

How Advanced is Nanomedicine to Treat Atherosclerosis? A Comprehensive Review of the Literature

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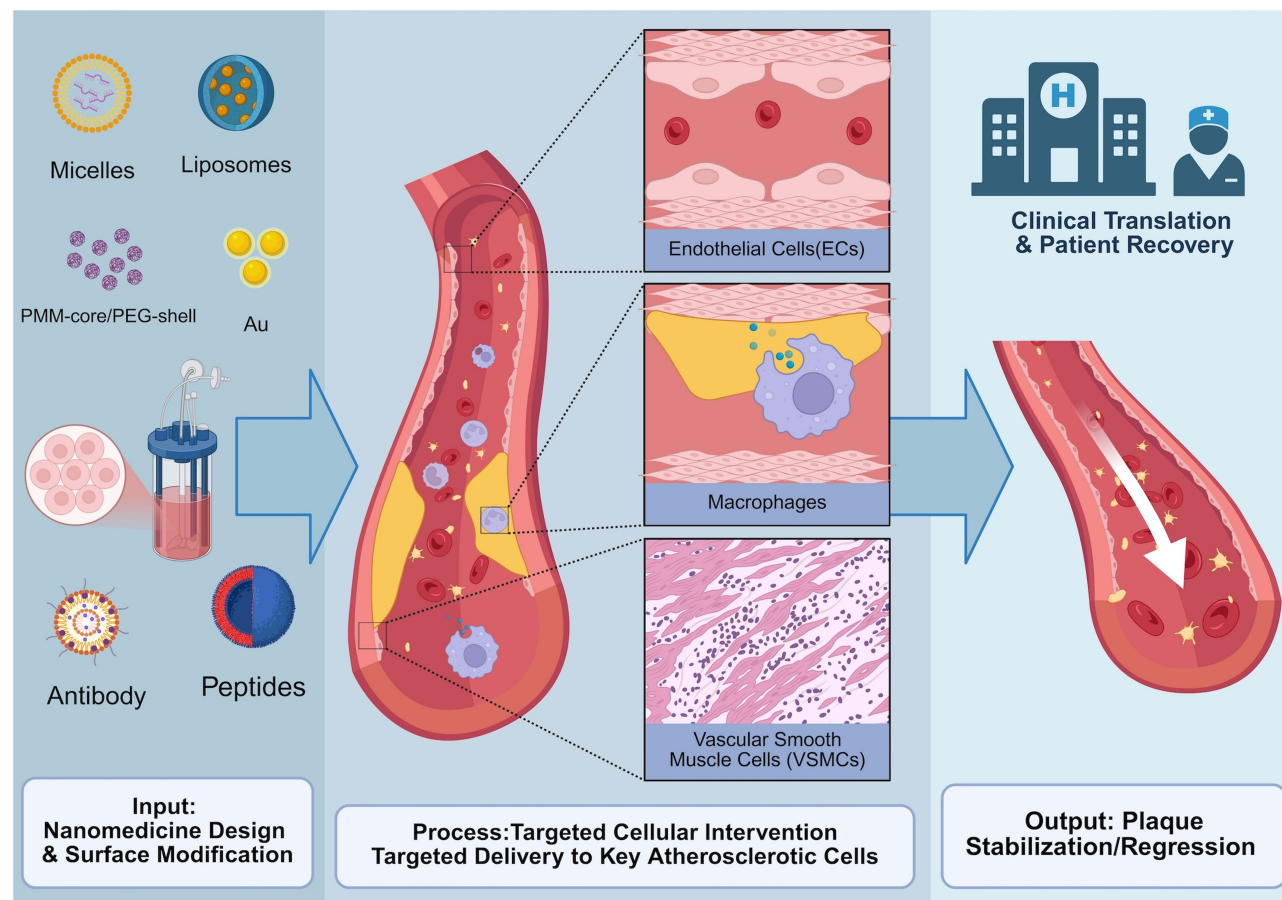
Abstract: Atherosclerosis (AS) is a major underlying cause of cardiovascular disease. Rupture of unstable atherosclerotic plaques can induce severe acute cardiovascular events and sudden cardiac death. Therefore, developing targeted interventional therapies for atherosclerotic plaques is clinically important to improve cardiovascular mortality. With the advancement of nanomedicine, nanomaterials have demonstrated great potential in atherosclerosis treatment due to their unique compositional/structural features, synthesis strategies, and surface modifications. Based on the pathological characteristics of atherosclerotic plaques, the design and preparation of stimulus-responsive, surface-functionalized, and conditionally-released nanomaterials have become an important approach to achieving precise intervention for atherosclerotic lesions. Considering the pathological features of different cell types involved in AS progression, this review describes the targeting strategies, structural and functional designs, and potential mechanisms of action of targeted nanotherapies in the treatment of atherosclerosis. By summarizing representative recent studies in detail, we reveal the intrinsic interactions and relationships between current targeted nanotherapies and atherosclerotic plaques. Finally, this review provides an outlook on the future application of nanomaterials by presenting key scientific questions that have not yet been addressed, to advance the clinical translation of targeted nanotherapies for atherosclerosis.

Keywords: atherosclerosis, nanomaterials, targeted therapies

Introduction

The prevalence of atherosclerotic cardiovascular disease is on the rise worldwide, leading to morbidity and mortality.^{1,2} Atherosclerosis is an inflammatory disease of the arteries, characterized by plaque formation, lipid accumulation, and intimal thickening.³ The disease onset begins with endothelial dysfunction in the arterial vasculature, followed by lipid accumulation, fibrous tissue proliferation, and calcification. Atherosclerotic plaques are formed when smooth muscle cells proliferate and immune cells invade vessels.^{4,5} In AS, high levels of low-density lipoprotein (LDL) are the main risk factor.⁶ Activation of endothelial cells and recruitment of monocytes into the subendothelial space is caused by cholesterol and oxidized phospholipids in these lipoproteins. As monocytes differentiate into pro-inflammatory macrophages, they amplify local inflammation. Atherosclerotic lesion progression is also accelerated by macrophage phagocytosis of lipoproteins in the intima, which leads to lipid-rich foam cells.⁷⁻⁹ Atherosclerotic lesions progress to an advanced stage characterized by increased macrophage apoptosis and defective clearance of apoptotic cells when the pro-

Graphical Abstract



inflammatory state persists.^{10,11} Atherosclerotic plaques can be classified as either stable or unstable. Plaques that are unstable have a thin fibrous cap that can rupture under dynamic changes in blood flow, resulting in clot formation. As a result of these clots, the heart, brain, and other organs are severely impeded, leading to coronary artery disease, strokes, and peripheral artery disease.^{5,12}

Currently, the treatment of AS consists primarily of pharmacological and surgical interventions.¹³ Pharmacological treatment relies heavily on lipid-lowering therapies, including statins and PCSK9 inhibitors.^{14,15} The adverse effects of poor drug targeting include gastrointestinal reactions, liver damage, and muscle damage.^{16,17} In patients with severe AS, surgical interventions, such as stenting or vascular bypass, are typically reserved. Restenosis is the most common side effect of surgery, which negatively impacts long-term outcomes.^{18,19} Therefore, there is an urgent need for targeted drugs with high efficacy and low side effects for the treatment of AS.

The emergence of nanotechnology brings new directions to AS treatment.²⁰ Nanomedicines possess ultra-small nanostructures with active surface properties, which enhance the therapeutic effects of drugs compared to traditional formulations.²¹ The use of nanocarriers can solve various challenges in free drug delivery. Nanocarriers can enhance the solubility and stability of insoluble drugs, as well as improve their dissolution or release properties, which increases their bioavailability.^{22–24} Further, nanocarriers can enhance the selectivity of drugs to specific tissues, organs, or cells, enabling new routes for drug delivery.^{25,26} In various disease areas, such as cardiovascular disease, bacterial and viral infections, and malignant tumors, nanocarriers show great potential for application through rational design.^{27–29} AS begins at the cellular level, so the anatomical features and inflammatory changes in diseased arterial regions provide

many opportunities for nanomedicine. Biological, physical, and chemical modifications on the surface of nanoparticles can improve targeting capabilities and are expected to be utilized for precision-targeted therapy of atherosclerotic lesions. This review focuses on the advances, challenges, and prospects of targeted nanomaterials in AS therapy (Figure 1).

