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Metal-based nanoparticles: Promising tools for the management of cardiovascular diseases

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Abstract

Cardiovascular disease (CVD) is the leading cause of death worldwide. A search for more effective treatments of CVD is increasingly needed. Major advances in nanotechnology opened new avenues in CVD therapeutics. Owing to their special properties, iron oxide, gold and silver nanoparticles (NPs) could exert various effects in the management and treatment of CVD. The role of iron oxide NPs in the detection and identification of atherosclerotic plaques is receiving increased attention. Moreover, these NPs enhance targeted stem cell delivery, thereby potentiating the regenerative capacity at the injured sites. In addition to their antioxidative and antihypertrophic capacities, gold NPs have also been shown to be useful in the identification of plaques and recognition of inflammatory markers. Contrary to first reports suggestive of their cardio-vasculoprotective role, silver NPs now appear to exert negative effects on the cardiovascular system. Indeed, these NPs appear to negatively modulate inflammation and cholesterol uptake, both of which exacerbate atherosclerosis. Moreover, silver NPs may precipitate bradycardia, conduction block and sudden cardiac death. In this review, we dissect the cellular responses and toxicity profiles of these NPs from various perspectives including cellular and molecular ones.

Key words: Cardiovascular disease; Nanomedicine; Silver nanoparticles; Iron oxide nanoparticles; Gold nanoparticles; Atherosclerosis

Cardiovascular disease (CVD) is the primary cause of global mortality.[1] According to the World Health Organization (WHO), CVD accounts for around 31% of all deaths.[1] Of this heavy proportion, 85% is due to myocardial infarction and cerebrovascular accidents.[1] Nonetheless, around 75% of these deaths are heavily concentrated in the less fortunate areas of the world that include countries of low and middle economies.[1] Importantly, CVD-associated deaths could be dramatically

Abbreviations: CVD, Cardiovascular disease; **NPs**, Nanoparticles; **ACEi/ACEis**, Angiotensin-converting enzyme inhibitor/inhibitors; **LPL**, lipoprotein lipase; **ARB/ARBs**, Angiotensin II receptor blocker/blockers; **FDA**, Food and drug administration; **MRI**, Magnetic Resonance Imaging; **SPIONs**, Superparamagnetic iron oxide nanoparticles; **ICAM-1**, Intercellular adhesion molecule-1; **VCAM-1**, Vascular cell adhesion molecule-1; **ERK1/2**, Extracellular signal-regulated protein kinase 1/2; **HDL**, High-density lipoprotein; **AgNPs**, Silver NPs; **NF-kB**, Nuclear factor kappa B; **NLRP3**, NLR pyrin domain containing 3; **eNOS/iNOS**, Endothelial/Inducible nitric oxide synthase; **ROS**, Reactive oxygen species; **CNS**, Central nervous system; **BBB**, Blood–brain barrier; **AuNPs**, Gold NPs

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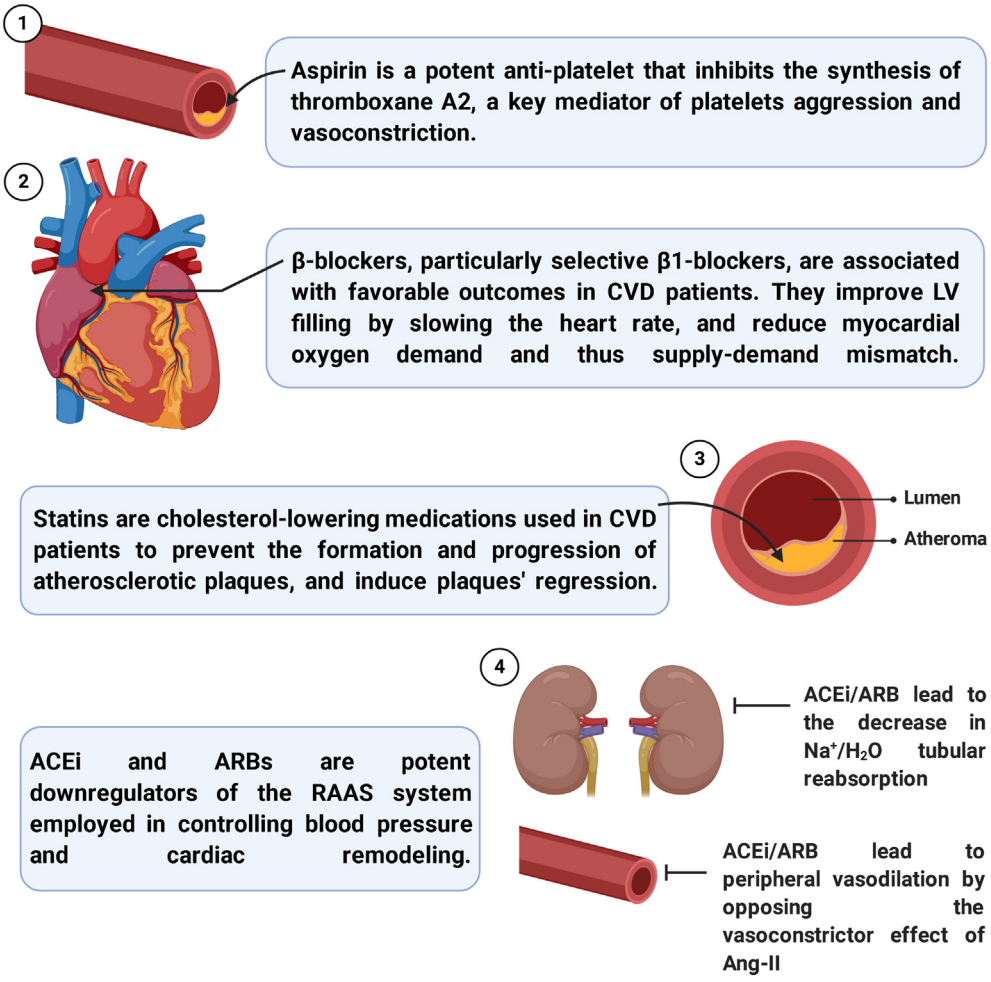

Figure 1. **The key therapeutics of CVD.** CVD management entails both non-pharmacological and pharmacological therapies. Among the widely-applied pharmacological therapies, aspirin, β-blockers, statins, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin II receptor blockers (ARB) are given to most CVD patients to reduce the risk of CVD progression and complications. Aspirin is a potent anti-thrombotic medication employed in primary and secondary prevention of CVD. β-Blockers are heart rate-lowering medications used to improve left ventricular (LV) filling, and mismatch of oxygen supply and demand. Statins are cholesterol-lowering medications employed in treating and reverting atherosclerosis. ACEis and ARBs are anti-hypertensive medications used to optimize blood pressure in hypertensive patients and prevent cardiac remodeling in CVD patients.

reduced by a series of primary interventions that include smoking cessation, physical activity or weight control among others.[1–3] Similarly, people with a risky CVD profile require a thorough assessment and management of CVD modifiable risk factors that include diabetes mellitus, hypertension and hyperlipidemic disorders.[1,4–6] These preventive measures include both medical and behavioral interventions.[1,6,7] For instance, adequate control of blood pressure or glucose level would greatly reduce the occurrence and recurrence of CVD.[1,6–8] To this end, many highly effective medications are used to control these risk factors and thus to prevent their subsequent cardiovascular complications (Figure 1). These medications primarily include aspirin, angiotensin-converting enzyme inhibitors (ACEis), beta-blockers or statins as anti-thrombotic, anti-hypertensive, or anti-arrhythmic and anti-atherosclerotic, respectively.[1,7–13]

In addition to these conventional therapies, novel tools and inventions have emerged as potentially more effective therapeutic modalities, and are indeed being applied in the treatment of CVD complications. These new interventions are directed toward specific molecular and genetic targets. They are employed primarily in the management of genetic and familial CVD.[14,15] In this context, genetic therapy was formally approved for the treatment of familial hypertriglyceridemia caused by lipoprotein lipase (LPL) deficiency.[14] Furthermore, gene therapy was heavily investigated in the treatment of arrhythmias, coronary heart diseases and myocardial failure.[16–19] Similarly, stem cell application was recently introduced as a potential regenerative tool for the treatment of heart failure secondary to sustained ischemia.[20–23]

Despite all these interventions, CVD continues to be a significant global burden that prompts a quest for further investigations. In this review, we discuss the potential therapeutic effects of the latest nano-inventions in managing CVD. We focus mainly on the advantages of utilizing metal-based nanoparticles in CVD treatment.

