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Biomimetic Nanoparticle Applications for Treatment of Atherosclerosis

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Abstract

Atherosclerosis is the leading cause of myocardial infarctions, or heart attacks. To combat atherosclerosis, current regenerative medicine and tissue engineering research focuses on using nanoparticles to repair damaged arteries. Of the various types of nanoparticles, researchers have paid special focus on biomimetic nanoparticles for their long circulation times and ability to evade the immune system. Current treatment options for atherosclerosis contribute to disease management and symptom relief, but they fall short of regenerating the damaged vascular wall. Animal studies using biomimetic nanoparticles have shown promising results, but clinical trials lack the same level of enthusiasm. Continued research and innovative approaches toward nanoparticles hold great potential for transforming and improving patient outcomes. This review aims to establish a concrete understanding of the various biomimetic nanoparticle applications to atherosclerosis treatment.

Keywords: Atherosclerosis, Regenerative Medicine, Nanoparticles, Biomimetic Nanoparticles

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Introduction

Heart attacks remain a leading global health challenge. In the United States alone, one heart attack occurs every forty seconds, contributing to more than 800,000 cases annually (CDC, 2023). Many risk factors of heart attacks, such as hypertension, high LDL cholesterol, smoking, diabetes, obesity, and poor diet, can be taken care of with lifestyle changes.

Of these factors, high LDL cholesterol and obesity are major contributors to atherosclerosis, the buildup of plaque in arterial walls, causing roughly half the deaths in Western nations. Recent studies show about a quarter of American adults had elevated LDL, and over 70% were overweight or obese (Tsao et al., 2023).

Globally, coronary artery disease, a form of atherosclerosis, was responsible for 8.9 million deaths in 2015, accounting for roughly 15.6% of all global deaths (Roth et al., 2017). In 2023, heart disease claimed over 919,000 lives in the U.S. alone, costing the economy more than $418 billion in healthcare and lost productivity (CDC, 2023).

Even asymptomatic individuals can harbor significant coronary atherosclerosis, often undetectable without advanced imaging like coronary CT angiography (Strong et al., 1999). As a result, atherosclerosis remains a major driver of heart attacks, underscoring the need for early detection and innovative therapeutic approaches.

Atherosclerosis Pathogenesis

Atherosclerosis is a chronic, progressive disease of the arterial wall characterized by the buildup of plaques composed of lipids, inflammatory cells, and fibrous tissue. As seen in Figure

1, development involves a complex interplay of endothelial dysfunction, lipid accumulation, immune activation, and structural remodeling of the vessel wall (Figure 1).

Endothelium

The process typically begins with dysfunction of the vascular endothelium, the thin monolayer lining the interior of blood vessels. Under normal conditions, the endothelium regulates vascular tone, prevents thrombosis, and inhibits leukocyte adhesion. However, risk factors such as hypertension, cigarette smoking, hyperglycemia, and oxidative stress impair these protective functions.

Dysfunctional endothelial cells become more permeable and upregulate adhesion molecules, such as VCAM-1 and ICAM-1, facilitating the recruitment of circulating monocytes to the subendothelial space (Libby, 2021; Gimbrone & García-Cardeña, 2016). This initial insult primes the arterial wall for the development of atherosclerotic lesions.

Lipoproteins

Low-density lipoprotein (LDL) particles are the primary carriers of cholesterol in the bloodstream and play a crucial role in the development of atherosclerosis. In a dysfunctional endothelium, LDL particles infiltrate the intima and become trapped in the extracellular matrix.

These trapped lipoproteins undergo oxidative modifications, forming oxidized LDL (oxLDL), which is highly pro-inflammatory and cytotoxic (Tabas et al., 2007). OxLDL promotes further endothelial activation and serves as a chemotactic agent for monocytes, amplifying the

inflammatory cascade. Elevated circulating LDL, especially small, dense LDL particles, significantly increases atherogenic potential.

Inflammatory Cells

Monocytes adhere to activated endothelial cells and transmigrate into the intima, where they differentiate into macrophages. These macrophages engulf oxLDL and become foam cells, forming the fatty streak, the earliest visible atherosclerotic lesion (Moore et al., 2013).

Foam cells and other immune cells secrete pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), which sustain the local inflammatory response. T lymphocytes also participate by recognizing modified lipoproteins and releasing cytokines that further activate macrophages and vascular cells. This sustained inflammation plays a crucial role in the progression and destabilization of plaque.