How Nanotherapeutics Can Treat Atherosclerosis

Nanomaterials offer a robust drug delivery system for treating AS (Figure 2). Drug delivery via intravenous injection is the most direct and effective way to treat AS. However, the therapeutic efficacy of nanomedicines is significantly compromised by nonspecific removal through the mononuclear phagocyte system (MPS).^{34,35} MPS can affect nanocarrier biodistribution and blood circulation time, often causing a decrease in nanocarrier concentration in the bloodstream through phagocytic clearance.³⁶ AS is a vascular condition where reduced drug levels in the blood vessels can greatly diminish the treatment's effectiveness at the plaque sites. The tight junctions of the normal endothelium limit the distribution of nanomaterials, and the large gaps present in damaged endothelial cells allow nanomaterials to accumulate. The heightened permeability of the endothelium in an atherosclerotic blood vessel enables nanomaterials to be passively directed to the AS, utilizing the enhanced permeability and retention (EPR) effect due to the damaged vessel.^{37–39} Targeting the AS microenvironment with responsive nanomaterials is a strategy that has emerged in recent years, and they achieve passive targeting in atherosclerotic plaques through pH-responsiveness and ROS-responsiveness.⁴⁰ In

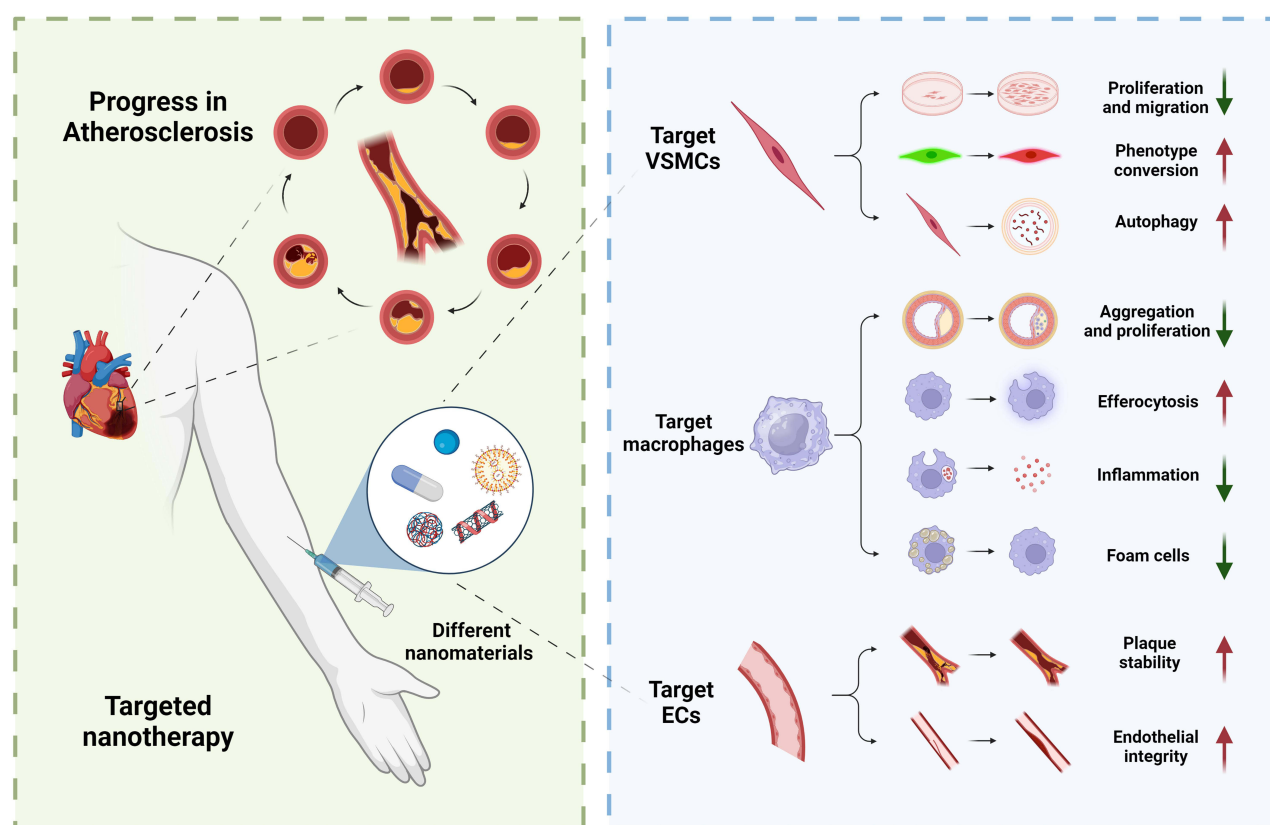


Figure 1 Overview of targeted nanotherapeutic strategies for atherosclerosis. This schematic summarizes how nanomedicines are used to intervene across atherosclerosis progression and highlights three major plaque-associated cellular targets. Left panel: disease evolution is illustrated from early endothelial activation and lipid deposition to plaque growth and complication, together with a representative clinical delivery route (systemic administration) for nanomaterial-based therapeutics. Right panel: three principal cellular targets within lesions are depicted—vascular smooth muscle cells, macrophages, and endothelial cells—with key therapeutic objectives aligned to each target. For vascular smooth muscle cells, nanotherapeutic strategies aim to reduce proliferation and migration, modulate maladaptive phenotypic switching, and enhance protective autophagy to mitigate neointimal formation. For macrophages, approaches focus on limiting recruitment and proliferation, reducing inflammatory activation and foam-cell formation, and restoring efferocytosis to constrain necrotic core expansion. For endothelial cells, nanotherapies are designed to improve endothelial integrity, suppress leukocyte adhesion and endothelial inflammation, and thereby support plaque stabilization. Arrow annotations indicate the intended therapeutic direction (upward arrows denote enhancement; downward arrows denote suppression).^{13,30–33}