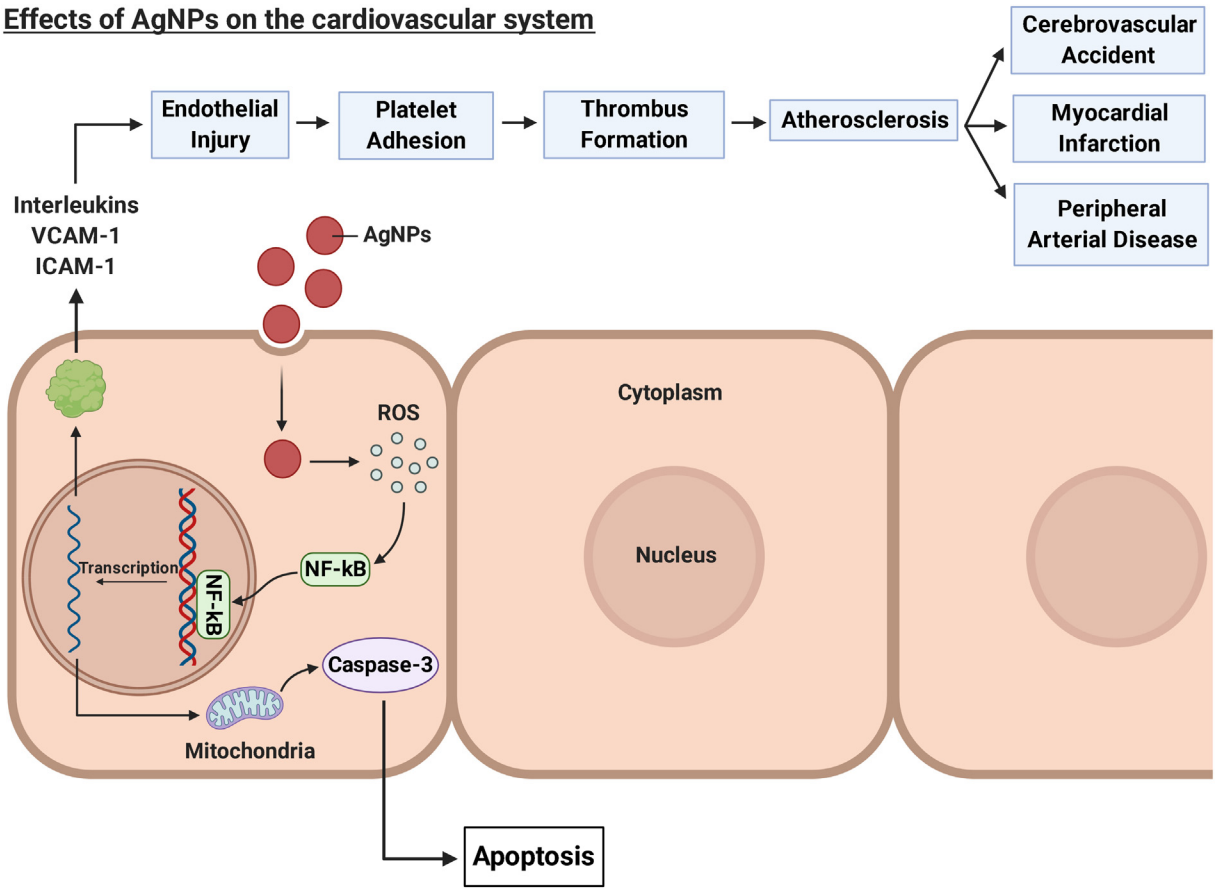

Figure 2. **Cardiotoxic effects of AgNPs.** This schematic diagram shows the cardiovascular sequelae of AgNP administration. Initially, AgNPs enter the cell and induce oxidative stress causing the release of ROS and subsequently the activation of NF-kB. NF-kB localizes to the nucleus and combines with a specific sequence of DNA to induce the transcription of various inflammatory mediators. Then, many inflammatory cytokines and modulators, including interleukins and VCAM-1/ICAM-1, are upregulated. The enhanced expression of these inflammatory molecules predisposes in turn to endothelial injury, thrombosis, atherosclerosis, and further cardiovascular complications. Additionally, caspase-3 is activated indirectly by the inflammatory cascade of AgNPs, and cellular apoptosis is prompted by this activation.

Nanomedicine and CVD

New diagnostic, therapeutic and prognostic tools are used to assess, evaluate and treat various cardiovascular conditions. Nanomedicine has gained increased attention over the last few decades. Indeed, it has been perceived as a pivotal, harmless and powerful platform that can be employed in the management of angiogenic, inflammatory, ischemic and metabolic disorders such as atherosclerosis, hyperlipidemia and hypertension.[24–27] Moreover, nanomedicine is currently being used in imaging techniques, design of medical tools, drug delivery, stem cell applications and wound healing.[28–35] This drastic improvement adds to the previously discovered applications which included anti-bacterial, anti-viral and anti-fungal effects of nanoparticles (NPs).[28,29,36–39]

Nanoparticles (NPs) exert their various distinctive biological effects in size, shape, and concentration-dependent manners.[28,40–42] These physicochemical properties represent the major determinants of NPs biological activities. Indeed, the therapeutic effects and *in vivo* toxicities of NPs are governed by these properties.[43–45] Moreover, different physiological targets might respond differently to the applied NPs, and *vice versa.*[28,43]

Different classes of NPs have been fostered and examined in a multitude of in-vitro and in-vivo studies.[46,47] They include organic NPs like dendrimers and lipid-based NPs, inorganic NPs like carbon- and metal-based NPs, and organic–inorganic hybrid NPs like magnetoliposomes.[47] The selection of the proper class of NPs is based on the physiologic milieu as well as the therapeutic aim of NPs use. For instance, organic NPs are proven to be highly biodegradable and biocompatible vehicles for drug and cell delivery. They are characterized by their eased fabrication and increased biological stability. Lipid-based NPs are also distinguished by their cell membrane like chemistry.[47] On the contrary, inorganic NPs are recognized by their electrical properties that allow magnetic-guided delivery of therapeutics and diagnostic imaging. Inorganic NPs can be easily coupled to a wide range of ample biologics. They enable adequate tissue penetration and are timely degraded. Hybrid NPs own properties of both organic and inorganic NPs.[47]

NPs have shown promising potentials in *in vivo* studies and are currently approved by the Food and drug administration (FDA).[44,48–50] They were introduced to the market and were safely applied in cancer treatment, genetic interventions, and imaging techniques as well as in the treatment of multiple

Table 1
Experimental trials implicating iron oxide nanoparticles in the evaluation and treatment of CVD.

Study	Description	Year of publication	Ref.
Treatment of infarcted heart tissue *via* the capture and local delivery of circulating exosomes through antibody-conjugated magnetic nanoparticles	Antibody-conjugated magnetic nanoparticles targeting CD63 or myosin-light-chain surface markers were applied in rabbit and rat models with myocardial infarction. Favorable cardiac events were attained. An improvement in infarct recovery, angiogenesis, and cardiac contractility was achieved in these models.	2020	[84]
Molecular imaging of activated platelets *via* antibody-targeted ultra-small iron oxide nanoparticles displaying unique dual MRI contrast.	Ultra-small iron oxide nanoparticles acted as MRI contrast agent employed in the detection of vascular thrombi in both *in vivo* (animal) and *in vitro* studies.	2017	[85]
In vivo MRI tracking of transplanted superparamagnetic iron oxide-labeled bone marrow mesenchymal stem cells in rats with myocardial infarction.	Superparamagnetic iron oxide allowed tracking of bone marrow mesenchymal stem cells migration to the infarcted region that was assessed using serial MRI.	2015	[86]
Abdominal aortic aneurysm growth predicted by uptake of ultra-small superparamagnetic particles of Iron oxide: A pilot study.	Ultra-small iron oxide nanoparticles are used as MRI contrast agent. Subsequently, the extent of iron oxide nanoparticles uptake is used to predict risk of abdominal aortic aneurysm progression and rupture in asymptomatic patient.	2011	[87]
In vivo MRI imaging of injected mesenchymal stem cells in rat myocardial infarction; simultaneous cell tracking and left ventricular function measurement.	Superparamagnetic iron oxide nanoparticles added magnetic properties to the injected mesenchymal stem cells and allowed tracking of these cells by MRI.	2009	[88]
In vivo MRI imaging of mesenchymal stem cells in myocardial infarction.	Ferumoxide was combined with mesenchymal stem cells in order to allow tracking of these cells by MRI, in a swine model of myocardial infarction.	2003	[89]

immunological and infectious diseases.[44,49,50] In 1995, the first nanomedicine (**Doxil®**) was employed in the treatment of relapsing ovarian cancer and Kaposi's sarcoma.[44,51,52] This preparation has enabled tunable and well-controlled release of doxorubicin as well as improved doxorubicin's bioavailability and duration of action.[44,51]

Similarly, nanotechnologies have allowed thorough DNA analysis and genomic detection.[44,53] Gold NP (AuNP)-based genetic technologies have been approved by the FDA. They are currently implied in the detection of various genetic and molecular biomarkers.[44,53] Furthermore, other NPs, most importantly superparamagnetic iron oxide nanoparticles (SPIONs), are recognized as effective and safe MRI contrast agents for specific molecule-targeting or therapeutic assessment.[42,44,53–55] Interestingly, delicate manipulation of NPs physicochemical properties greatly facilitates the emergence of patient-specific medical interventions. Subsequently, this furthers the era of targeted and personalized medicine.[44]

Unlike their increased utilization in cancer and genetic diseases, the use of NPs in managing or treating CVD is relatively in its infancy. This review highlights the cardiovascular effects of metal-based NPs, and their promising CVD therapeutic potentials. Herein, we address the importance of iron oxide, gold and silver nanoparticles in CVD management, owing to the extensive biomedical evaluation of these nanoelements in animal and *in vitro* studies. We shed light on the application of these NPs in detecting atherosclerosis, delivering drugs and stem cells, and manufacturing synthetic cardioprotective molecules like HDL.