Vascular Smooth Muscle Cells (VSMCs)

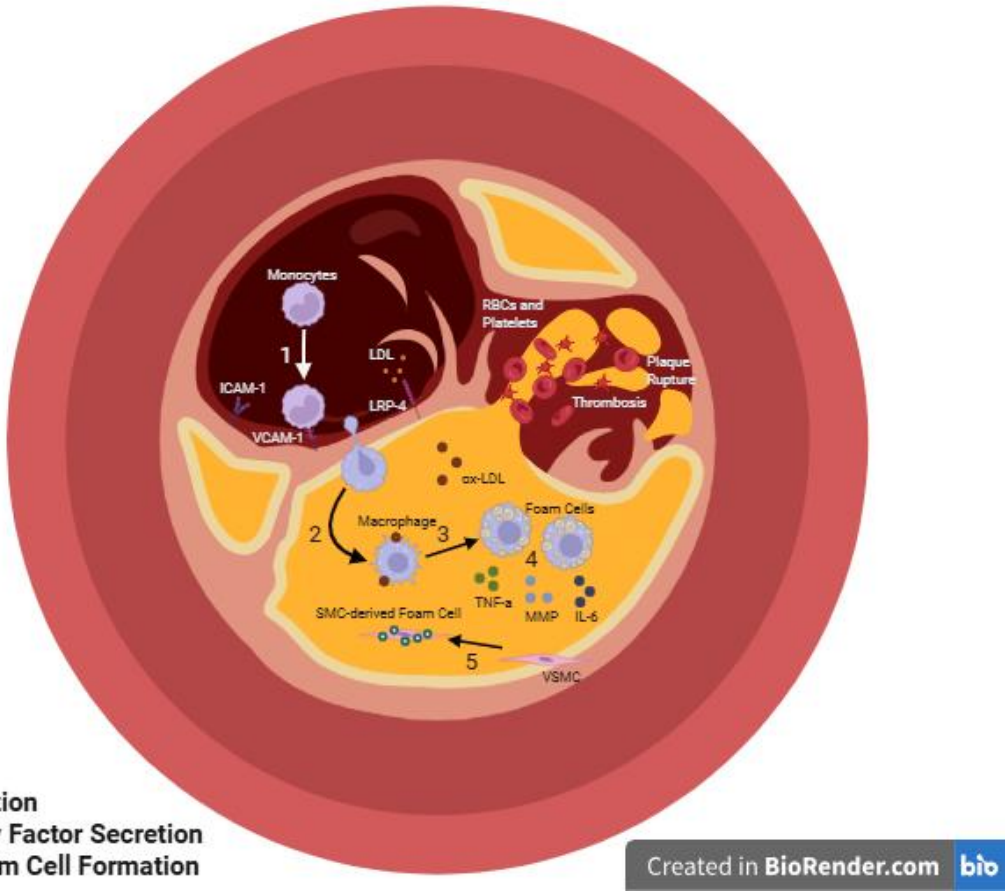
VSMCs, which normally reside in the tunica media, are recruited into the intima by growth factors and inflammatory mediators such as platelet-derived growth factor (PDGF). Once in the intima, VSMCs switch from a contractile to a synthetic phenotype, characterized by increased proliferation, migration, and extracellular matrix production (Bennett et al., 2016).

These cells synthesize fibrous components such as collagen and elastin, which form the fibrous cap over the lipid core, initially stabilizing the plaque. However, ongoing inflammation

and secretion of matrix-degrading enzymes (e.g., MMPs) can weaken the cap, making it prone to rupture. A thin fibrous cap over a large necrotic lipid core is the hallmark of vulnerable plaques, which are most likely to trigger thrombosis and acute myocardial infarction (Libby, 2021).

Figure 1

Atherosclerosis Pathogenesis



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Biomimetic Nanoparticles: The Frontier of Regenerative Medicine in Atherosclerosis

Nanoparticles are rapidly emerging as promising platforms for targeted therapy in atherosclerosis. They offer several advantages, including programmable size, shape, and surface chemistry; the ability to selectively target inflamed plaques or macrophages; enhanced delivery efficiency; and reduced off-target effects (Ou et al., 2020; Mulder, 2016; Liang et al., 2018; Bartusik-Aebisher et al., 2025).