Assembly of nanomaterials

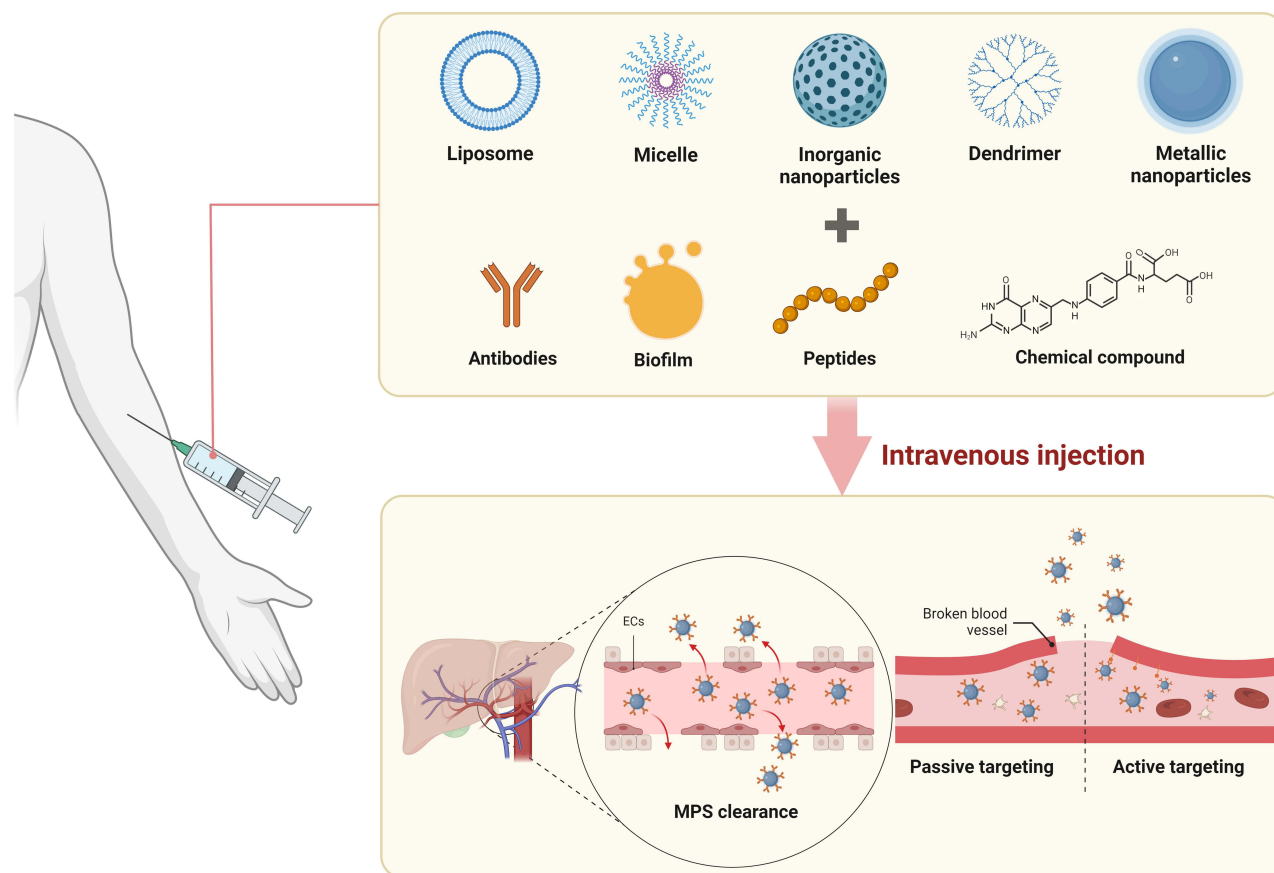


Figure 2 Assembly, systemic administration, and biodistribution fates of nanomedicines for atherosclerosis. This schematic summarizes how nanomedicines are constructed and how they distribute after systemic administration, highlighting major barriers and targeting routes relevant to atherosclerosis therapy. The upper panel depicts representative nanocarrier backbones (liposomes, polymeric micelles, dendrimers, and inorganic/metallic nanoparticles) that can be functionalized with antibodies, biomimetic coatings, targeting peptides, or small-molecule cargos to modulate stability and circulation. The lower panel illustrates the post-injection fate of nanomedicines in blood: many particles are opsonized and cleared by the mononuclear phagocyte system (MPS), mainly in the liver and spleen, and this clearance is influenced by hydrodynamic size, surface chemistry, and protein Corona formation. Particles that partially evade MPS uptake may reach plaques through passive targeting associated with increased endothelial permeability and retention in inflamed regions, or through active targeting via ligand–receptor interactions with endothelial adhesion molecules, extracellular matrix components, or receptors on plaque-associated cells.^{44–49}

addition, some natural nanocarriers mainly include heat shock proteins, ferritin nanocages, and high-density lipoprotein (HDL),^{41–43} which can evade MPS, and has also been used in the diagnosis and treatment of AS.

However, the efficiency of passive targeting is not sufficient to ensure the accumulation of nanomaterials at a single specific site. Nanomaterials for AS therapy still face delivery challenges. Active targeting strategies have addressed this problem to some extent.⁵⁰ Receptors such as MSR-A, SR-BI, and CD-36 located on macrophages, mannose receptors like CD206, endothelial markers such as VCAM-1, indicators of new endothelial growth within plaques (like integrins $\alpha\beta3$), and type IV collagen found on the surface of advanced plaques can act as key targets to guide nanomaterials precisely to plaques, enabling focused therapeutic action.⁵¹ Following intravenous injection, biomolecules adhere to the nanomaterial surfaces, leading to charge development, which is vital for influencing the pharmacokinetics, biodistribution, and cellular absorption of nanomaterials.⁵² Surface modification of nanomaterials with polymers (eg, polyethylene glycol) or biomimetic materials (eg, biofilm encapsulation) can alter their charge attraction, enabling specific biodistribution and escape from the MPS.^{53–56} Peptides, generally made up of between 2 and 50 amino acids, play a significant part in many biological processes. Because they can self-assemble and selectively interact with specific receptors, peptides have found successful applications in both targeted therapies and diagnostic tools.^{57,58} These targeted peptides are ideal candidates for delivering

drugs specifically and are increasingly used alongside nanomaterials to treat AS.^{59,60} Their low likelihood of inducing toxicity or adverse reactions in other tissues and organs ensures a high level of biosafety.⁵³

After entering the blood circulation, the effective accumulation of nanomaterials in the atherosclerotic plaque region is dependent on the EPR effect.³⁸ Specifically, for nanoparticles to reach the subendothelial plaques, they must first move through the compromised vascular lining or openings within the neointima. During this process, attributes such as nanoparticle dimensions, electrical charge, morphology, elasticity, chemical makeup, and the presence of specific surface groups and ligands play a role in determining how effectively they gather in atherosclerotic plaques.⁶¹ More importantly, as atherosclerosis progresses, the damaged endothelial connections tend to become intact, which also affects the accumulation of nanomaterials.^{37,62} When nanoparticles gather within atherosclerotic lesions, they are absorbed by different cells in the plaque's microenvironment. This process involves recognition via targeted proteins or specific ligands on the nanoparticle surface.^{50,63–65} Successful uptake of nanoparticles is essential for boosting therapeutic outcomes, as many treatments delivered by nanoparticles are intended to interact with intracellular structures and compartments. This becomes particularly crucial for molecular payloads like siRNAs and miRNAs, which participate in RNA interference pathways and require endosomal release followed by cytoplasmic delivery post-uptake.^{66–68}

From a translational standpoint, nanotherapeutics for atherosclerosis should be positioned as adjuncts to contemporary standard-of-care (statins/ezetimibe/PCSK9 inhibitors and antithrombotic regimens), with a clearly defined clinical use-case (eg, early plaque control vs secondary prevention after an acute coronary event). One important signal that the field is moving toward clinically testable hypotheses is that plaque biology-motivated mechanisms (eg, boosting cholesterol efflux capacity) have already been evaluated in large post-myocardial infarction populations using biologic infusion strategies, such as CSL112 (apolipoprotein A-I) in the AEGIS-II program.⁶⁹ While the AEGIS-II results underscore that mechanistic plausibility does not automatically translate into short-term MACE reduction, they also provide a practical blueprint for nanomedicine translation: define a high-risk window, select endpoints that are clinically accepted, and align dosing/feasibility with real-world practice. For nanocarriers, this implies that route of administration, dosing frequency, manufacturability, and safety monitoring must be discussed alongside efficacy, and that early translational studies should incorporate clinically relevant readouts (eg, plaque inflammation imaging, lipid biomarkers, and vascular event surrogates) rather than relying solely on histology at a single terminal time point.

How Precise is Advancing Nanomedicine to Treat Atherosclerosis?

Nanomaterials are often sized between 1 and 100 nanometers, comparable to biological macromolecules. Unlike bulk materials, nanomaterials vary in their inherent physical properties. Examples of frequently used nanomaterials include liposomes, micelles, dendrimers, and nanoparticles composed of metals or inorganic substances.⁷⁰ Currently, most nanomedicines are based on liposomal nanomaterials.⁷¹ Doxil (polyethylene glycol-coated liposomal doxorubicin) was the first liposome with extended circulation to receive approval from the US Food and Drug Administration (FDA) for cancer treatment.⁷² Lipid nanomaterials, particularly liposomes, are widely applied in the treatment of AS. These liposomes, consisting of a double-layered lipid membrane, are traditional carriers for nanomedicines. Depending on whether the internal environment of the liposomes is hydrophilic or lipophilic, they can transport a variety of therapeutic agents.⁷³ In recent years, with breakthroughs in delivery systems, chemical modifications, and other key technologies, nucleic acid drugs have developed rapidly.⁷⁴ One major issue with external nucleic acids, especially RNA types such as siRNAs and miRNAs, is that they are quickly broken-down during transit and face challenges in penetrating the membrane of target cells. Encapsulation of nucleic acids in positively charged liposomes overcomes these difficulties, allowing them to be active within the target cells.⁷⁵ Therefore, to precisely deliver drugs in atherosclerotic plaques, nanomaterials need to be further designed and modified to better utilize their therapeutic effects. Collectively, these material platforms illustrate the expanding functional repertoire of nanomedicine, although their translational maturity varies substantially depending on compositional complexity, manufacturability, and safety profiles.

In AS, the assembly of nanomaterials is usually determined by the purpose of use, including the nanomaterial itself, the loader, and the targeting strategy. To mimic the function of natural mimetic organisms as much as possible, nanomaterials frequently incorporate functional elements like lipid molecules and proteins. The construction of nanocarriers involves straightforward techniques, such as incubation, chemical bonding, and other methods.⁷⁶ For instance,

exosomes have been developed to transport drug proteins and nucleic acids. As components within an organism, exosomes contain a wide range of biological information, which facilitates their ability to perform additional roles.⁷⁷ Nevertheless, the complex nature of natural exosomes can lead to unexpected challenges, as many components may not be essential for effective delivery. A viable alternative is exosome mimics synthesized through the assembly of lipid molecules and functional proteins.⁷⁸ Moreover, nanocarriers composed of hyaluronic acid (HA) and poly (lactic-co-glycolic acid) (PLGA) are frequently utilized to carry natural substances for AS therapy.^{37,79,80} Metallic and inorganic nanomaterials with enzyme-like activity have enhanced stability and functionality as nanocarriers.⁸¹ Artificial nanoenzymes with enhanced catalytic efficiency have been developed to overcome the inherent limitations of natural enzymes, which are crucial for sustaining physiological functions in living organisms.⁸² Some early investigations suggest that these enzyme analogs could function as effective tools for numerous biomedical disorders, especially those involving inflammation.^{83,84} The FeN3P-SAzyme, a monoatomic iron-based nanoenzyme, modifies the electronic characteristics of the iron's active core through the targeted coordination of nitrogen and phosphorus, giving it a strong peroxidase-like catalytic activity.⁸⁵ In addition, Pd nanozyme,⁸⁶ gold nanoparticles,⁸⁷ cyclodextrins (CD),⁸⁸ and carbon-based nanomaterials⁸⁹ have seen extensive application in managing inflammatory diseases.