Iron oxide NPs, atherosclerosis and heart failure

Due to their unique chemical and magnetic properties, iron oxide NPs have been employed in numerous biomedical applications. They are clinically approved as biocompatible systems for drug delivery and as MRI contrast agents.[25,41] Additionally, recent studies underscore the importance of these chemically inert molecules in delivery and tracking of mesenchymal stem cells. They have been used in treating debilitating conditions such as multiple sclerosis and myocardial failure.[41] Furthermore, iron oxide NPs were utilized in tumor detection and evaluation by virtue of their exclusive magnetic properties and extensive biostability.[41] Additionally, one of these iron-derived nanomaterials, ferumoxytol, has been approved for treating iron deficiency anemia in patients with chronic kidney disease.[25,56,57]

For CVD management, iron oxide NPs have been investigated only in animal and in vitro studies. Recent evidence highlights few potential applications of these iron nanoelements in diagnosis, evaluation and treatment of various life-threatening CVDs.[24,58,59] Indeed, iron oxides NPs are primarily designated for atherosclerotic plaque tailoring and stem cell applications.[60–66] A recent animal study highlighted their involvement in the radiological detection of atherosclerotic plaques.[63] Moreover, these NPs were utilized for detecting the presence of CD163, a marker of M2 macrophages, in atherosclerotic lesions.[63,67–69] To this end, iron oxide NPs were actually used as MRI contrast agent and were tagged by anti-CD163 antibodies.[63] M2 macrophages represent a subtype of monocyte-derived macrophages that are commonly encountered in atheroma and most importantly in asymptomatic lesions, where they are abundant.[63,69,70] These macrophages elicit a protective anti-inflammatory role by secreting various anti-inflammatory molecules such as IL10, TGF-β and IL1 receptor antagonist.[63,67,70–73] Ultimately, employment of safe techniques in the detection of these atherosclerotic lesions would substantially help in mitigating the progression of atherosclerosis and the ensuing health effects. Thus, as MRI contrast agents, these iron-derived nanomaterials

Table 2
Studies discussing the role of AuNPs in CVD evaluation.

Study	Description	Year of publication	Ref.
Gold nanorod-based nanoplatform catalyzes constant NO generation and protects from cardiovascular injury	A nitric oxide synthase (NOS)-like nanoplatfrom was fostered and used to ensure continuous supply of NO. The use of this technology may attenuate and prevent cardiac injury.	2020	[107]
Light-induced release of the cardioprotective peptide angiotensin-(1-9) from thermosensitive liposomes with gold nanoclusters	Gold NPs-based nanosystem was used to optimize the delivery of angiotensin-(1-9) to the myocardium. This can improve in turn hypertension and myocardial remodeling.	2020	[108]
Labeling monocytes with AuNPs to track their recruitment in atherosclerosis with computed tomography.	Inflammatory cells' predilection for atherosclerotic lesions was assessed using CT scan. This was permitted because of the optical properties of the AuNPs to which the cells were tagged.	2016	[109]
Syntheses and characterization of lisinopril-coated AuNPs as highly stable targeted CT contrast agents in cardiovascular diseases	Lisinopril-coated AuNPs acted as CT contrast agent allowing the visualization of heart and lungs; tissues where angiotensin converting enzyme is mainly secreted.	2012	[110]
Intravascular photoacoustic imaging of exogenously labeled atherosclerotic plaque through luminal blood.	Gold nanorods enabled assessment and evaluation of rabbits atherosclerotic lesions using intravascular photoacoustic imaging.	2012	[111]
Atherosclerotic plaque composition: analysis with multicolor CT and targeted AuNPs.	Mice atherosclerotic lesions were evaluated through the employment of HDL-coated AuNPs as contrast media for spectral CT scan.	2010	[112]
Plasmonic intravascular photoacoustic imaging for detection of macrophages in atherosclerotic plaques.	AuNPs permitted detection and localization of macrophage rich atheroma *via* intravascular photoacoustic imaging.	2009	[113]

would be superior to the classical contrast medium, gadolinium, which induces nephrotoxicity in susceptible patients with compromised renal functions.[41,63]

Iron oxide NPs are shown to be involved in the magnetic-guided delivery of mesenchymal stem cells to the infarcted myocardium.[60–62,64] Indeed, the use of these magnetic elements seems to improve several aspects of stem cell therapy. It enhances the regenerative capacity of stem cells by promoting their availability in the vicinity of the injured site.[74–77] Stem cell therapy is originally limited by the increased migratory rate of these cells to alternative organs. This limitation is reflected by the very small percentage (~3.5%) of injected mesenchymal stem cells being detected at the ischemic site several weeks after infusion of cells.[78,79] By enhancing availability of stem cells in the myocardium, combined with diminished migration of these cells to other organs, the use of iron oxide NPs in heart failure management will be a favorable and attractive approach.

Magnetic-guided delivery of superparamagnetic iron oxide NPs-labeled mesenchymal cells has shown better preservation of myocardial functions denoted by left ventricular ejection fraction (EF) and fractional shortening (FS). Lower levels of myocardial fibrosis were also detected.[64] As such, iron oxide NPs are favored over classical contrast agents by virtue of their low toxicity. Interestingly, this toxicity can also be further reduced by coating NPs with biocompatible and biodegradable agents such as polyethylene glycol, polydopamine, and chitosan- or dextran-based polysaccharrides.[64,74] Coating is a major determinant of the toxicity and biodistribution of NPs, particularly small sized NPs with a diameter of less than 40 nm. In one study, Kania et al suggested that the coating of iron oxide NPs with chitosan derivatives enhances their blood circulation through the reduction of their degradation and elimination by the reticuloendothelial system, and confines their biodistribution to the liver and kidneys.[80] They argued that their hepatic localization infers a shorter T2 relaxation time which favors then their use as T2 contrast agent particularly when screening for liver diseases. The prolonged circulation and the delayed elimination of these chitosan-coated iron oxide NPs may allow also extended imaging and evaluation.[80] These findings suggest that coating is a key modulator of NPs physiologic function and toxicity.

Furthermore, other studies highlight the intrinsic cardioprotective properties of these iron-derived nanoparticles and their ability to guide mesenchymal stem cells to the infarcted site even in the absence of applied magnetic beams.[74,81] Additional studies have endorsed the use of these NPs in diagnosing atherosclerosis and thrombosis.[82,83] As mentioned earlier, monocytes are important contributors to atherosclerosis development and progression to thrombosis.[83] They can be detected through both active and passive targeting. For instance, these cells are involved in uptaking and degrading NPs, and are thus expected to be targeted passively by the administration of these elements. Moreover, they can be targeted by the addition of monocyte-specific ligands to the surface of iron oxide NPs.[83] This allows precise and exclusive targeting of monocytes. These target-specific iron oxide NPs can be applied in identifying additional contributors to atherosclerosis and thrombosis like endothelial cells, platelets, and vascular smooth muscle cells.[82,83] Table 1 displays a few additional studies highlighting the therapeutic roles of these NPs.

Overall, animal and in vitro studies reveal promising therapeutic potentials for iron oxide NPs in CVD management. Nonetheless, lack of human experiments necessitates further research in this field.

Gold nanoparticles, drug delivery and cardiac remodeling

Like iron oxide NPs, AuNPs have been heavily investigated and applied in various fields including biological, chemical and medical ones. Due to their exceptional bio-optical properties, AuNPs are currently employed as contrast agents for most radiological modalities like photoacoustic imaging, optical

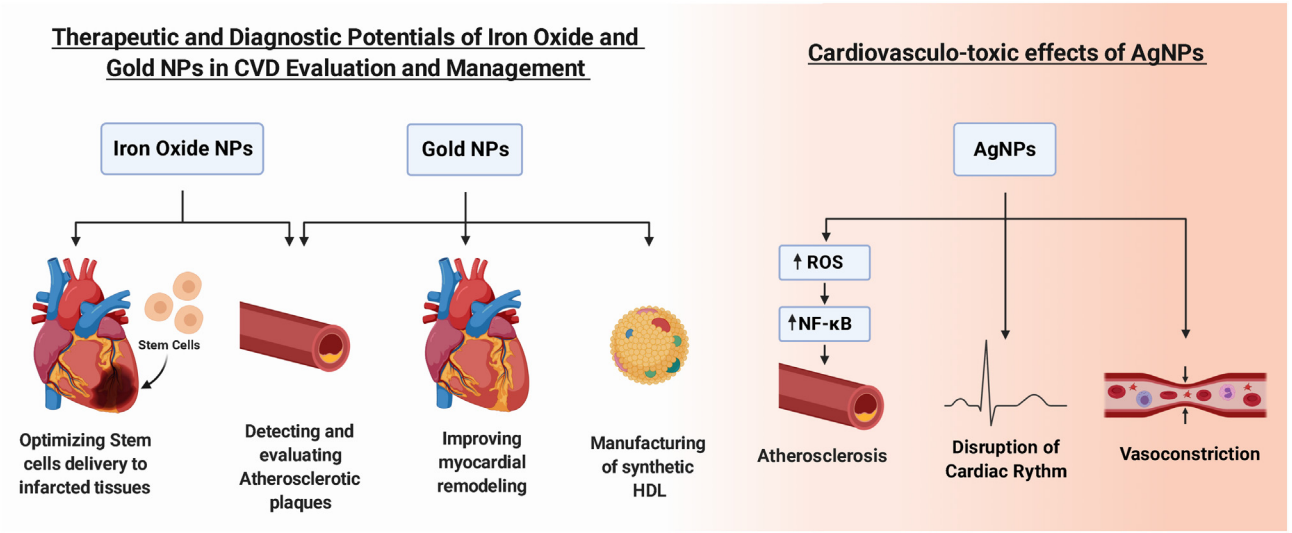

Figure 3. **Favorable cardiovascular effects of Iron Oxide and Gold NPs, along with the undesirable cardiovasculopathic effects of AgNPs.** Both iron oxide and gold NPs have been used in detecting and evaluating atherosclerotic plaques. The role of iron oxide NPs in optimizing stem cells delivery to infarcted tissues has been discussed. Similarly, gold NPs have been found to have intrinsic cardioprotective properties and associated with improved cardiac remodeling. Gold NPs were likely utilized in the manufacturing of synthetic HDL and improvement of CVD profile. On the contrary, AgNPs have been widely recognized for their cardiovasculo-toxic effects denoted by (1) atherosclerosis initiation, (2) cardiac rhythm disruption, and (3) vasoconstriction.

coherence tomography, surface enhanced Raman scattering, computed tomography (CT) scan, intravascular ultrasound and X-ray imaging. [32,90–92] Besides, owing to their feasible synthesis, relative ease of manipulation and unique biofunctionalization, these elements can react with various biochemical agents.[32,93] Indeed, their vast application in drug delivery and specific molecule targeting is explained by these distinctive properties.