Biomimetic nanoparticle designs have demonstrated superior plaque targeting, reduced systemic toxicity, improved biocompatibility, and supporting regenerative processes within vascular tissue by modulating key pathological mechanisms of atherosclerosis, including chronic inflammation, defective efferocytosis, and pathological neovascularization (Li et al., 2023; Feng et al., 2025).

As traditional treatments focus on symptom control rather than tissue repair, biomimetic nanoparticles offer a transformative approach by enabling precise, targeted delivery of therapeutic agents that actively promote vascular healing and support the restoration of healthy tissue architecture. The versatility of biomimetic nanoparticles paves the way for therapies that may promote the health of cardiac tissues, unlike existing treatments that merely slow down disease progression.

As our understanding of atherosclerosis deepens (particularly its molecular and cellular underpinnings) biomimetic nanoparticles could be tailored to target different stages of plaque development or specific subtypes of the disease, offering truly personalized therapeutic

strategies. With continued research and clinical validation, these particles may play a key role in revolutionizing cardiovascular treatment in the coming decades (Anghelache et al., 2024; Wang et al., 2019).

Animal Studies

Human atherosclerotic studies face ethical, logistical, and technical challenges, making it difficult to obtain ideal specimens. Consequently, animal models, primarily mice, rats, rabbits, pigs, and non-human primates, are used due to their comparable disease mechanisms and manageable experimental conditions (Getz & Reardon, 2016).

Mice, especially genetically modified strains such as ApoE-/-, are widely used due to their ease of handling, rapid reproduction, and suitability for genetic editing. $ApoE^{-/-}$ mice develop severe hypercholesterolemia and spontaneous atherosclerosis on a standard diet due to impaired clearance of remnant lipoproteins like VLDL and chylomicrons (Plump et al., 1992; Véniant et al., 2001). Their lesions form early and exhibit features such as inflammation and calcification, making them ideal for studying plaque progression and immune involvement (Zhang et al., 2002).

Passive systems such as Simvastatin/ECGC-coloaded liposomes (SE LNPs) and anti-IL-1β-loaded mesoporous silica nanoparticles (MSNs) have shown benefits in ApoE-/- mice by reducing oxidative stress, protecting endothelial cells, and lowering inflammation (Wan et al., 2023; Rong et al., 2024).

Ligand-mediated approaches enhance specificity in the mice. NLRP3 siRNA-loaded VCAM-1 liposomes target endothelial VCAM-1 to suppress inflammasome activation, while Naringenin-loaded, folic acid-coated nanoparticles (FA-LNPs/Nrg) cross intestinal barriers to bind folate receptor β on macrophages, reducing plaque burden (Jia et al., 2022; Guo et al., 2023). Similarly, VEGF/paclitaxel nanomotors use anti-VCAM-1 antibodies and light-triggered release to promote endothelial repair and inhibit inflammation (Li et al., 2021; Huang et al., 2022; Wu et al., 2023).

Some biomimetic coatings further improve nanoparticle targeting in animal studies. TRAF6i-HDL and Simvastatin-HDL nanoparticles exploit HDL binding to macrophage SR-B1 receptors, reducing inflammatory cell burden (Lameijer et al., 2018; Duivenvoorden et al., 2014). SHP1i-loaded macrophage membrane nanoparticles use natural chemotaxis to lesion sites, while Colchicine-coated macrophage-membrane PLGA nanoparticles stabilize plaques via VCAM-1 targeting (Sha et al., 2022; Li et al., 2022). Platelet-mimicking systems such as RAP-PNPs adhere to damaged endothelium and reduce plaque progression (Song et al., 2019).

Stimulus-responsive designs add precision; for example, a ROS-responsive simvastatin nanoprodrug with ticagrelor delivery activates in oxidative environments, inhibiting macrophage proliferation and exerting anti-inflammatory effects (Zhao et al., 2022). Together, these diverse strategies highlight the therapeutic potential of biomimetic nanomaterials in modulating inflammation, enhancing macrophage polarization, and stabilizing plaques in atherosclerosis.