Nanomaterials offer large surface area-to-volume ratios, enabling versatile drug loading strategies.⁹⁰ Statins remain the most commonly loaded drugs for AS therapy.⁹¹ Gao et al introduced reactive oxygen species-responsive nanoparticles (MM-NPs), encapsulated in a macrophage membrane, to deliver atorvastatin (MM-AT-NPs). This biomimetic approach not only reduced nanomaterial removal by the MPS but also targeted inflamed areas, allowing atorvastatin to be selectively released in response to ROS. The sequestration of inflammatory cytokines by macrophage membranes enhances the therapeutic efficacy of MM-AT-NPs in treating AS.⁵⁶ Building on this ROS-rich plaque microenvironment, ROS-responsive theranostic nanoplateforms, typically constructed with a ROS-degradable polymeric shell and lipid-affinitive components, enable plaque-localized drug release (eg, site-specific delivery of prednisolone) while supporting plaque imaging, and have been reported to reduce macrophage infiltration, inflammatory cytokine expression, and lipid accumulation, thereby decreasing overall plaque burden. Beyond ROS-triggered drug release, ROS-responsive size-reducible nanoassemblies have been reported to undergo in situ size reduction within ROS-rich plaque microenvironments, thereby improving deep plaque penetration and macrophage uptake, which translates into reduced lipid deposition, suppressed inflammatory signaling, and an overall decrease in plaque burden.⁹² Along the same rationale, macrophage membrane-camouflaged ROS-responsive rapamycin nanoparticles preferentially accumulate in inflamed plaques and release rapamycin in a ROS-triggered manner, thereby suppressing macrophage activation and smooth muscle cell proliferation.⁹³ Similarly, macrophage membrane-coated, ROS-responsive hyaluronic acid nanoparticles have been reported to enhance plaque accumulation and macrophage uptake while evading immune clearance; ROS-responsive release further promoted cholesterol efflux and attenuated inflammation, leading to reduced plaque growth compared with non-coated controls.⁹⁴ Notably, even without an explicit enzymatic/oxidative trigger, macrophage membrane-camouflaged PLGA nanoparticles can prolong circulation and enhance plaque accumulation in ApoE^{-/-} mice, and rapamycin delivery via this biomimetic platform reduces macrophage infiltration and smooth muscle cell proliferation, thereby decreasing plaque area and improving plaque stability.⁹⁵ During the early stages of AS, activated endothelial cells exhibit increased levels of adhesion molecules and chemokines, facilitating leukocyte recruitment. Thus, drugs that reduce the inflammatory response can reduce disease progression. The most common drugs are rapamycin (RAP)⁹⁶ and paclitaxel.⁹⁷ RNA interference (RNAi) therapy, a cutting-edge method, shows great potential in combating cardiovascular diseases. Small interfering RNAs (siRNAs) can suppress the expression of specific cellular genes or cause the degradation of their mRNAs, interfering with disease progression at the genetic level.⁹⁸ Combining siRNAs with nanocarriers effectively avoids the fate of siRNAs being degraded, improving their therapeutic efficacy and prolonging the duration of treatment at disease sites.⁹⁹ MicroRNAs (miRNAs) are small, non-coding RNA sequences that control gene expression post-transcriptionally by interacting with the 3'-untranslated region (UTR) of target mRNAs, either blocking or breaking them down. Therefore, many studies have also used miRNAs as drug therapy for AS.^{68,100} Notably, while small-molecule-loaded nanocarriers often benefit from well-established pharmacology, nucleic acid-based formulations face additional translational hurdles related to stability, immune activation, and dose optimization.

Achieving targeted drug delivery remains a central challenge in clinical therapy. Surface modification and biomimicry substantially enhance nanocarrier targeting capability.^{101,102} Tao et al constructed a nanomaterial using PLGA polymers to achieve macrophage targeting in atherosclerotic plaques by recognizing macrophage receptor stabilizing protein-2 through a peptide called S2P.⁵³ Li et al Binding of vesicles to platelet membranes to achieve AS targeting.¹⁰³ Disruption of the endothelial layer, leading to exposure of the subendothelial matrix, causes rapid platelet adhesion to the injured endothelium.¹⁰⁴ The key initial step involves the interaction of the GP Ib-IX-V complex with vascular hemophilic factor (vWF) in exposed subendothelial cells, along with a lesser involvement of platelet receptors (GPVI and integrin $\alpha 2\beta 1$) binding to collagen.^{104,105} In addition, neutrophil membranes,¹⁰⁶ macrophage membranes,¹⁰⁷ and erythrocyte membranes¹⁰⁸ are widely used for targeted delivery nanocarriers. Although these strategies markedly improve plaque specificity, they also introduce added design and regulatory complexity that must be balanced against incremental gains in targeting precision.

To evaluate “how advanced” atherosclerosis nanomedicine truly is, it is useful to distinguish (i) robust preclinical efficacy, (ii) clinically realistic dosing, and (iii) alignment with endpoints that matter in patients. Encouragingly, several platforms have begun to address feasibility explicitly by testing durable efficacy windows and practical dosing schedules. For example, miRNA-based nanotherapy has been evaluated not only for plaque reduction but also for durability after a single administration and, more recently, under dosing schedules framed as clinically feasible.^{109,110} Such designs help bridge the gap between proof-of-concept and translational plausibility by directly confronting a core constraint of chronic disease therapy: sustained benefit with acceptable treatment burden. At the same time, clinical experience from non-nanoparticle biologic strategies reminds the field that translation is ultimately endpoint-driven; even when a therapy is mechanistically coherent, demonstrating reductions in hard outcomes can be challenging in short follow-up windows.⁶⁹ Therefore, in addition to summarizing nanomaterial innovation, the revised discussion should explicitly emphasize what kind of evidence would move the field forward (eg, standardized reporting of plaque targeting, immune safety, and dose–response; longitudinal imaging; and harmonized inflammatory readouts), and clarify which strategies are closest to trial-ready implementation based on dosing feasibility, manufacturability, and safety signal strength.

Nanotherapies Target Cells Within Plaques

The pathogenesis of AS involves multiple steps, lipid deposition, damage to the endothelium, inflammatory responses, platelet accumulation, and thrombosis. Based on the individual components involved in AS disease progression, nanotherapies have carried out multiple targeting strategies respectively. This section will review the therapeutic strategies that focus on using nanomaterials to target vascular smooth muscle cells (VSMCs), macrophages, and endothelial cells (ECs) (Figure 3).

Nanotherapies Targeting Vascular Smooth Muscle Cells

In the initial stages of AS, VSMCs show abnormal growth and move towards the endothelium in reaction to oxidized LDL and inflammatory triggers, resulting in thickening of the endothelial layer. Subsequently, VSMCs differentiate into distinct phenotypes, such as myofibroblast-like, macrophage-like, and osteoblast-like VSMCs.^{114,115} Within atherosclerotic plaques, myofibroblast-like VSMCs cooperate with collagen deposition to form the fibrous cap, thereby contributing to plaque stability. In contrast, macrophage-like VSMCs promote lipid uptake and foam cell formation, leading to necrotic core expansion, while osteoblast-like VSMCs drive plaque calcification during advanced disease stages.^{116–118} This phenotypic heterogeneity highlights the complex and sometimes opposing roles of VSMCs in plaque progression and stabilization, indicating that VSMC-targeted therapies must achieve precise functional regulation rather than indiscriminate suppression (Table 1).