AuNPs were initially fostered for cancer management and employed as drug delivery systems, contrast media and radio-enhancers.[94–96] However, little is currently known regarding their therapeutic applications in the cardiovascular field.[32] Recent evidence, emanating from pre-clinical and in vitro studies, accentuates the promising potential of AuNPs in both CVD imaging and treatment. [32,97,98] By acting as probes targeting specific atheromarkers, AuNPs can be used for the radiological detection and evaluation of atherosclerosis.[32] For instance, incorporation of these biologically and optically unique molecules in the bioimaging of atherosclerosis allows precise targeting of various inflammatory markers such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and $\alpha_5\beta_3$-integrin. These markers are expressed by activated endothelial cells, monocytes and smooth muscle cells during the different phases of the inflammatory process.[99–101] Additionally, AuNPs tagged with anti-collagen I peptides allow the detection of cardiac scarred tissues, and thus provide an impressive evaluation of myocardial ischemia.[102]

AuNPs also display potential cardioprotective properties. This is largely due to their anti-oxidative and anti-hypertrophic effects which are exerted via the downregulation of β-adrenoceptors and the subsequent decrease in the ERK1/2-mediated hypertrophic pathway.[103] Indeed, β-adrenoceptors are the key mediators of myocardial hypertrophy and thus, inhibiting them is key for improving heart failure mortality.[104–106]

A role for AuNPs in modulating levels of lipoproteins has been suggested. Indeed, these nano-elements enable effective replication of HDL as well as the production of synthetic HDL-like molecules that can impart both diagnostic and therapeutic roles in atherosclerosis management.[98] These synthetic molecules are made of AuNPs mixed with the key biological constituents of HDL, namely, apolipoprotein A1 and phospholipids.[98] Consequently, fostering of such molecules carrying HDL-like biological properties augments HDL plasma levels and imparts, in turn, a significant atheroprotection.[98] Table 2 describes additional studies examining the cardiovascular effects of AuNPs.

Silver nanoparticles and cardiotoxicity

Silver nanoparticles (AgNPs) are important tools applied in multiple fields including health care and medical ones. The use of AgNPs is largely due to their distinctive physicochemical properties reflected by their electrical, optical, biological, and thermal characteristics.[114–117] AgNPs have gained increased attention over the past few decades and have been increasingly used in medical and non-medical disciplines.[118] As a result, human exposure to AgNPs is considered relatively common because of their widespread distribution.[119,120]

Synthetic AgNPs have been previously utilized in imaging modalities and drug-delivery systems.[121,122] Coating of cardiac stents and pacemakers with these particles has been applied to reduce the risk of acquired foreign body associated infections.[122] This favorable reduction of infections is attributed to the antimicrobial effects of AgNPs. However, there has been growing confirmation that AgNPs utilization is not without side effects, and that it may indeed be associated with cellular damage.[123,124] Moreover, AgNPs have been correlated with the initiation of atherosclerosis.[125,126] The most plausible

Table 3
Additional experimental trials on AgNPs toxicities.

Study	Description	Year of publication	Ref.
Comparison of silver nanoparticle-induced inflammatory responses between healthy and metabolic syndrome mouse models	AgNPs were administered to healthy mice and metabolic syndrome mouse models to assess the impact of metabolic syndrome on AgNPs biodistribution and toxicity. Comparable AgNPs toxicities were encountered in the two groups of mice.	2020	168
Exacerbation of nanoparticle-induced acute pulmonary inflammation in a mouse model of metabolic syndrome	AgNPs-associated pulmonary toxicity was enhanced in metabolic syndrome mouse models. AgNPs-induced inflammation and pulmonary toxicity were attenuated by statins.	2020	169
Non-cytotoxic silver nanoparticle levels perturb human embryonic stem cell-dependent specification of the cranial placode in part *via* FGF signaling.	AgNPs were studied for potential teratogenicity. It was postulated that AgNPs may impair human embryogenesis.	2020	170
Early postnatal exposure to a low dose of nanoparticulate silver induces alterations in glutamate transporters in brain of immature rats.	AgNPs were studied for post-natal neurotoxicity in immature rats. It was speculated that AgNPs may accumulate in the brain for a long period which disrupt then proper brain development.	2020	171
Hepatic histopathological and ultrastructural alterations induced by 10 nm silver nanoparticles.	The hepatoxicity of AgNPs was assessed in healthy mice. It was hypothesized that AgNPs can disrupt liver structure and physiology even at the ultracellular level.	2020	172
Pulmonary exposure to silver nanoparticles impairs cardiovascular homeostasis: effects of coating, dose and time	Inhaled AgNPs were found to be cardio- and pulmo-toxic in healthy mice. They exerted oxidative damage and pro-thrombosis.	2019	162
Evaluation of cardiovascular responses to silver nanoparticles (AgNPs) in spontaneously hypertensive rats	AgNPs cardiovascular toxicity was assessed in hypertensive and healthy rats, respectively. AgNPs' cardiotoxicity, reflected by vasoconstriction and myocardial damage, was amplified by hypertension.	2018	143

mechanism proposed to explain this association is AgNP-induced oxidative damage (Fig. 2).[127,128]

The small size of AgNPs allows them to readily enter the blood circulation. Owing to this property, the endothelial lining of blood vessels displays the highest exposure to these nanoparticles and is the most susceptible to their side effects.[129] Subsequently, endothelial damage may precipitate a multitude of pathophysiological conditions such as myocardial infarction and atherosclerosis.[130] It was also shown that administration of AgNPs evokes oxidative stress, damage to cell membrane, apoptosis, and inhibition of cell proliferation.[126] Moreover, AgNPs upregulate the expression of inflammatory interleukins and the recruitment of monocytes, which are both considered mediators of atherosclerosis.[126,131] Adhesion molecules expressed in early atherosclerosis are also elevated following exposure to these NPs.[126,132,133] Likewise, an increase in the expression of VCAM-1 and ICAM-1 is thought to be triggered by AgNPs.[125] Other studies have also reported that AgNPs also have an activating effect on NLR pyrin domain containing 3 (NLRP3) inflammasome in human macrophages.[134] Importantly, NLR family pyrin domain containing 3 (NLRP3) is indicative of increased risk of atherogenesis.[135] Taken together, these results support the notion that AgNPs may indeed promote an atherosclerotic milieu.

In atherosclerosis, the uptake of cholesterol by macrophages is a major contributor to the formation of an atherosclerotic plaque. Because of their antigen-presenting and phagocytic properties, macrophages are among the first cells to respond to and interact with AgNPs. This interaction is mediated via superficial scavenger receptors expressed on macrophage plasma membrane.[136–138] In this context, a close association exists between lipid metabolism or atherosclerosis and scavenger receptors.[139] Interestingly, a size-dependent modification of macrophage function was observed in one study. Indeed, the addition of small-sized AgNPs (20 nm) resulted in reduced uptake of cholesterol by macrophages.[140] On the contrary, the utilization of large AgNPs (110 nm) had no effect on macrophages' uptake of cholesterol.[140] Hence, one can postulate that this structural modification imparts a dramatic functional effect that can be employed in mitigating the progression of atherosclerosis. Yet, further studies are needed to elucidate the exact vasculopathic effects of these particles.

It appears that AgNPs modulate myocardial voltage-gated sodium (I_{Na}) and potassium (I_K) current channels, transmembrane potential (TMP), and heart rhythm. AgNPs impart a depolarizing effect on the resting potential in a concentration-dependent manner. They also decrease the action potential amplitude and the maximal depolarization velocity (V_{max}) by inhibiting sodium and potassium channels.[141] Moreover, AgNPs cause a significant prolongation of the action potential duration, indicative of slowing down of the repolarization speed.[141] As a result, it is speculated that AgNPs may cause bradyarrhythmias, cardiac conduction block, sudden cardiac death and cardiac asystole (Figure 3).[141] Indeed, direct testing showed that AgNPs have an inhibiting effect on heart rate at higher concentrations.[141]

There are other effects that AgNPs impart onto the cardiovasculature. For instance, some studies report that AgNPs enhance cardiac contractility and cause vasoconstriction.[135] This potentiation constriction may then explain AgNP-

increased velocity of blood flow.[142] Similarly, AgNPs appear to suppress the expression of nitric oxide synthase, which in turn leads to a decrease in the production of nitrogen oxide, a potent vasodilator.[143] By suppressing levels of NO and creating an oxidative milieu,[143] it becomes evident how AgNPs can further exacerbate cardiovascular events.

With the increase in commercial use of AgNPs, and given their various effects on the cardiovascular system, further investigations are certainly warranted especially because most of the available literature is not conclusive. In addition, discrepancies in the parameters used in the analysis of AgNPs as a function of concentration, size, and mode of exposure suggest the need for a more cohesive experimental approach in order to obtain a clearer image of their effects.

Toxicities of iron oxide, gold and silver nanoparticles

The toxicity profile of NPs is dependent on many factors such as size, shape, coating, method of production, dispersion, and charge.[144–155] As a consequence of this, research into nanoparticle toxicity has suffered due to the lack of established protocols and guidelines in the characterization and production of nanoparticles.[156] For instance, studies have found that smaller NP size is linked to higher toxicity.[146,147,157,158] In addition, different NP coatings affect toxicities primarily through the modification of uptake and localization.[148,151,152,158] Mechanistically, it is widely agreed that nanoparticles exert many of their toxic effects through the production of reactive oxygen species (ROS), which is a major instigator of oxidative stress.

