 307
PLGA nanoparticles	Inhibits atherosclerotic plaque destabilization/rupture in mice	Monocytes	308
Exosomes nanoparticles	Polarizing cardiac macrophages toward a distinctive cardioprotective phenotype	Monocytes/Macrophages	309
Albumin-based nanoparticle	Prevention of vascular inflammation	Neutrophils	310

Table 7:

Examples of the use of cardiac nanotechnologies in large animals

Nanoparticle/Material	Physicochemical properties	Animal model	Remark	Ref
Peptide (HA, YPYDVPDYA) loaded calcium phosphate nanoparticles (CaP-HA)	Size: < 50 nm surface charge: (−32 ± 3 mV)	landrace pig	CaP inhalation is an effective strategy for intramyocardial delivery of peptides/therapeutics for treatment of heart diseases. After inhalation, CaP-HA was specifically localized in myocardium, where the loaded peptides (HA) were rapidly released. CaP-HA showed no adverse effect on blood pressure and functions of cardiac, LV, and respiratory system.	325
Curcumin-nisin based poly lactic acid nanoparticle (CurNisNp)	Size: 284.0 ± 17.9 nm. surface charge: (−12 ± 3 mV)	Guinea Pig	CurNis nanoparticles showed cardioprotective effects in a pig model of MI. They improved antioxidant defense and decreased the ROS level.	257
Lipidoid Nanoparticle	Size: ~155 nm	Female Yorkshire pig	Direct myocardial injection and percutaneous intracoronary delivery of lipidoid nanoparticles was found to be an effective approach for overexpression of mRNA in heart and gene therapy.	146
Pitavastatin-loaded poly(lactic acid/glycolic acid) (PLGA)	Size: 159nm surface charge: −4.1 mV	Bama mini-pigs domestic pig	PLGA delivered pitavastatin into IR-injured myocardium and showed protective effects. Pitavastatin-loaded PLGA had no adverse effects on cardiac function.	326
SPION-labeled endothelial progenitor cells (EPCs)	Size: < 20 nm	mature Chinese pig	SPION-labeled EPCs reduced acute MI size and restored heart function. SPIONs were used to monitor the therapeutic efficacy of EPCs via MRI.	327
Exosomes (Nanovesicles produced by cardiosphere-derived cells)	Size: 192+17 nm	female adult Yucatan mini-pig	The intracoronary (IC) or open-chest intramyocardial (IM) delivery of exosomes prevented adverse remodeling and improved LVEF in acute and chronic MI pig models of.	328
Liposomal nanoparticles	143 nm 108 nm	domestic male Yorkshire pig	Liposomal nanoparticles did not induce the hypersensitivity reaction in pigs and showed no immunogenic effect. Therefore, these nanoparticles can be used for therapeutic or drug delivery approaches.	329
Basic fibroblast growth factor (bFGF) incorporating gelatine microsphere	ND	healthy adult mongrel dog	Intramyocardial injection of bFGF microsphere enhanced angiogenesis and improved LV, myocardial function, and ejection fraction.	330
Hydrogel microspheres with bFGF	ND	Pig	Biodegradable hydrogel microspheres loaded with bFGF increased angiogenesis and vascular density, improved LV function, and prevented LV remodeling.	331
Gelatine hydrogel containing bFGF	50–100 μm	Human patients had critical limb ischemia	Sustained release of bFGF improved angiogenesis and distance walked in 6 minutes.	332
Liposomal PGE1	150–200 μm	Dog	Liposomal PGE1 limited reperfusion injury, reduced infarct size, and restored myocardium	333
Collagen patch containing epicardial fstl1 protein	2 cm	Swine	Collagen patch containing epicardial fstl1 protein induced proliferation of cardiomyocytes and improved cardiac function and survival in a MI model of swine	189

Table 8.