Excessive proliferation and migration of VSMCs play a central role in plaque growth and restenosis, and a variety of nanotherapeutic strategies have been developed to address these processes using small-molecule drugs or RNA interference. Zhang et al designed dual-responsive nanomaterials sensitive to pH and reactive oxygen species (RAP/AOCD NPs) that specifically target type IV collagen (Col-IV) within atherosclerotic plaques.¹¹⁹ These nanoparticles were fabricated from pH-responsive and oxidation-sensitive components via β -cyclodextrin modification and further functionalized with a Col-IV–targeting peptide (KLWVLPKGGGC), enabling preferential localization to plaque regions. In the



Figure 3 Cell-specific nanotherapeutic strategies in atherosclerosis. This schematic summarizes how nanomedicines are tailored toward three major plaque-associated cellular targets—vascular smooth muscle cells, macrophages, and endothelial cells—by aligning carrier type, surface engineering, and therapeutic modality with distinct disease-driving processes. Representative platforms include liposomes, polymeric and inorganic nanoparticles, drug–polymer conjugates, rHDL-mimetic particles, and exosomes. Surface-design strategies such as peptide ligands, biomimetic coatings, and electrostatic interactions are used to enhance lesion localization and cell selectivity via passive or active targeting, enabling delivery of cargos ranging from small molecules and antibodies to RNA-interference agents and photothermal/photodynamic therapeutics. Functionally, smooth muscle cell-directed systems aim to limit proliferation/migration and modulate phenotype switching, macrophage-targeted systems suppress inflammation and foam-cell formation or restore efferocytosis, and endothelial-targeted systems improve endothelial integrity and promote re-endothelialization.^{48,106,111–113}

acidic and oxidative microenvironment characteristic of atherosclerotic lesions, RAP was efficiently released from RAP/AOCD NPs, resulting in enhanced anti-proliferative and anti-migratory effects on VSMCs. Following intravenous administration, these nanoparticles accumulated in balloon-injured rat arteries and effectively suppressed neointimal hyperplasia, thereby improving anti-restenosis outcomes. Using a similar design principle, Feng et al developed pH/ROS dual-reactive nanomaterials (Ox-bCD) loaded with RAP, which further confirmed the benefit of microenvironment-responsive delivery for enhancing therapeutic efficacy against VSMC proliferation and migration.¹²⁰ Collectively, these

Table 1 Representative Nanotherapeutic Platforms for Atherosclerosis Categorized by Targeting Mode, Design Features, and Primary Therapeutic Functions

Type	Category	Size (nm)	Surface Ligand	Function
Passive/HDL-mimetic	HDL-mimetic/lipid metabolism modulation	~20–30	HDL-mimetic phospholipid shell with ApoA-I mimetic peptide	Selectively accumulated in plaques and promoted macrophage cholesterol efflux; reduced plaque lipid burden, macrophage content, and inflammatory markers; supported plaque regression/stabilization.
Endothelium-targeted	Inflamed endothelium targeting + protease-responsive release	~100–150	c(RGDfC) targeting $\alpha v\beta 3$ integrin + cathepsin K-responsive linker	Actively targeted inflamed endothelium/neovessels; cathepsin K-triggered release increased intraplaque drug exposure; reduced plaque size and inflammatory cytokines; increased collagen content and features of plaque stabilization.
	ROS-responsive theranostics/site-specific anti-inflammatory delivery	~80–120	ROS-responsive polymeric shell with lipid-affinitive components	Enabled plaque-local drug release (eg, prednisolone) in ROS-rich microenvironments and supported plaque imaging; reduced macrophage infiltration, inflammatory cytokine expression, and lipid accumulation; decreased plaque burden.
Macrophage-targeted	Macrophage membrane-camouflaged, ROS-triggered delivery	~120–150	Macrophage membrane coating on ROS-responsive rapamycin nanoparticles	Preferentially accumulated at inflamed vascular regions/plaques; ROS-triggered rapamycin release suppressed macrophage activation and smooth muscle cell proliferation, supporting anti-inflammatory and anti-proliferative effects relevant to atherosclerosis therapy.
	Macrophage membrane-camouflaged rapamycin delivery	~130–170	Macrophage membrane-camouflaged PLGA nanoparticles	Prolonged circulation and enhanced plaque accumulation in ApoE ^{-/-} mice; rapamycin delivery reduced macrophage infiltration and smooth muscle cell proliferation; decreased plaque area and improved plaque stability.
	Macrophage-targeted gene therapy (anti-inflammatory cytokine induction)	~80–100	Macrophage-targeted lipid nanoparticles	Delivered IL-10 mRNA to lesional macrophages and induced local anti-inflammatory cytokine expression; reduced macrophage activation/inflammatory signaling and necrotic core size; promoted overall plaque stabilization.
Microenvironment-responsive	ROS-responsive size-reducible nanoassemblies (deep plaque penetration)	~100–150	ROS-responsive, size-reducible nanoassemblies	Underwent size reduction in ROS-rich plaque microenvironments to improve penetration and macrophage uptake; reduced lipid deposition, suppressed inflammation, and decreased plaque burden.
Immunomodulatory/plaque-stabilizing	Pro-efferocytic immunomodulation (necrotic core reduction)	~100–150	Engineered macrophage membrane with pro-efferocytic signals	Enhanced efferocytosis within plaques; reduced necrotic core formation and inflammatory burden; improved plaque stability without obvious systemic toxicity.
	P-selectin targeting + ROS-triggered release	~100	Low-molecular-weight heparin-lipoic acid shell targeting P-selectin	Selectively accumulated at inflamed endothelium via P-selectin recognition; ROS-triggered release suppressed oxidative stress and inflammation; reduced plaque area and lipid content and improved endothelial function in ApoE ^{-/-} mice.
	Macrophage membrane-coated, ROS-responsive HA nanoparticles	~100–150	Macrophage membrane-coated, ROS-responsive hyaluronic acid nanoparticles	Enhanced plaque accumulation and macrophage uptake while evading immune clearance; ROS-responsive release promoted cholesterol efflux and attenuated inflammation; reduced plaque growth compared with non-coated controls.

studies demonstrate that stimulus-responsive nanocarriers can exploit plaque-specific microenvironments to achieve localized inhibition of VSMC-driven lesion growth while minimizing systemic drug exposure.

Gene therapy offers an additional avenue for regulating VSMC behavior by targeting key signaling pathways that govern proliferation and migration. Wang et al engineered a polyethylene glycol-grafted polyethyleneimine derivative (PEG-Et 1:1) to deliver Smad3 shRNA (shSmad3) selectively to VSMCs.¹²¹ Transforming growth factor- β (TGF- β) is a major driver of VSMC proliferation and migration, and its pro-atherogenic effects are mediated largely through the downstream effector Smad3.^{122,123} Delivery of shSmad3 using PEG-Et 1:1 effectively reduced Smad3 expression, suppressed VSMC growth both in vitro and in vivo, and significantly attenuated intima-media thickening following vascular injury. Despite their therapeutic promise, RNA-based approaches face challenges related to degradation, delivery efficiency, and toxicity, underscoring the need for optimized carriers capable of cytoplasmic delivery. Cationic liposomes (CLs) have been widely used to facilitate siRNA uptake due to electrostatic interactions with negatively charged cell membranes,¹²⁴ but their clinical translation is limited by immune activation and cytotoxicity associated with poor intracellular degradation.¹²⁵ To mitigate these issues, Fisher et al developed neutral polyethylene glycolylated liposomes (PLPs) modified with cell-penetrating peptides (CPPs), which exhibited substantially lower cytotoxicity while maintaining effective siRNA delivery to VSMCs.¹²⁶ In a related study, CPP-modified multilayer liposomes delivering ribonucleotide reductase M2 (RRM2) siRNA (RRM2-CLPD) achieved robust knockdown of RRM2 expression, leading to marked inhibition of VSMC proliferation and migration.¹²⁷ Together, these examples illustrate how rational carrier design can improve the safety and efficacy profile of gene-based nanotherapies targeting VSMCs.

Multilayer cationic liposomes (MLL) were prepared based on a hydrated thin film method followed by extrusion to form monolayer DOTAP/cholesterol liposomes. Subsequently, positively charged complexes were mixed with negatively charged siRNA/calf thymus DNA to create liposome-polycation-DNA assemblies (LPDs). Finally, PEG and CPP modifications enhanced their stability and targeting. Upon internalization by VSMCs, Upon entering VSMCs, RRM2-CLPD delivered RRM2 siRNA into the cytoplasm, triggering various therapeutic outcomes, including enhanced growth and migration inhibition. This is due to RRM2's critical involvement in DNA synthesis and repair, which is essential for VSMC proliferation and migration. RRM2-CLPD showed strong binding affinity to VSMCs and decreased RRM2 expression in VSMCs by about 80%. VSMC migration and viability were reduced by approximately 90% compared to untreated controls.