Table 1

Animal Studies of Biomimetic Nanoparticles on ApoE-/- mice

Study	Biomimetic Nanomaterial	Targeting Strategy	Key Findings
Wan et al., 2023	Simvastatin/ECGC-coloaded liposomes (SE LNPs)	Passive target	Removes ROS, inhibits apoptosis, induces M2 polarization, and decreases inflammation cytokines
Jia et al., 2022	NLRP3 siRNA-loaded VCAM-1 binding peptide targeting cationic liposomes (siRNA PCLs)	VCAM-1 binding peptide target VCAM-1 on endothelial cells	Inhibits the formation of NLRP3 inflammasome, inhibiting any subsequent inflammatory reactions
Guo et al., 2023	Naringenin (Nrg)-loaded, folic acid-coated lipid-polymer nanoparticle (FA-LNPs/Nrg)	Folic acid mediated strid over the intestinal mucosal-epithelial barrier and targets the folate receptor β	Anti-inflammatory effects and reduce plaque burden

		on M1 macrophages.	
Li et al., 2021; Huang et al., 2022; Wu et al., 2023	Vascular endothelial growth factor/paclitaxel-loaded porous micro/nanomotor	Anti-VCAM-1 antibody targets VCAM-1 on endothelial cells	Release VEGF and paclitaxel under near-infrared light excitation, promotes endothelial proliferation, and has anti-inflammatory effects
Rong et al., 2024	Anti-interleukin-1β (anti-IL-1β)-loaded mesoporous silica nanoparticles MSNs at anti-IL-1β	Passive target	Protects vascular endothelial cells and inhibits VSMC proliferation
Xu et al., 2023	Rapamycin-loaded UiO-66-NH-FAM-IL-1Ra (RUFI)	IL-1Ra target macrophage	Promotes M2 polarization, induces autophagy, and has anti-inflammatory and antioxidizing effects
Lameijer et al., 2018	TRAF6i-HDL	HDL target scavenger receptor type B-1	Reduces monocyte migration

		(SR-B1) on macrophages	
Duivenvoorden et al., 2014	Simvastatin-loaded high-density lipoprotein (S-HDL) nanoparticles	HDL target scavenger receptor type B-1 (SR-B1) on macrophages	Clears excessive inflammatory cells and reduces plague burden
Song et al., 2019	Rapamycin-loaded, platelet membrane-coated nanoparticles (RAP-PNP)	Adhesion of platelets to damaged vascular endothelium	Anti-inflammatory effects and reduce plaque burden
Sha et al., 2022	SHP1i-loaded, macrophage membrane-coated biomimetic nanoparticle	The inherent protein on the macrophage membrane ensures an active chemotaxis towards the inflammatory lesion sites	Enhances efferocytosis and stabilizes atherosclerosis

Li et al., 2022	Colchicine-loaded, modified macrophage-membrane (MMM)-coated PLGA nanoparticles	Integrin $\alpha 4/\beta 1$ targets VCAM-1 on vascular endothelial cells	Has strong anti-inflammatory effects and stabilizes vulnerable plaques
Zhao et al., 2022	ROS-responsive simvastatin nanoprodrug with ticagrelor-loaded drug delivery system	ROS-responsive and fibronectin-targeted	Has anti-inflammatory and antioxidant effects; inhibits macrophage proliferation

Clinical Studies

Clinical trials investigating nanoparticle-based therapies for atherosclerosis remain limited and largely in early-phase development due to several biological, technical, and regulatory challenges. One major hurdle is the complexity of atherosclerotic plaque biology, which involves diverse cellular and molecular processes that are difficult to replicate and effectively target in humans.

Although animal models have shown promising results, translating these findings into clinical efficacy has proven challenging. For instance, while liposomal prednisolone effectively reduced inflammation in animal models, it failed to show significant anti-inflammatory effects in human patients due to differences in plaque composition and immune response (van der Valk et al., 2015). Moreover, nanoparticles must navigate a complex in vivo environment, including

avoiding rapid clearance by the reticuloendothelial system and ensuring selective accumulation in atherosclerotic plaques, which remains a formidable task (Mulder et al., 2016).

Additionally, regulatory barriers and safety concerns hinder the progress of clinical trials. Since atherosclerosis typically develops over decades, demonstrating meaningful therapeutic benefit within a limited trial duration is difficult. There are also concerns about off-target effects, long-term toxicity, and the immunogenicity of nanoparticle materials (Gould et al., 2023).

As a result, most clinical investigations have focused on proof-of-concept studies, such as improving cholesterol efflux capacity or delivering anti-inflammatory agents, rather than evaluating hard cardiovascular outcomes. Despite these limitations, the ongoing refinement of nanoparticle design and targeting strategies, coupled with advances in imaging and molecular diagnostics, suggests that clinical translation remains a promising but gradual endeavor (Choi et al., 2020).