Potential adverse effects of nanoparticles used for CVDs diagnosis and treatment

NP	Adverse effects	NP size	Model of use/ Animal	Administration route	Remark	Ref
Citrate-covered silver NP	Induction of inflammation and I/R injury	21.3 ± 3.2 nm	*In vivo* Sprague Dawley rats	Intratracheal instillation		362
Zinc oxide nanoparticles	Toxic effects against coronary artery endothelial cells. Induction of inflammation and oxidative stress.	20 and 90 nm	*In vitro*	-	Zn ions, released from ZnO nanoparticles, enhanced the toxic impacts of ZnO nanoparticles.	360
Cerium Oxide nanoparticles	Enhancement of I/R injury. Induction of pulmonary and cardiac inflammation.	70 nm	*In vivo* C57BL/6 and B6.Cg-*KitW-sh*	Pulmonary instillation	Cerium oxide nanoparticles can disturb the vascular relaxation	368
Multi-walled carbon nanotubes Single-walled carbon nanotubes Carbon black Titanium Dioxide nanoparticles	Pulmonary acute phase response	2–10 μm	*In vivo* Female C57BL/6J mic	Pulmonary exposure	There is a direct relationship among acute phase response, neutrophil influx, and CVD risk	369
Single-walled carbon nanotubes	Induction of inflammation and acute phase responses		*In vivo* C57BL/6 mice	Pharyngeal aspiration	SWCNTs induced oxidative stress	370
Single-walled carbon nanotubes	Atherosclerosis development		*In vivo* ApoE(−/−) transgenic mice	Pulmonary exposure	SWCNTs induced mitochondrial damage	371
Titanium Dioxide nanoparticles	Atherosclerosis development	21.6 nm	*In vivo* (ApoE−/−) transgenic mice	Pulmonary exposure	TiO_2 nanoparticles did not induce vasodilatory malfunction and inflammation	372
Titanium Dioxide nanoparticles	Induction of myocarditis	5 nm	*In vivo* (ICR) male mice	Nasal instillation	TiO_2 nanoparticles induced cardiac and pulmonary inflammation	354
Titanium Dioxide nanoparticles	Nitrosative and oxidative stress induction	21 nm	*In vivo* Sprague-Dawley rats	Aerosol inhalation		373
Titanium Dioxide nanoparticles	Disruption of microvascular reactivity	21 nm	*In vivo* male Sprague-Dawley rats	Inhalation exposure	Impairment of microvascular reactivity affects cardiac function	355
Multi-walled carbon nanotubes	Exacerbation of myocardium I/R injury		*In vivo* Sprague-Dawley rats	Intratracheal instillation	MWCNTs enhanced coronary vasoconstriction	374
Multi-walled carbon nanotubes	Exacerbation of myocardium I/R injury	Diameter: 29–23 nm Length: from 10–100 μm	*In vivo* male C57BL/6J mice	Oropharyngeal aspiration	MWCNTs did not induce pulmonary inflammation	375
Multi-walled carbon nanotubes	coronary microvascular dysfunction		*In vivo* male Sprague Dawley	Inhalation exposure		376
Polystyrene NP	Dysregulation of blood coagulation	PS-COOH: 24 and 220 nm $PS-NH_2$: 57 and 330 nm	*In vitro*	-	PS-NH2 Captured FVII and FIX and enhanced bleeding. PS-COOH triggered intrinsic coagulation pathway.	363

NP	Adverse effects	NP size	Model of use/ Animal	Administration route	Remark	Ref
Silica nanoparticles	Dysregulation of blood coagulation	4, 7, 12, 22, 50 and 85 nm	*In vitro*	-	Large nanoparticles strongly denatured the FXII and activated intrinsic coagulation	377
NH_2 modified dendrimer	Enhancement of thrombus formation	3–7 nm	*In vitro*	-	NH_2 modified dendrimer-activated platelets by destroying their membranes	378
Titanium Dioxide anatase Titanium Dioxide rutile Zinc Oxide Silica nanoparticles Silver	TiO_2 anatse triggered platelet aggregation	38 nm 67 nm 150 nm 47 nm 15 nm	*In vivo* C57BL/6	Systemic injection		364
Single-walled carbon nanotubes Multi-walled carbon nanotubes	Enhancement of vascular thrombosis		*In vivo* Wistar-Kyoto rats subjected to thrombosis	Intravenous injection		365
Silver NP	Enhancement of thrombosis	10–100 nm	*In vivo* Sprague-Dawley rat thrombosis model	Intravenous injection		366
Ultrasmall SPIONs	Enhancement of thrombosis	5 nm	*In vivo* BALB/C mice	Intravenous injection	-	367