Beyond suppressing proliferation, promoting the transition of VSMCs from a synthetic or macrophage-like phenotype toward a contractile, stabilizing state has emerged as a complementary therapeutic strategy. Macrophage-like VSMCs contribute to plaque inflammation by releasing pro-inflammatory mediators, whereas contractile VSMCs support fibrous cap integrity. Maiseyeu et al developed protease-resistant nanomaterials for delivering the glucagon-like peptide-1 receptor agonist liraglutide (GlpNP), specifically targeting macrophage-like VSMCs.¹²⁸ The GlpNP system incorporates a phosphatidylserine-based “eat-me” signal that resists plasma proteases while being selectively degraded by plaque-associated gelatinases, thereby prolonging circulation and enhancing plaque targeting. Treatment with GlpNPs resulted in reduced cholesterol accumulation and increased expression of α -smooth muscle actin and type I collagen, consistent with a shift toward a stabilizing VSMC phenotype. Proprotein convertase subtilisin/kexin type 9 (PCSK9) has also been implicated in regulating VSMC phenotypic transformation by modulating markers such as α -SMA and osteopontin.¹²⁹ Li et al engineered macrophage membrane-coated nanoliposomes ((Lipo+M)@E NPs) to deliver the PCSK9 inhibitor evolocumab directly to atherosclerotic plaques.¹³⁰ This biomimetic system significantly reduced VSMC viability and migration, highlighting how phenotype-modulating interventions can be selectively deployed within lesions. In another example, Ma et al designed human serum albumin-based nanomaterials (ICG/SRT@HSA-pept NMs) incorporating osteopontin-targeting peptides and loaded with the Sirt1 activator SRT1720.¹³¹ Targeted delivery of SRT1720 increased Sirt1 expression within plaques and suppressed ox-LDL-induced phenotypic switching of VSMCs. Gene-based strategies further support this concept; miR-145, a key regulator of VSMC differentiation, was delivered using CCR2-targeted micelles, restoring contractile markers and significantly reducing plaque burden in ApoE-deficient mice as well as in patient-derived VSMCs.¹¹¹ These miR-145 micelles restored contractile markers protective against AS, such as cardiac myosin, α -SMA, and calmodulin, in synthetic VSMCs during in vitro experiments. In mid-stage atherosclerotic ApoE mice, miR-145 micelles decreased plaque development by 35% and 43% when compared to free miR-145 and PBS,

respectively. Chin et al also validated this in patient-derived VSMCs.¹³² Expression of contraction markers in VSMCs from various levels of disease severity normalized following miR-145 micelle treatment.

Impaired autophagy of VSMCs in AS accelerates the formation of foam cells, thus inducing autophagy in VSMCs is an effective therapeutic strategy. Nanomaterials have been designed to modulate cell signaling by optical, electrical, and magnetic methods in addition to signaling through biochemical methods.^{133–136} Photothermal therapy (PTT) and photodynamic therapy (PDT), which utilize targeted nanocarriers, are currently significant strategies to promote autophagy in VSMCs. Gao et al developed a switch based on copper sulfide nanoparticles (CuS NPs) for photothermal activation of transient receptor potential vanilloid subfamily 1 (TRPV1) signaling to halt the progression of AS.¹³⁷ TRPV1, a heat-sensitive cation channel activated by capsaicin, reduces foam cell formation through autophagy induction in ox-LDL-exposed VSMCs. A significant temperature increase from 37 °C to 42.7 °C occurred in VSMCs with CuS-TRPV1 following a 30-second exposure to 980 nm laser light at 5 W cm⁻². This process activates the TRPV1 channel, leading to calcium influx and the initiation of autophagy. As a result, the ATP-binding cassette transporter protein A1 (ABCA1) enhances cholesterol efflux, thereby decreasing lipid buildup and reducing foam cell formation in ox-LDL-exposed VSMCs. PDT activates photosensitizing drugs by laser irradiation at specific wavelengths, inducing them to accumulate in the target area and producing therapeutic effects, including induction of autophagy, apoptosis, and necrosis.¹³⁸ PDT presents an effective strategy for managing AS, with the ability to selectively target primarily atherosclerotic lesions while preserving healthy tissue as a key advantage, allowing for localized treatment while minimizing systemic effects.^{139,140} In their study, Zou et al developed an innovative liposomal system to encapsulate Ce6 for improved loading efficiency, subsequently conjugating CD68 to the surface of Ce6 liposomes through covalent binding.¹⁴¹ Ce6, a highly effective photosensitizer, is incorporated into the phospholipid bilayer of liposomes to form Ce6-loaded liposomes (Ce6-lip). Afterwards, the carboxyl group of DSPE-PEG-COOH was activated using EDC and N-hydroxysuccinimide (NHS), enabling the CD68 antibody to couple to the surface of Ce6-lip via amide bonds, resulting in CD68-modified liposomes (CD68-Ce6-lip). Laser irradiation of these CD68-Ce6-liposomes produces temporary and moderate levels of reactive oxygen species (ROS), which inhibit smooth muscle cell migration and promote cholesterol efflux from cells; additionally, the activation of autophagy further reduces foam cell formation. Similar efficacy was demonstrated by curcumin (CUR)-mediated PDT (CUR-PDT) therapy established by Wang et al¹⁴² CUR prevented the transformation of phenotype, inhibited migration, and reduced foam cell generation in VSMCs treated with ox-LDL. Additionally, it stimulated autophagy, leading to increased cholesterol excretion.¹⁴³

Smooth muscle cell-oriented nanotherapies are particularly attractive for translation because they map to clinically meaningful plaque features, including fibrous cap integrity, plaque stability, and remodeling, rather than lipid lowering alone. A representative example is miR-145 micelle delivery, which was developed to restore contractile smooth muscle cell programs and has demonstrated anti-atherosclerotic effects in vivo.¹¹¹ Importantly, translational credibility improves when a platform goes beyond a single short-term terminal endpoint and instead evaluates durability and dosing feasibility; the sustained in vivo benefit after a single administration and the subsequent exploration of clinic-like dosing schedules together illustrate how a VSMC-targeted strategy can be framed in a manner compatible with chronic disease management.^{109,110} In the revised text, a practical translational emphasis is to link VSMC-targeted interventions to measurable endpoints that could plausibly be tracked clinically (eg, imaging proxies of cap thickness and plaque composition, circulating inflammatory biomarkers, and functional vascular readouts), and to explicitly note the value of testing human-relevant cells and treatment timing windows that resemble clinical trajectories rather than only early-stage murine disease.

Nanotherapies Targeting Macrophages in Atherosclerotic Plaques

Macrophages are central drivers of atherosclerosis owing to their roles in lipid uptake, inflammatory amplification, and plaque destabilization.¹⁴⁴ During early lesion development, endothelial activation promotes monocyte recruitment to the arterial wall, where these cells differentiate into macrophages and acquire distinct functional phenotypes in response to local microenvironmental cues.¹⁴⁵ Early in AS, the main role of macrophages is to absorb and break down lipoproteins trapped under the endothelium. Internalized ox-LDL is degraded into cholesterol and free fatty acids by lysosomal acid lipase. A portion of the free cholesterol is esterified by cholesterol acyltransferase-1 (ACAT-1) and stored as lipid

droplets in the endoplasmic reticulum of macrophages. The remaining free cholesterol can be exported by ABC transporters, including ABCA1, ABCG1, and SR-B1.¹⁴⁶ Under disease conditions, abnormal macrophage metabolism causes the excessive accumulation of cholesterol esters in macrophages, leading to the development of foam cells.¹⁴⁷ Inflammatory macrophages may enhance vascular inflammation by secreting chemokines and cytokines.^{4,148} ox-LDL is recognized by CD14-TLR4-MD2 and stimulates macrophage inflammatory factor production.^{149,150} Cholesterol crystals activate protein 3 (NLRP3) inflammasomes, composed of NACHT, LRR, and PYD domains in foam cells, leading to the secretion of IL-1 β .¹⁵¹ Moreover, macrophages serve as antigen-presenting cells, displaying MHC-I molecules to naive CD8 T cells. CD8 T cells trigger apoptosis and necrosis in target cells via cytotoxic agents or cytokines, thereby worsening the inflammatory reaction in atherosclerotic plaques and accelerating lesion progression and instability.^{152–154} Increased inflammation not only promotes the accumulation of more circulating monocytes in atherosclerotic areas but also induces the transformation of atherosclerotic plaques to a vulnerable phenotype.¹⁵⁵ Proinflammatory macrophages decrease the stability of lesions by limiting collagen synthesis by smooth muscle cells and by promoting the production of matrix metalloproteinases (MMPs), which break down the protective fibrous cap.^{156–158} MMPs are localized in the shoulder regions of unstable atherosclerotic plaques and are involved in different phases of AS.^{7,159} Thus, regulatory macrophages are potential targets for modulating lipid and inflammatory responses in atherosclerotic plaques. In contrast, pro-resolving macrophages perform efferocytosis to clear apoptotic cells, thereby reducing plaque necrosis and enhancing lesion stability.^{10,160} Through efferocytosis, macrophages also trigger anti-inflammatory pathways, resulting in the production of mediators that resolve inflammation, including IL-10, transforming growth factor-beta (TGF- β), and specialized pro-resolving mediators derived from long-chain polyunsaturated fatty acids, all of which inhibit inflammation and aid in tissue repair.¹⁶¹ Thus, the promotion of efferocytosis and inflammatory abatement are promising approaches to impede the advancement of AS and promote its reversal. More directly, engineered macrophage membranes functionalized with pro-efferocytic signals have been used as biomimetic coatings to boost efferocytosis within plaques, thereby limiting necrotic core expansion, lowering inflammatory burden, and improving plaque stability without obvious systemic toxicity.¹⁶² In parallel, macrophage-targeted lipid nanoparticles have been developed to deliver IL-10 mRNA to lesional macrophages, inducing local IL-10 expression within plaques and dampening macrophage inflammatory signaling, which supports a more pro-resolving plaque microenvironment and contributes to plaque stabilization.¹⁶³