Silver nanoparticles

Like other NPs, AgNPs create a pro-oxidant milieu, although the exact mechanism for this increased ROS remains elusive.[146,159–163] Some hypotheses pin this increased ROS production on intracellular Ag^+ release and accumulation. However, recent reports suggest that AgNPs themselves and not the released ions lead to the production of ROS.[151,157,164]

Various and accumulating evidences establish AgNP toxicity on an array of bodily systems. Indeed, AgNPs have been found to cause toxic effects on the liver, bone marrow, lungs, thymus, spleen, kidneys, vasculature, sperm cells, heart, and skin.[165] At the subcellular level, evidence suggests that these NPs cause defective ubiquitination autophagosome-lysosome fusion.[166] Since several studies showed that AgNPs are genotoxic, future long term research into the role of these particles in cancer becomes of interest.[157,159,160,162,164] Interestingly, while some studies argue that these particles largely spare the blood–brain barrier (BBB) from toxicity, other reports noted changes in BBB permeability as a result of AgNP administration, opening up interesting avenue for future applications.[167] Table 3 includes a few additional animal and *in-vitro* studies examining the potential toxicities of AgNPs.

Gold nanoparticles

Studies conducting direct comparisons between different types of NPs have established that despite similarities in toxic profiles of NPs, some interesting differences exist. Indeed, a comparison between AuNPs and AgNPs found that while both deposit in the mononuclear phagocyte system, their distribution varies according to their metal composition. For instance, AuNPs accumulate in the liver while AgNPs were mostly found in other organs like the kidney and heart.[173,174] Furthermore, a study examining the effect of protein coronas on the toxicity profiles of NPs found that some variants of these albumin or serum protein coronas may decrease hepatic uptake of AuNPs and ROS-mediated hepatotoxicity, and thus may improve the toxicity profile of these particles. This finding raises in turn the possibility that further advances in the production of AuNPs' coating materials could eventually decrease their overall toxicity.[175]

Iron nanoparticles

Unlike the aforementioned NPs, iron oxide NPs toxic effects were the least studied. Yet, CNS toxicity caused by a positive feedback loop mediated by the Fenton reaction and protein aggregation has been documented.[176,177] Moreover, in one study examining a variety of cell lines, it was found that iron oxide NPs may play a significant role in downregulating the expression of Id-family of genes, which are genetic sequences intimately linked to growth and development.[178] Recently, it was found that human monocytes responded to these NPs by executing an autophagic program in order to decrease the cytotoxic effects of the nanoparticles. However, the mechanism for this increased autophagy is not yet fully understood.[179]

Conclusion

New paths in the comprehension of nanoparticles and their application in CVD management are opening. While iron oxide NPs and AuNPs have shown promising roles in the detection and treatment of atherosclerotic plaques, AgNPs have been recently associated with unfavorable cardiovascular effects. Hence, it is of great importance to further investigate the adverse effects associated with these different nanoparticles, taking into account their various routes of administration and the contradictory findings associated with their distinct properties including concentrations, sizes, shapes, and ionic charges. Nonetheless, we argue that nanoparticles can play a decisive role in the treatment of CVD. We also anticipate that nanotechnology will be one of the attractive therapeutic approaches for managing CVD in the foreseeable future.

References

1 WHO. *Cardiovascular diseases (CVDs)*; 2019.
2 Gillman MW. Primordial prevention of cardiovascular disease. *Circulation* 2015;**131**:599-601.
3 Chomistek AK, Chiuve SE, Eliassen AH, Mukamal KJ, Willett WC, Rimm EB. Healthy lifestyle in the primordial prevention of cardiovascular disease among young women. *J Am Coll Cardiol* 2015;**65**:43-51.
4 Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**:937-52.

5 Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation* 2007;**115**:114-26.

6 Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice. *Rev Esp Cardiol (Engl Ed)*. 2016; 69: 939.

7 Hobbs FD. Cardiovascular disease: different strategies for primary and secondary prevention? *Heart* 2004;**90**:1217-23.

8 American Diabetes A. 9. Cardiovascular disease and risk management: standards of medical care in diabetes—2018. *Diabetes Care* 2018;**41**: S86-S104.

9 Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005;**353**:2373-83.

10 Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;**141**:e637S e68S.

11 Taylor F, Ward K, Moore TH, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2011: CD004816.

12 Zhang H, Yuan X, Zhang H, et al. Efficacy of long-term beta-blocker therapy for secondary prevention of long-term outcomes after coronary artery bypass grafting surgery. *Circulation* 2015;**131**:2194-201.

13 Bertrand ME. Provision of cardiovascular protection by ACE inhibitors: a review of recent trials. *Curr Med Res Opin* 2004;**20**:1559-69.

14 Yla-Herttuala S, Baker AH. Cardiovascular gene therapy: past, present, and future. *Mol Ther* 2017;**25**:1095-106.

15 Rincon MY, VandenDriessche T, Chuah MK. Gene therapy for cardiovascular disease: advances in vector development, targeting, and delivery for clinical translation. *Cardiovasc Res* 2015;**108**:4-20.

16 Wolfram JA, Donahue JK. Gene therapy to treat cardiovascular disease. *J Am Heart Assoc* 2013;**2**e000119.

17 Tilemann L, Ishikawa K, Weber T, Hajjar RJ. Gene therapy for heart failure. *Circ Res* 2012;**110**:777-93.

18 Hajjar RJ. Potential of gene therapy as a treatment for heart failure. *J Clin Invest* 2013;**123**:53-61.

19 Bongianino R, Priori SG. Gene therapy to treat cardiac arrhythmias. *Nat Rev Cardiol* 2015;**12**:531-46.

20 Pandey AC, Lancaster JJ, Harris DT, Goldman S, Juneman E. Cellular therapeutics for heart failure: focus on mesenchymal stem cells. *Stem Cells Int* 2017;**2017**:9640108.

21 Chou SH, Lin SZ, Kuo WW, et al. Mesenchymal stem cell insights: prospects in cardiovascular therapy. *Cell Transplant* 2014;**23**:513-29.

22 Menasche P. Cell therapy trials for heart regeneration — lessons learned and future directions. *Nat Rev Cardiol* 2018;**15**:659-71.

23 Clifford DM, Fisher SA, Brunskill SJ, et al. Stem cell treatment for acute myocardial infarction. *Cochrane Database Syst Rev*. 2012: CD006536.

24 Martin Gimenez VM, Kassuha DE, Manucha W. Nanomedicine applied to cardiovascular diseases: latest developments. *Ther Adv Cardiovasc Dis* 2017;**11**:133-42.

25 Katsuki S, Matoba T, Koga JI, Nakano K, Egashira K. Anti-inflammatory nanomedicine for cardiovascular disease. *Front Cardiovasc Med* 2017;**4**:87.

26 Lobatto ME, Fuster V, Fayad ZA, Mulder WJ. Perspectives and opportunities for nanomedicine in the management of atherosclerosis. *Nat Rev Drug Discov* 2011;**10**:835-52.

27 Karimi M, Zare H, Bakhshian Nik A, et al. Nanotechnology in diagnosis and treatment of coronary artery disease. *Nanomedicine (Lond)* 2016;**11**:513-30.

28 Gonzalez C, Rosas-Hernandez H, Ramirez-Lee MA, Salazar-Garcia S, Ali SF. Role of silver nanoparticles (AgNPs) on the cardiovascular system. *Arch Toxicol* 2016;**90**:493-511.

29 Ge L, Li Q, Wang M, Ouyang J, Li X, Xing MM. Nanosilver particles in medical applications: synthesis, performance, and toxicity. *Int J Nanomedicine* 2014;**9**:2399-407.

30 Passaro F, Testa G, Ambrosone L, et al. Nanotechnology-based cardiac targeting and direct cardiac reprogramming: the betrothed. *Stem Cells Int* 2017;**2017**:4940397.

31 Zhu K, Li J, Wang Y, Lai H, Wang C. Nanoparticles-assisted stem cell therapy for ischemic heart disease. *Stem Cells Int* 2016;**2016**:1384658.

32 Varna M, Xuan HV, Fort E. Gold nanoparticles in cardiovascular imaging. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 2018;**10**.

33 Mulder WJ, Jaffer FA, Fayad ZA and Nahrendorf M. Imaging and nanomedicine in inflammatory atherosclerosis. *Sci Transl Med*. 2014; 6: 239sr1.

34 Ho YT, Poinard B, Kah JC. Nanoparticle drug delivery systems and their use in cardiac tissue therapy. *Nanomedicine (Lond)* 2016;**11**:693-714.

35 Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**63**:2889-934.

36 Singh L, Kruger HG, Maguire GEM, Govender T, Parboosing R. The role of nanotechnology in the treatment of viral infections. *Ther Adv Infect Dis* 2017;**4**:105-31.

37 Yah CS, Simate GS. Nanoparticles as potential new generation broad spectrum antimicrobial agents. *Daru* 2015;**23**:43.

38 Galdiero S, Falanga A, Vitiello M, Cantisani M, Marra V, Galdiero M. Silver nanoparticles as potential antiviral agents. *Molecules* 2011;**16**:8894-918.

39 Kandi V, Kandi S. Antimicrobial properties of nanomolecules: potential candidates as antibiotics in the era of multi-drug resistance. *Epidemiol Health* 2015;**37**e2015020.

40 Chang MY, Yang YJ, Chang CH, et al. Functionalized nanoparticles provide early cardioprotection after acute myocardial infarction. *J Control Release* 2013;**170**:287-94.

41 Montiel Schneider MG, Lassalle VL. Magnetic iron oxide nanoparticles as novel and efficient tools for atherosclerosis diagnosis. *Biomed Pharmacother* 2017;**93**:1098-115.

42 Jin R, Lin B, Li D, Ai H. Superparamagnetic iron oxide nanoparticles for MR imaging and therapy: design considerations and clinical applications. *Curr Opin Pharmacol* 2014;**18**:18-27.