CSL112 is a reconstituted HDL nanoparticle administered via a 2-hour intravenous infusion. As shown in Figure 2, it consists of disc-shaped phosphatidylcholine molecules that function as an HDL mimetic by delivering apolipoprotein A-I (ApoA-I) to promote cholesterol efflux from macrophages to the liver (Figure 2). In a Phase 2a clinical trial involving patients with atherosclerosis, CSL112 was shown to be safe and effectively increased cholesterol efflux capacity, with a strong enhancement of ABCA1-dependent cholesterol efflux. These results are promising and represent an improvement over previous HDL mimetics such as CER-001 and MDCO-216 (Gille et al., 2018).

CER-001 is an HDL mimetic nanoparticle administered via intravenous infusion, composed of recombinant apolipoprotein A-I combined with sphingomyelin and dipalmitoyl- phosphatidylglycerol. It is designed to promote reverse cholesterol transport (RCT) by mimicking natural HDL particles. However, early-stage clinical trials have not demonstrated significant reductions in plaque volume, indicating limited efficacy in plaque regression to date (Tardif et al., 2014).

MDCO-216 is an HDL mimetic nanoparticle administered via intravenous infusion, containing the ApoA-I Milano variant, a naturally occurring mutant form of apolipoprotein A-I thought to have enhanced cardioprotective properties. Despite its promising design, a Phase I clinical trial showed no significant reduction in atherosclerotic plaque, indicating limited efficacy in plaque regression at this stage (Mishra et al., 2020).

Liposomal prednisolone (LN-PLP) is administered via intravenous infusion using PEGylated liposomes, which are designed to circulate in the bloodstream for extended periods. The PEGylation facilitates passive targeting, allowing the nanoparticles to accumulate within plaque macrophages by exploiting leaky neovessels and monocyte uptake mechanisms. In human clinical studies, LN-PLP successfully accumulated in plaque macrophages, demonstrating the feasibility of targeted nanomedicine delivery to atherosclerotic lesions. However, despite effective localization, a short-term clinical trial revealed no significant anti-inflammatory efficacy, indicating that while the delivery system shows promise, further optimization is needed to achieve therapeutic benefits (van der Valk et al., 2015).

Table 2

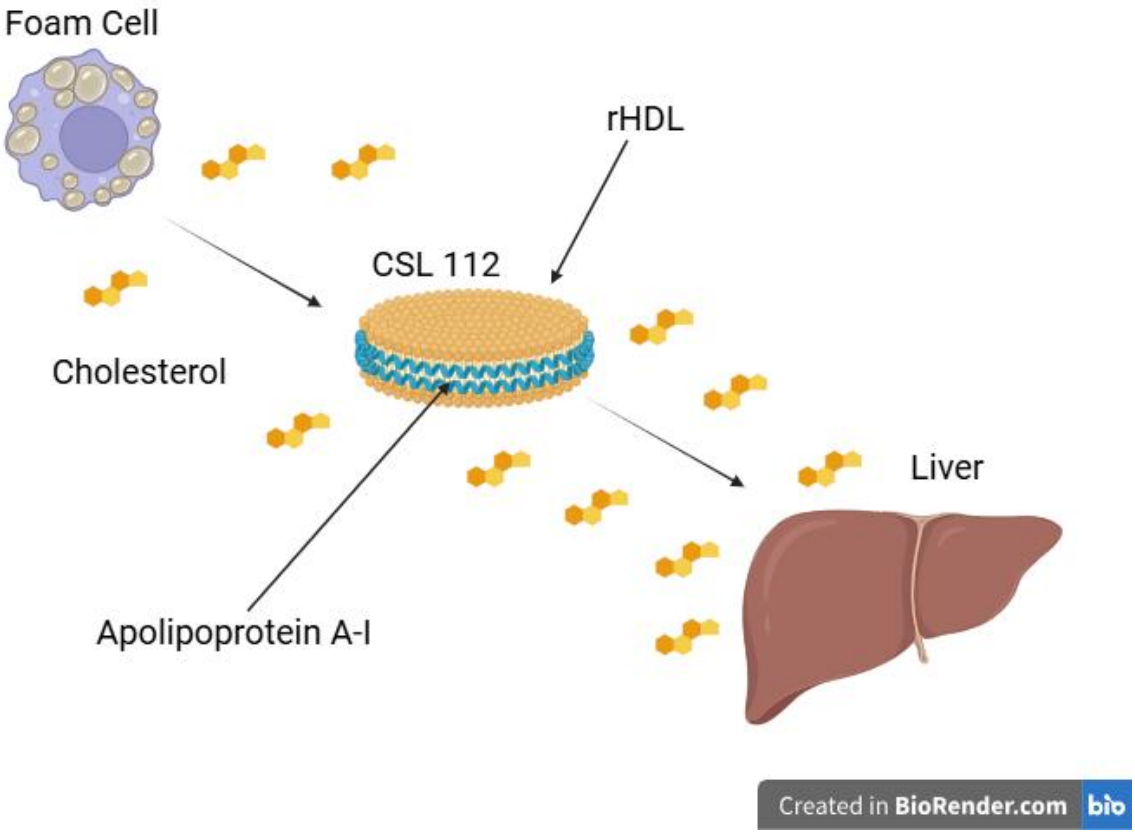
Clinical Studies of Biomimetic Nanoparticles