Taken together, macrophage-targeted nanotherapies reported to date address several interconnected pathological processes, including inflammatory monocyte recruitment, macrophage proliferation, impaired efferocytosis, and defective cholesterol efflux. One major line of investigation focuses on limiting the recruitment and expansion of inflammatory macrophages within plaques. Katsuki et al developed biodegradable PLGA-based pitavastatin nanoparticles that were preferentially internalized by monocytes and macrophages and accumulated within atherosclerotic lesions, resulting in a reduction in circulating Ly-6Chigh inflammatory monocytes. In parallel, modulation of inflammatory signaling pathways has been explored using recombinant HDL nanoparticles carrying inhibitors of CD40–TRAF6 signaling.^{164,165} Lameijer et al demonstrated that short-term administration of TRAF6i-HDL markedly reduced plaque inflammation by limiting Ly-6Chigh monocyte influx and decreasing macrophage accumulation in ApoE^{−/−} mice.¹⁶⁶ Together, these studies illustrate how nanoparticle-mediated delivery can recontextualize established anti-inflammatory agents to achieve lesion-biased effects that are difficult to replicate through systemic therapy alone.¹⁶⁷ Thus, inhibition of inflammatory macrophage proliferation within plaques can stabilize them. The serine/threonine protein kinase mTOR, known for its high conservation, is a member of the phosphatidylinositol kinase-related kinase (PIKK) family and is crucial for autophagy regulation.¹⁶⁸ Rapamycin, one of the mTOR inhibitors, is the most commonly used autophagy inducer. Boada et al developed a biomimetic nanoparticle, encapsulated with a leukocyte membrane (Leuko-Rapa), to inhibit macrophage growth in the aorta and lessen inflammation through targeted rapamycin delivery. Dissociated aortic tissue exposed to Leuko-Rapa had fewer dividing macrophages (15.6 $\pm$ 9.79%) compared to untreated controls (30.2 $\pm$ 13.34%) and those receiving only rapamycin (26.8 $\pm$ 9.87%). In mice administered Leuko-Rapa, the reduction in macrophage proliferation correlated with lower MCP-1 and IL-1 β levels. Statins target the mevalonate pathway, which plays a crucial role in the attachment of many small GTPases to the cell membrane and their involvement in cell proliferation.¹⁶⁹ Statins are effective in inhibiting macrophage proliferation.^{170,171} A simvastatin-loaded recombinant HDL (rHDL) nanoparticle designed by Tang et al inhibits the proliferation of injured macrophages and resolves local inflammation in

atherosclerotic ApoE^{-/-} mice.¹⁷² Collectively, these antiproliferative strategies highlight how nanocarriers can enhance the local efficacy of growth- and metabolism-targeting agents in plaque macrophages while reducing off-target exposure that limits their long-term systemic use.

Efferocytosis is the biological process by which phagocytosis-competent cells engulf apoptotic cells and actively participate in maintaining tissue and organ homeostasis by reducing the deleterious effects of cell death. Macrophage-driven efferocytosis prevents the buildup of foam cells in atherosclerotic plaques, thereby indirectly counteracting the production of ROS and proinflammatory mediators by foam cells and limiting the progression of AS.¹⁷³ The upregulation of CD47, a so-called “don’t eat me” signal, in atherosclerotic plaques leads to impaired efferocytosis of macrophages within the plaques.¹⁷⁴ Chen et al engineered platelet membrane-wrapped porous silica nanoparticles loaded with anti-CD47 antibodies (aCD47@PMSN), which significantly enhanced the phagocytic clearance of necrotic cells in ApoE^{-/-} mice compared with free antibodies.¹⁷⁵ Following administration in ApoE^{-/-} mice, aCD47@PMSN greatly improved the phagocytosis of necrotic cells within plaques when compared to free anti-CD47 antibodies. The removal of dead cells substantially reduced the atherosclerotic plaque area, strengthened plaque stability, and lowered the risk of rupture and advanced thrombosis. In a separate study, nanotubes filled with a chemical inhibitor targeting the anti-phagocytic CD47-SIRP α signaling axis were used to reactivate efferocytosis and decrease plaque load in ApoE^{-/-} mice.⁸⁹ Ca²⁺/calmodulin-dependent protein kinase γ (CaMKII γ) is a protein expressed in macrophages, contributes to acute thrombotic vascular events like heart attacks, sudden cardiac death, and unstable angina by facilitating the progression of fibrous atherosclerotic plaques into necrotic lesions with fragile fibrous caps. This is because CaMKII γ blocks a key pathway for efferocytosis and protectively activates transcription factor 6 (ATF6)/liver X receptor α (LXR α)/c-Mer proto-oncogene tyrosine kinase (MerTK).^{160,176,177} Tao et al designed macrophage-targeted PLGA nanoparticles delivering siCamk2g (S2P-siCamk2g), which enhanced efferocytosis, increased fibrous cap thickness, and reduced plaque necrosis in ApoE^{-/-} mice.⁵³ Compared with approaches that primarily suppress inflammation, these efferocytosis-restoring nanotherapies emphasize active plaque repair through functional reprogramming of macrophages, representing a mechanistically distinct route toward plaque stabilization.^{178,179}

Atherosclerosis (AS) represents a persistent inflammatory disorder. Evidence from the CANTOS and COLCOT studies indicates that mitigating inflammation can help decrease the likelihood of ischemic heart-related events. However, the side effects of systemic administration have hampered the clinical use of these drugs, as evidenced by immunosuppression-induced lethal infections.^{180,181} The emergence of targeted nanomaterials brings a turnaround in precision therapy.¹⁸² Francesco et al developed a liposomal nanoparticle based on lipid-conjugated methotrexate (MTX-LIP), which preferentially accumulated in atherosclerotic plaques and reduced circulating CCL5 levels, resulting in a significant decrease in plaque burden in ApoE^{-/-} mice.¹⁸³ Another study using cRGD conjugated pluronic-based nanocarriers (NC) also achieved targeted delivery of the anti-inflammatory cytokine IL-10.¹⁸⁴ Macrophage phenotype modulation further represents a complementary strategy, as the balance between pro-inflammatory M1 and reparative M2 macrophages critically influences disease progression.^{185,186} Mesenchymal stem cell-derived exosomes (MSCs-Exo) were shown to reduce macrophage infiltration and promote M2 polarization in ApoE^{-/-} mice, an effect largely attributed to exosomal miR-let7 regulation of HMGA2 and IGF2BP1.¹⁸⁷ Similarly, PLGA nanoparticles delivering the PPAR γ agonist pioglitazone promoted M2 polarization and attenuated plaque inflammation.⁷⁹ Together, these examples illustrate how nanomedicine can enable localized immunomodulation within plaques while avoiding the dose-limiting adverse effects of systemic anti-inflammatory therapy.

Lipids are key to atherosclerotic vascular disease modifiable risk factors.¹⁸⁸ In AS, monocyte-derived macrophages engulf ox-LDL through various scavenger receptors (SRs), such as CD36 and Fc receptors (FcR γ s), which are involved in the formation of foam cells derived from monocytes.¹⁸⁹ Therefore, the lipid metabolism of macrophages is closely associated with the extent of foam cell formation and the severity of AS.¹⁹⁰ The expulsion of cholesterol from macrophages is the first, and likely the most vital, step in reverse cholesterol transport (RCT). This pathway transfers excess cholesterol from peripheral cells to the liver for disposal, thereby playing an essential role in preventing lipid accumulation and the advancement of AS.^{191,192} Studies have shown that ABCA1/ABCG1 gene disruption leads to RCT abnormalities that result in exacerbation of AS.^{193,194} RNAi therapy plays an important role here. Various miRNAs have been discovered to regulate cholesterol efflux by directly targeting ABCA1. For example, upregulation of miR-33, miR-