43 Yildirimer L, Thanh NT, Loizidou M, Seifalian AM. Toxicology and clinical potential of nanoparticles. *Nano Today* 2011;**6**:585-607.

44 Zhang XQ, Xu X, Bertrand N, Pridgen E, Swami A, Farokhzad OC. Interactions of nanomaterials and biological systems: implications to personalized nanomedicine. *Adv Drug Deliv Rev* 2012;**64**:1363-84.

45 Albanese A, Tang PS, Chan WC. The effect of nanoparticle size, shape, and surface chemistry on biological systems. *Annu Rev Biomed Eng* 2012;**14**:1-16.

46 Gupta P, Garcia E, Sarkar A, et al. Nanoparticle based treatment for cardiovascular diseases. *Cardiovasc Hematol Disord Drug Targets* 2019;**19**:33-44.

47 Fan C, Joshi J, Li F, et al. Nanoparticle-mediated drug delivery for treatment of ischemic heart disease. *Front Bioeng Biotechnol* 2020;**8**:687.

48 Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. *Pharm Res* 2016;**33**:2373-87.

49 Caster JM, Patel AN, Zhang T, Wang A. Investigational nanomedicines in 2016: a review of nanotherapeutics currently undergoing clinical trials. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 2017;**9**.

50 Ventola CL. Progress in nanomedicine: approved and investigational nanodrugs. *P T* 2017;**42**:742-55.

51 Udhrain A, Skubitz KM, Northfelt DW. Pegylated liposomal doxorubicin in the treatment of AIDS-related Kaposi's sarcoma. *Int J Nanomedicine* 2007;**2**:345-52.

52 Cooley T, Henry D, Tonda M, Sun S, O'Connell M, Rackoff W. A randomized, double-blind study of pegylated liposomal doxorubicin for the treatment of AIDS-related Kaposi's sarcoma. *Oncologist* 2007;**12**:114-23.

53 Kim BY, Rutka JT, Chan WC. Nanomedicine. *N Engl J Med* 2010;**363**:2434-43.
54 Chen R, Ling D, Zhao L, et al. Parallel comparative studies on mouse toxicity of oxide nanoparticle- and gadolinium-based T1 MRI contrast agents. *ACS Nano* 2015;**9**:12425-35.
55 Estelrich J, Sanchez-Martin MJ, Busquets MA. Nanoparticles in magnetic resonance imaging: from simple to dual contrast agents. *Int J Nanomedicine* 2015;**10**:1727-41.
56 Spinowitz BS, Kausz AT, Baptista J, et al. Ferumoxytol for treating iron deficiency anemia in CKD. *J Am Soc Nephrol* 2008;**19**:1599-605.
57 McCormack PL. Ferumoxytol: in iron deficiency anaemia in adults with chronic kidney disease. *Drugs* 2012;**72**:2013-22.
58 Sosnovik DE, Nahrendorf M. Cells and iron oxide nanoparticles on the move: magnetic resonance imaging of monocyte homing and myocardial inflammation in patients with ST-elevation myocardial infarction. *Circ Cardiovasc Imaging* 2012;**5**:551-4.
59 Ma LL, Feldman MD, Tam JM, et al. Small multifunctional nanoclusters (nanoroses) for targeted cellular imaging and therapy. *ACS Nano* 2009;**3**:2686-96.
60. Jasmin, de Souza GT, Louzada RA, Rosado-de-Castro PH, Mendez-Otero R and Campos de Carvalho AC. Tracking stem cells with superparamagnetic iron oxide nanoparticles: perspectives and considerations. *Int J Nanomedicine*. 2017; 12: 779–93.
61 Kraitchman DL, Gilson WD, Lorenz CH. Stem cell therapy: MRI guidance and monitoring. *J Magn Reson Imaging* 2008;**27**:299-310.
62 Santoso MR, Yang PC. Magnetic nanoparticles for targeting and imaging of stem cells in myocardial infarction. *Stem Cells Int* 2016;**2016**:4198790.
63 Tarin C, Carril M, Martin-Ventura JL, et al. Targeted gold-coated iron oxide nanoparticles for CD163 detection in atherosclerosis by MRI. *Sci Rep* 2015;**5**:17135.
64 Naseroleslami M, Aboutaleb N, Parivar K. The effects of superparamagnetic iron oxide nanoparticles-labeled mesenchymal stem cells in the presence of a magnetic field on attenuation of injury after heart failure. *Drug Deliv Transl Res* 2018;**8**:1214-25.
65 Han J, Park J, Kim BS. Integration of mesenchymal stem cells with nanobiomaterials for the repair of myocardial infarction. *Adv Drug Deliv Rev* 2015;**95**:15-28.
66 Dadfar SM, Roemhild K, Drude NI, et al. Iron oxide nanoparticles: diagnostic, therapeutic and theranostic applications. *Adv Drug Deliv Rev* 2019;**138**:302-25.
67 Peled M, Fisher EA. Dynamic aspects of macrophage polarization during atherosclerosis progression and regression. *Front Immunol* 2014;**5**:579.
68 Hu JM, Liu K, Liu JH, et al. CD163 as a marker of M2 macrophage, contribute to predicte aggressiveness and prognosis of Kazakh esophageal squamous cell carcinoma. *Oncotarget* 2017;**8**:21526-38.
69 de Gaetano M, Crean D, Barry M, Belton O. M1- and M2-type macrophage responses are predictive of adverse outcomes in human atherosclerosis. *Front Immunol* 2016;**7**:275.
70 Chinetti-Gbaguidi G, Colin S, Staels B. Macrophage subsets in atherosclerosis. *Nat Rev Cardiol* 2015;**12**:10-7.
71 Randolph GJ. Mechanisms that regulate macrophage burden in atherosclerosis. *Circ Res* 2014;**114**:1757-71.
72 Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. *Nat Rev Immunol* 2011;**11**:723-37.
73 Gui T, Shimokado A, Sun Y, Akasaka T, Muragaki Y. Diverse roles of macrophages in atherosclerosis: from inflammatory biology to biomarker discovery. *Mediators Inflamm* 2012;**2012**:693083.
74 Li X, Wei Z, Lv H, et al. Iron oxide nanoparticles promote the migration of mesenchymal stem cells to injury sites. *Int J Nanomedicine* 2019;**14**:573-89.
75 Huang Z, Shen Y, Sun A, et al. Magnetic targeting enhances retrograde cell retention in a rat model of myocardial infarction. *Stem Cell Res Ther* 2013;**4**:149.
76 Vandergriff AC, Hensley TM, Henry ET, et al. Magnetic targeting of cardiosphere-derived stem cells with ferumoxytol nanoparticles for treating rats with myocardial infarction. *Biomaterials* 2014;**35**:8528-39.
77 Ottersbach A, Mykhaylyk O, Heidsieck A, et al. Improved heart repair upon myocardial infarction: combination of magnetic nanoparticles and tailored magnets strongly increases engraftment of myocytes. *Biomaterials* 2018;**155**:176-90.
78 Jiang Q, Yu T, Huang K, Zhang H, Zheng Z, Hu S. Systemic redistribution of the intramyocardially injected mesenchymal stem cells by repeated remote ischaemic post-conditioning. *J Cell Mol Med* 2018;**22**:417-28.
79 Muller-Ehmsen J, Krausgrill B, Burst V, et al. Effective engraftment but poor mid-term persistence of mononuclear and mesenchymal bone marrow cells in acute and chronic rat myocardial infarction. *J Mol Cell Cardiol* 2006;**41**:876-84.
80 Kania G, Sternak M, Jasztal A, et al. Uptake and bioreactivity of charged chitosan-coated superparamagnetic nanoparticles as promising contrast agents for magnetic resonance imaging. *Nanomedicine* 2018;**14**:131-40.
81 Xiong F, Wang H, Feng Y, et al. Cardioprotective activity of iron oxide nanoparticles. *Sci Rep* 2015;**5**:8579.
82 Kaczyńska A, Guzdek K, Derszniak K, et al. Novel nanostructural contrast for magnetic resonance imaging of endothelial inflammation: targeting SPIONs to vascular endothelium. *RSC Adv* 2016;**6**:72586-95.
83. Vazquez-Prada KX, Lam J, Kamato D, Ping Xu Z, Little PJ and Ta HT. Targeted molecular imaging of cardiovascular diseases by iron oxide nanoparticles. *Arterioscler Thromb Vasc Biol*. 2020: ATVBAHA120315404.
84 Liu S, Chen X, Bao L, et al. Treatment of infarcted heart tissue via the capture and local delivery of circulating exosomes through antibody-conjugated magnetic nanoparticles. *Nat Biomed Eng* 2020;**4**:1063-75.
85 Ta HT, Li Z, Hagemeyer CE, et al. Molecular imaging of activated platelets via antibody-targeted ultra-small iron oxide nanoparticles displaying unique dual MRI contrast. *Biomaterials* 2017;**134**:31-42.
86 Hua P, Wang YY, Liu LB, et al. In vivo magnetic resonance imaging tracking of transplanted superparamagnetic iron oxide-labeled bone marrow mesenchymal stem cells in rats with myocardial infarction. *Mol Med Rep* 2015;**11**:113-20.
87 Richards JM, Semple SI, MacGillivray TJ, et al. Abdominal aortic aneurysm growth predicted by uptake of ultrasmall superparamagnetic particles of iron oxide: a pilot study. *Circ Cardiovasc Imaging* 2011;**4**:274-81.
88 Kim YJ, Huh YM, Choe KO, et al. In vivo magnetic resonance imaging of injected mesenchymal stem cells in rat myocardial infarction; simultaneous cell tracking and left ventricular function measurement. *Int J Cardiovasc Imaging* 2009;**25**(Suppl 1):99-109.
89 Kraitchman DL, Heldman AW, Atalar E, et al. In vivo magnetic resonance imaging of mesenchymal stem cells in myocardial infarction. *Circulation* 2003;**107**:2290-3.
90 Li W, Chen X. Gold nanoparticles for photoacoustic imaging. *Nanomedicine (Lond)* 2015;**10**:299-320.
91. Cole LE, Ross RD, Tilley JM, Vargo-Gogola T and Roeder RK. Gold nanoparticles as contrast agents in x-ray imaging and computed tomography. *Nanomedicine (Lond)*. 2015; 10: 321–41.
92 Cormode DP, Naha PC, Fayad ZA. Nanoparticle contrast agents for computed tomography: a focus on micelles. *Contrast Media Mol Imaging* 2014;**9**:37-52.
93 Cabuzu D, Cirja A, Puiu R, Grumezescu AM. Biomedical applications of gold nanoparticles. *Curr Top Med Chem* 2015;**15**:1605-13.
94 Dreaden EC, Austin LA, Mackey MA, El-Sayed MA. Size matters: gold nanoparticles in targeted cancer drug delivery. *Ther Deliv* 2012;**3**:457-78.
95 Cai W, Gao T, Hong H, Sun J. Applications of gold nanoparticles in cancer nanotechnology. *Nanotechnol Sci Appl* 2008;**1**:17-32.