Study	Therapy / Nanocarrier	Application Method	Modality	Targeting Strategy	Key Findings
Gille et al., 2018	CSL112	Intravenous infusion	Cholesterol efflux enhancer	Mimics HDL function	Safe, Phase III ongoing, aims to reduce CV events
Tardif et al., 2014	CER-001	Intravenous infusion	Reverse cholesterol transport	HDL mimic	No significant plaque regression in trials
Mishra et al., 2020	MDCO-216	Intravenous infusion	HDL mimetic	ApoA-I Milano variant	No significant plaque reduction (Phase I)

van der Valk et al., 2015	Liposomal Prednisolone	Intravenous infusion	Anti-inflammatory drug delivery	Macrophage-targeted	No significant anti-inflammatory effects

Figure 2

CSL112 Targeting Strategy



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Limitations and Future Directions

There are several limitations with the current treatment options for atherosclerosis. While lifestyle changes, medications, angioplasty, bypass grafting, and stenting all contribute to disease management and symptom relief, they fall short of regenerating the damaged vascular wall. This recognition has sparked interest in regenerative medicine and tissue engineering, aiming not just to manage but to repair damaged arteries using nanotechnology-based strategies. A special focus in the field is spent on biomimetic nanoparticles due to their long circulation times and ability to remain undetected by the immune system.

Despite their promising advantages, several challenges must be overcome before biomimetic nanoparticles can be widely used in clinical settings. One major hurdle is the complexity of manufacturing these systems at scale while maintaining consistency and stability. The process of harvesting, purifying, and coating cell membranes onto nanoparticles requires sophisticated techniques and rigorous quality control (Li, 2023). Additionally, ensuring the long-term storage stability and bioactivity of the coated nanoparticles remains a technical obstacle.

Another critical aspect is the potential for immunogenicity or unintended biological interactions. Although biomimetic coatings are designed to evade immune detection, there is still a risk that the body could mount an immune response, especially with repeated administrations. Furthermore, the dynamic nature of the circulatory system and the complex composition of atherosclerotic plaques pose challenges for ensuring that the nanoparticles reach their intended target effectively and consistently in all patients (Gao et al., 2020; Wang et al., 2021).

Theranostics (nanoparticles that combine therapeutic and diagnostic functions) present a promising strategy for managing atherosclerosis. These multifunctional particles can deliver drugs to inflamed plaques while enabling real-time imaging, improving precision and reducing systemic side effects (Mulder et al., 2014). By targeting inflammatory markers like VCAM-1 or CD36, they help localize treatment to active lesions.

Looking ahead, future nanoparticle therapies will focus on stimuli-responsive systems, gene-silencing technologies, and biodegradable carriers for safer and more effective interventions. Nanoparticles that release drugs in response to local triggers (e.g., low pH or enzyme activity) and those delivering siRNA to silence pro-atherogenic genes are under development (Chatzizisis et al., 2021). Integration with AI and wearable diagnostics could further support real-time, personalized cardiovascular care.

Conclusion

In conclusion, while current treatments for atherosclerosis (such as drugs, angioplasty, and stents) have reduced acute events, they mainly manage symptoms without addressing underlying vascular damage (Libby, 2021). These approaches lack regenerative capacity and fail to prevent long-term plaque progression. Nanotechnology offers a promising alternative, with nanoparticles delivering anti-inflammatory or lipid-lowering agents directly to plaques in preclinical models, showing improved targeting and reduced toxicity (Mulder et al., 2014; Beldman et al., 2020). This suggests a shift toward disease-modifying therapies rather than symptomatic relief.

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