96 Jain S, Hirst DG, O'Sullivan JM. Gold nanoparticles as novel agents for cancer therapy. *Br J Radiol* 2012;**85**:101-13.

97 Dong C, Ma A, Shang L. Nanoparticles for postinfarct ventricular remodeling. *Nanomedicine (Lond)* 2018;**13**:3037-50.

98 Luthi AJ, Patel PC, Ko CH, Mutharasan RK, Mirkin CA, Thaxton CS. Nanotechnology for synthetic high-density lipoproteins. *Trends Mol Med* 2010;**16**:553-60.

99 Pan D, Pramanik M, Senpan A, et al. Molecular photoacoustic imaging of angiogenesis with integrin-targeted gold nanobeacons. *FASEB J* 2011;**25**:875-82.

100 Rouleau L, Berti R, Ng VW, et al. VCAM-1-targeting gold nanoshell probe for photoacoustic imaging of atherosclerotic plaque in mice. *Contrast Media Mol Imaging* 2013;**8**:27-39.

101 McQueenie R, Stevenson R, Benson R, et al. Detection of inflammation in vivo by surface-enhanced Raman scattering provides higher sensitivity than conventional fluorescence imaging. *Anal Chem* 2012;**84**:5968-75.

102 Danila D, Johnson E, Kee P. CT imaging of myocardial scars with collagen-targeting gold nanoparticles. *Nanomedicine* 2013;**9**:1067-76.

103 Qiao Y, Zhu B, Tian A, Li Z. PEG-coated gold nanoparticles attenuate beta-adrenergic receptor-mediated cardiac hypertrophy. *Int J Nanomedicine* 2017;**12**:4709-19.

104 Shimizu I, Minamino T. Physiological and pathological cardiac hypertrophy. *J Mol Cell Cardiol* 2016;**97**:245-62.

105 Chatterjee S, Biondi-Zoccai G, Abbate A, et al. Benefits of beta blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. *BMJ* 2013;**346**:f55.

106 Gheorghiade M, Colucci WS, Swedberg K. Beta-blockers in chronic heart failure. *Circulation* 2003;**107**:1570-5.

107 Li H, Yan J, Meng D, et al. Gold nanorod-based nanoplatform catalyzes constant NO generation and protects from cardiovascular injury. *ACS Nano* 2020;**14**:12854-65.

108 Bejarano J, Rojas A, Ramirez-Sagredo A, et al. Light-induced release of the cardioprotective peptide angiotensin-(1-9) from thermosensitive liposomes with gold nanoclusters. *J Control Release* 2020;**328**:859-72.

109 Chhour P, Naha PC, O'Neill SM, et al. Labeling monocytes with gold nanoparticles to track their recruitment in atherosclerosis with computed tomography. *Biomaterials* 2016;**87**:93-103.

110 Ghann WE, Aras O, Fleiter T, Daniel MC. Syntheses and characterization of lisinopril-coated gold nanoparticles as highly stable targeted CT contrast agents in cardiovascular diseases. *Langmuir* 2012;**28**:10398-408.

111 Yeager D, Karpiouk A, Wang B, et al. Intravascular photoacoustic imaging of exogenously labeled atherosclerotic plaque through luminal blood. *J Biomed Opt* 2012;**17**:106016.

112 Cormode DP, Roessl E, Thran A, et al. Atherosclerotic plaque composition: analysis with multicolor CT and targeted gold nanoparticles. *Radiology* 2010;**256**:774-82.

113 Wang B, Yantsen E, Larson T, et al. Plasmonic intravascular photoacoustic imaging for detection of macrophages in atherosclerotic plaques. *Nano Lett* 2009;**9**:2212-7.

114 Gurunathan S, Park JH, Han JW, Kim JH. Comparative assessment of the apoptotic potential of silver nanoparticles synthesized by Bacillus tequilensis and Calocybe indica in MDA-MB-231 human breast cancer cells: targeting p53 for anticancer therapy. *Int J Nanomedicine* 2015;**10**:4203-22.

115 Li WR, Xie XB, Shi QS, Zeng HY, Ou-Yang YS, Chen YB. Antibacterial activity and mechanism of silver nanoparticles on Escherichia coli. *Appl Microbiol Biotechnol* 2010;**85**:1115-22.

116 Mukherjee P, Ahmad A, Mandal D, et al. Fungus-mediated synthesis of silver nanoparticles and their immobilization in the mycelial matrix: a novel biological approach to nanoparticle synthesis. *Nano Lett* 2001;**1**:515-9.

117 Zhang XF, Liu ZG, Shen W, Gurunathan S. Silver nanoparticles: synthesis, characterization, properties, applications, and therapeutic approaches. *Int J Mol Sci* 2016;**17**.

118 Hernandez-Sierra JF, Ruiz F, Pena DC, et al. The antimicrobial sensitivity of Streptococcus mutans to nanoparticles of silver, zinc oxide, and gold. *Nanomedicine: nanotechnology, biology, and medicine* 2008;**4**:237-40.

119 Chaloupka K, Malam Y, Seifalian AM. Nanosilver as a new generation of nanoproduct in biomedical applications. *Trends Biotechnol* 2010;**28**:580-8.

120 Yong KT, Law WC, Hu R, et al. Nanotoxicity assessment of quantum dots: from cellular to primate studies. *Chem Soc Rev* 2013;**42**:1236-50.

121 Lee SH, Jun BH. Silver nanoparticles: synthesis and application for Nanomedicine. *Int J Mol Sci* 2019;**20**.

122 Talapko J, Matijević T, Juzbašić M, Antolović-Požgain A, Škrlec I. Antibacterial activity of silver and its application in dentistry. *Cardiology and Dermatology Microorganisms* 2020;**8**:1400.

123 Kalishwaralal K, Banumathi E. Ram Kumar Pandian S, et al. *Silver nanoparticles inhibit VEGF induced cell proliferation and migration in bovine retinal endothelial cells Colloids Surf B Biointerfaces* 2009;**73**:51-7.

124 Wang Z, Liu S, Ma J, et al. Silver nanoparticles induced RNA polymerase-silver binding and RNA transcription inhibition in erythroid progenitor cells. *ACS Nano* 2013;**7**:4171-86.

125 Danielsen PH, Cao Y, Roursgaard M, Møller P, Loft S. Endothelial cell activation, oxidative stress and inflammation induced by a panel of metal-based nanomaterials. *Nanotoxicology* 2015;**9**:813-24.

126 Shi J, Sun X, Lin Y, et al. Endothelial cell injury and dysfunction induced by silver nanoparticles through oxidative stress via IKK/NF-kappaB pathways. *Biomaterials* 2014;**35**:6657-66.

127 AshaRani PV. Low Kah Mun G, Hande MP and Valiyaveettil S. Cytotoxicity and genotoxicity of silver nanoparticles in human cells. *ACS Nano* 2009;**3**:279-90.

128 Guo D, Zhu L, Huang Z, et al. Anti-leukemia activity of PVP-coated silver nanoparticles via generation of reactive oxygen species and release of silver ions. *Biomaterials* 2013;**34**:7884-94.

129 Gurunathan S, Lee KJ, Kalishwaralal K, Sheikpranbabu S, Vaidyanathan R, Eom SH. Antiangiogenic properties of silver nanoparticles. *Biomaterials* 2009;**30**:6341-50.

130 Davda J, Labhasetwar V. Characterization of nanoparticle uptake by endothelial cells. *Int J Pharm* 2002;**233**:51-9.

131 Galkina E, Ley K. Immune and inflammatory mechanisms of atherosclerosis (*). *Annu Rev Immunol* 2009;**27**:165-97.

132 Blankenberg S, Barbaux S, Tiret L. Adhesion molecules and atherosclerosis. *Atherosclerosis* 2003;**170**:191-203.

133 Galkina E, Ley K. Vascular adhesion molecules in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2007;**27**:2292-301.

134 Murphy A, Casey A, Byrne G, Chambers G, Howe O. Silver nanoparticles induce pro-inflammatory gene expression and inflammasome activation in human monocytes. *J Appl Toxicol* 2016;**36**:1311-20.

135 Baldrighi M, Mallat Z, Li X. NLRP3 inflammasome pathways in atherosclerosis. *Atherosclerosis* 2017;**267**:127-38.

136 Rigotti A, Miettinen HE, Krieger M. The role of the high-density lipoprotein receptor SR-BI in the lipid metabolism of endocrine and other tissues. *Endocr Rev* 2003;**24**:357-87.

137 Shannahan JH, Bai W, Brown JM. Implications of scavenger receptors in the safe development of nanotherapeutics. *Receptors Clin Investig* 2015;**2**e811.

138. Wang H, Wu L and Reinhard BM. Scavenger receptor mediated endocytosis of silver nanoparticles into J774A.1 macrophages is heterogeneous. *ACS nano*. 2012; 6: 7122–32.

139 Rigotti A, Trigatti BL, Penman M, Rayburn H, Herz J, Krieger M. A targeted mutation in the murine gene encoding the high density lipoprotein (HDL) receptor scavenger receptor class B type I reveals its key role in HDL metabolism. *Proc Natl Acad Sci U S A* 1997;**94**:12610-5.

140 Shannahan JH, Sowrirajan H, Persaud I, Podila R, Brown JM. Impact of silver and iron nanoparticle exposure on cholesterol uptake by macrophages. *Journal of Nanomaterials* 2015;**2015**:127235.

141 Lin CX, Yang SY, Gu JL, Meng J, Xu HY, Cao JM. The acute toxic effects of silver nanoparticles on myocardial transmembrane potential, INa and IK1 channels and heart rhythm in mice. *Nanotoxicology* 2017;**11**:827-37.

142 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**:963-71.

143 Ramirez-Lee MA, Aguirre-Banuelos P, Martinez-Cuevas PP, et al. Evaluation of cardiovascular responses to silver nanoparticles (AgNPs) in spontaneously hypertensive rats. *Nanomedicine* 2018;**14**:385-95.

144 Gliga AR, Skoglund S, Wallinder IO, Fadeel B, Karlsson HL. Size-dependent cytotoxicity of silver nanoparticles in human lung cells: the role of cellular uptake, agglomeration and Ag release. *Part Fibre Toxicol* 2014;**11**:11.

145 Seiffert J, Hussain F, Wiegman C, et al. Pulmonary toxicity of instilled silver nanoparticles: influence of size, coating and rat strain. *PLoS One* 2015;**10**e0119726.

146 Lopez-Chaves C, Soto-Alvaredo J, Montes-Bayon M, Bettmer J, Llopis J, Sanchez-Gonzalez C. Gold nanoparticles: distribution, bioaccumulation and toxicity. In vitro and in vivo studies. *Nanomedicine* 2018;**14**:1-12.

147 Schmid G, Kreyling WG, Simon U. Toxic effects and biodistribution of ultrasmall gold nanoparticles. *Arch Toxicol* 2017;**91**:3011-37.

148 Deng J, Yao M, Gao C. Cytotoxicity of gold nanoparticles with different structures and surface-anchored chiral polymers. *Acta Biomater* 2017;**53**:610-8.

149 Wozniak A, Malankowska A, Nowaczyk G, et al. Size and shape-dependent cytotoxicity profile of gold nanoparticles for biomedical applications. *J Mater Sci Mater Med* 2017;**28**:92.

150 Pinzaru I, Coricovac D, Dehelean C, et al. Stable PEG-coated silver nanoparticles — a comprehensive toxicological profile. *Food Chem Toxicol* 2018;**111**:546-56.

151 Das B, Tripathy S, Adhikary J, et al. Surface modification minimizes the toxicity of silver nanoparticles: an in vitro and in vivo study. *J Biol Inorg Chem* 2017;**22**:893-918.

152 Chandran P, Riviere JE, Monteiro-Riviere NA. Surface chemistry of gold nanoparticles determines the biocorona composition impacting cellular uptake, toxicity and gene expression profiles in human endothelial cells. *Nanotoxicology* 2017;**11**:507-19.

153 Li X, Wang Z, Li Y, Bian K, Yin T, Gao D. Self-assembly of bacitracin-gold nanoparticles and their toxicity analysis. *Korean J Couns Psychother* 2018;**82**:310-6.

154 Huang D, Zhou H, Liu H, Gao J. The cytotoxicity of gold nanoparticles is dispersity-dependent. *Dalton Trans* 2015;**44**:17911-5.

155 El Mahdy MM, Eldin TA, Aly HS, Mohammed FF, Shaalan MI. Evaluation of hepatotoxic and genotoxic potential of silver nanoparticles in albino rats. *Exp Toxicol Pathol* 2015;**67**:21-9.

156 Teske SS, Detweiler CS. The biomechanisms of metal and metal-oxide nanoparticles' interactions with cells. *Int J Environ Res Public Health* 2015;**12**:1112-34.

157 Gliga AR, Skoglund S, Odnevall Wallinder I, Fadeel B, Karlsson HL. Size-dependent cytotoxicity of silver nanoparticles in human lung cells: the role of cellular uptake, agglomeration and Ag release. *Part Fibre Toxicol* 2014;**11**:11.

158 Pinzaru I, Coricovac D, Dehelean C, et al. Stable PEG-coated silver nanoparticles — a comprehensive toxicological profile. *Food Chem Toxicol* 2018;**111**:546-56.

159 El Mahdy MM, Eldin TAS, Aly HS, Mohammed FF, Shaalan MI. Evaluation of hepatotoxic and genotoxic potential of silver nanoparticles in albino rats. *Exp Toxicol Pathol* 2015;**67**:21-9.

160 He W, Liu X, Kienzle A, Muller WE, Feng Q. In vitro uptake of silver nanoparticles and their toxicity in human mesenchymal stem cells derived from bone marrow. *J Nanosci Nanotechnol* 2016;**16**:219-28.

161 Li Y, Qin T, Ingle T, et al. Differential genotoxicity mechanisms of silver nanoparticles and silver ions. *Arch Toxicol* 2017;**91**:509-19.

162 Ferdous Z, Al-Salam S, Greish YE, Ali BH, Nemmar A. Pulmonary exposure to silver nanoparticles impairs cardiovascular homeostasis: effects of coating, dose and time. *Toxicol Appl Pharmacol* 2019;**367**:36-50.

163 Moradi-Sardareh H, Basir HRG, Hassan ZM, Davoudi M, Amidi F, Paknejad M. Toxicity of silver nanoparticles on different tissues of Balb/C mice. *Life Sci* 2018;**211**:81-90.

164 Wen H, Dan M, Yang Y, et al. Acute toxicity and genotoxicity of silver nanoparticle in rats. *PLOS ONE* 2017;**12**e0185554.

165 Hadrup N, Sharma AK, Loeschner K. Toxicity of silver ions, metallic silver, and silver nanoparticle materials after in vivo dermal and mucosal surface exposure: a review. *Regul Toxicol Pharmacol* 2018;**98**:257-67.

166 Mao B-H, Tsai J-C, Chen C-W, Yan S-J, Wang Y-J. Mechanisms of silver nanoparticle-induced toxicity and important role of autophagy. *Nanotoxicology* 2016;**10**:1021-40.

167 Sokolowska P, Bialkowska K, Siatkowska M, et al. Human brain endothelial barrier cells are distinctly less vulnerable to silver nanoparticles toxicity than human blood vessel cells: a cell-specific mechanism of the brain barrier? *Nanomedicine* 2017;**13**:2127-30.

168 Kobos L, Alqahtani S, Xia L, et al. Comparison of silver nanoparticle-induced inflammatory responses between healthy and metabolic syndrome mouse models. *J Toxicol Environ Health A* 2020;**83**:249-68.

169 Alqahtani S, Kobos LM, Xia L, et al. Exacerbation of nanoparticle-induced acute pulmonary inflammation in a mouse model of metabolic syndrome. *Front Immunol* 2020;**11**:818.

170 Hu B, Yang R, Cheng Z, et al. Non-cytotoxic silver nanoparticle levels perturb human embryonic stem cell-dependent specification of the cranial placode in part via FGF signaling. *J Hazard Mater* 2020;**393**:122440.

171 Dabrowska-Bouta B, Sulkowski G, Salek M, Gewartowska M, Sidoryk-Wegrzynowicz M, Struzynska L. Early postnatal exposure to a low dose of nanoparticulate silver induces alterations in glutamate transporters in brain of immature rats. *Int J Mol Sci* 2020;**21**.

172 Al-Doaiss A, Jarrar Q, Moshawih S. Hepatic histopathological and ultrastructural alterations induced by 10 nm silver nanoparticles. *IET Nanobiotechnol* 2020;**14**:405-11.

173 Yang L, Kuang H, Zhang W, Aguilar ZP, Wei H, Xu H. Comparisons of the biodistribution and toxicological examinations after repeated intravenous administration of silver and gold nanoparticles in mice. *Sci Rep* 2017;**7**:3303.

174 Rambanapasi C, Zeevaart JR, Buntting H, et al. Bioaccumulation and subchronic toxicity of 14 nm gold nanoparticles in rats. *Molecules* 2016;**21**.

175 Choi K, Riviere JE, Monteiro-Riviere NA. Protein corona modulation of hepatocyte uptake and molecular mechanisms of gold nanoparticle toxicity. *Nanotoxicology* 2017;**11**:64-75.

176 Yarjanli Z, Ghaedi K, Esmaeili A, Rahgozar S, Zarrabi A. Iron oxide nanoparticles may damage to the neural tissue through iron accumulation, oxidative stress, and protein aggregation. *BMC Neurosci* 2017;**18**:51.

177 Valdiglesias V, Fernandez-Bertolez N, Kilic G, et al. Are iron oxide nanoparticles safe? Current knowledge and future perspectives. *J Trace Elem Med Biol* 2016;**38**:53-63.

178 Zou J, Wang X, Zhang L, Wang J. Iron nanoparticles significantly affect the in vitro and in vivo expression of Id genes. *Chem Res Toxicol* 2015;**28**:373-83.

179 Wu Q, Jin R, Feng T, et al. Iron oxide nanoparticles and induced autophagy in human monocytes. *Int J Nanomedicine* 2017;**12**:3993-4005.