144, miR-148a, and miR-302a decreases ABCA1 expression and suppresses cholesterol efflux to apoA1.^{195–198} Nguyen et al engineered chitosan nanoparticles (chNPs) to deliver miR-206 and miR-223 into macrophages.⁶⁸ Li et al further designed pH-responsive cyclodextrin-based nanoparticles to selectively silence miR-33 in inflamed lesions, thereby enhancing RCT and slowing disease progression.¹⁹⁹ Activation of liver X receptors (LXR α/β) also promotes ABCA1/ABCG1 expression,¹⁹⁰ but systemic LXR agonists induce hepatic steatosis. Nanoparticle-mediated targeted delivery of LXR agonists, such as sHDL-T1317 or collagen-targeted polymeric nanoparticles carrying GW3965, achieved plaque-selective lipid regulation with reduced hepatic side effects in murine models.^{200,201} Compared to T1317 alone, animals treated with sHDL-T1317 exhibited only a slight increase in hepatic LXR target gene expression, while ABCA1 mRNA levels were elevated in leukocytes. This indicates that sHDL successfully delivered LXR agonists directly to atherosclerotic plaques, avoiding the side effects seen with T1317 administered alone. In another study, type IV collagen-targeted poly(D,L-propionate) polymer nanoparticles were used to deliver the LXR agonist GW3965 to atherosclerotic lesions in *Ldlr*^{-/-} mice, leading to enhanced therapeutic efficacy and fewer adverse effects than GW3965 alone.⁶⁰ In addition, HDL-mimetic lipid nanoparticles in the ~20–30 nm range, typically engineered as a phospholipid shell displaying an ApoA-I mimetic peptide, preferentially accumulate in atherosclerotic plaques and enhance macrophage cholesterol efflux, thereby reducing plaque lipid burden, macrophage content, and inflammatory markers and ultimately promoting plaque regression and stabilization.²⁰²

Macrophage-directed nanotherapies are often positioned as anti-inflammatory solutions for atherosclerosis, but their translational success depends on achieving lesion-selective immunomodulation without systemic immune suppression. A representative strategy is exosome-mediated delivery of engineered IL-10 mRNA designed to be preferentially translated in inflammatory contexts, which supports the concept of “on-demand” anti-inflammatory activity within plaques.²⁰³ Another translationally relevant direction is the integration of targeting with mechanisms directly tied to plaque complications, such as platelet–plaque interactions; for instance, multifunctional peptide nanoparticles delivering rapamycin and simultaneously addressing platelet adhesion were reported to reduce plaque burden and inflammatory factors in vivo.²⁰⁴ For the revised manuscript, a key translational upgrade is to explicitly discuss how macrophage-targeted systems could be advanced toward the clinic: defining the intended patient population (eg, inflammatory high-risk plaques vs post-ACS secondary prevention), prioritizing safety endpoints (complement activation, cytokine perturbation, immunosuppression risk, and off-target organ accumulation), and emphasizing the need for standardized pharmacokinetic and biodistribution reporting that is comparable across studies.

Nanotherapies Targeting Endothelial Cells

ECs are the first sites to be invaded in atherosclerotic lesions. ECs activation and dysfunction can be triggered by oxidative stress, dyslipidemia, viral or bacterial infections, inflammation, blood flow turbulence, and low-shear stress.^{3,205–207} Activated ECs upregulate adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and P- and E-selectins, which play critical roles in leukocyte recruitment, platelet activation, and thrombus formation.^{208,209} Leveraging these accessible endothelial markers, P-selectin–targeted nanoplateforms for example those built with a low-molecular-weight heparin–lipoic acid shell, have been reported to selectively accumulate on inflamed endothelium via P-selectin recognition and to enable ROS-triggered release, thereby suppressing oxidative stress and inflammation, reducing plaque area and lipid content, and improving endothelial function in *ApoE*^{-/-} mice.²¹⁰ Beyond adhesion-molecule targeting, inflamed endothelium and plaque neovessels can also be addressed by integrin-directed strategies; for example, c(RGDfC)-decorated nanocarriers that recognize $\alpha v \beta 3$ integrin and incorporate a cathepsin K–responsive linker have been used to enable lesion-selective, protease-triggered drug release, thereby increasing intraplaque exposure, reducing plaque size and inflammatory cytokines, and increasing collagen content with features of improved plaque stabilization.²¹¹ Collectively, endothelial activation markers (eg, VCAM-1, ICAM-1, and selectins) and neovascular integrins (eg, $\alpha v \beta 3$) provide accessible molecular handles for endothelial targeting, enabling nanomaterials to be functionalized with peptides or ligands that preferentially recognize diseased endothelium.^{212–214} Based on this rationale, Dosta et al engineered VHPK-conjugated poly(β -amino ester) nanoparticles (pBAE NPs) to target VCAM-1–expressing inflamed ECs and deliver therapeutic RNA cargos, specifically anti-miR-712.¹¹³ The VHPK peptide (Val–His–Pro–Lys) selectively binds VCAM-1, facilitating preferential nanoparticle

accumulation in activated endothelium. A single administration of VHPK-coupled pBAE NPs significantly reduced miR-712 levels in endothelial cells while preserving the expression of its downstream target, tissue inhibitor of metalloproteinases-3 (TIMP3), thereby suppressing metalloproteinase activity and attenuating endothelial dysfunction. Using a similar targeting principle, a cationic liposomal system (VHPK-CCL-anti-miR-712) was developed by encapsulating anti-miR-712 into cationic lipid particles decorated with the VHPK peptide.²¹⁵ Notably, this formulation achieved significant inhibition of atherosclerosis progression in vivo at an approximately 80% lower dose compared with naked anti-miR-712, highlighting how endothelial-targeted nanodelivery can markedly enhance therapeutic efficiency while reducing systemic exposure. Together, these studies underscore the utility of VCAM-1-directed nanocarriers for selectively modulating endothelial gene expression under inflammatory conditions.

Beyond peptide-mediated targeting, biomimetic strategies based on cell membrane encapsulation have emerged as an effective approach for endothelial delivery. Liu et al constructed a neutrophil membrane-wrapped ZIF-8 nanoparticle system (AM@ZIF@NM) to deliver anti-miR-155 antisense oligonucleotides to endothelial cells within atherosclerotic plaques.¹⁰⁶ Following intravenous administration, these biomimetic nanocomplexes selectively accumulated in plaque-associated ECs through the interaction between ICAM-1 on the endothelial surface and CD18 expressed on the neutrophil membrane. Intracellular release of anti-miR-155 led to reduced miR-155 levels and restoration of its target gene BCL6, thereby alleviating endothelial inflammation. In a related study, nanoparticles coated with monocyte membranes (MoNPs) were designed to deliver the YAP/TAZ inhibitor verteporfin (VP) to inflamed endothelium.¹⁰⁷ Targeted delivery of VP significantly suppressed arterial YAP/TAZ signaling, reduced endothelial inflammation and macrophage infiltration, and ultimately attenuated plaque formation. Collectively, these biomimetic systems demonstrate how immune cell-derived membranes can be leveraged to enhance endothelial specificity and enable intracellular delivery of nucleic acids or small-molecule inhibitors.

In addition to suppressing endothelial activation, promoting endothelial repair has been explored as a prophylactic strategy, particularly to prevent restenosis following vascular interventions in advanced atherosclerosis.²¹⁶ Vascular endothelial growth factors (VEGFs) enhance endothelialization by stimulating the survival, proliferation, and migration of endothelial cells (ECs), and by increasing nitric oxide (NO) production in ECs. Although VEGFs have been extensively utilized for modifying the surfaces of vascular implants, directly immobilizing them on drug-eluting scaffolds is often limited due to their short in vivo half-life.²¹⁷ To address this challenge, nanoparticles loaded with VEGF or VEGF-related derivatives have been incorporated into scaffold coatings to achieve sustained and localized release.^{218,219} Tan et al fabricated heparin/poly-L-lysine (Hep-PLL) nanoparticles encapsulating VEGF and immobilized them onto dopamine-coated 316L stainless steel substrates.²²⁰ At an optimal VEGF concentration, the modified scaffolds exhibited reduced platelet adhesion, inhibited vascular smooth muscle cell (VSMC) proliferation, and significantly enhanced EC adhesion, migration, and bioactivity. Similarly, maleimide-poly(ethylene glycol)-poly(ϵ -caprolactone) (MAL-PEG-PCL) nanoparticles encapsulating VEGF were conjugated to thiolated decellularized porcine aortic valves, resulting in reduced hemolysis, antiplatelet properties, and accelerated endothelialization in vivo.²²¹ Beyond VEGF, alternative genetic regulators such as ZNF580 have also been explored for endothelial repair. ZNF580 not only promotes EC proliferation and migration but also suppresses VSMC growth. Incorporation of ZNF580-loaded complexes into artificial blood vessels significantly accelerated endothelialization in rat abdominal aorta models.²²² In parallel, RNA interference strategies targeting endothelial-associated microRNAs, including miR-126,²²³ miR-92a antagonists,²²⁴ and miR-652-3p antagonists,²²⁵ have been widely investigated to mitigate restenosis and endothelial dysfunction. Taken together, these approaches highlight the versatility of nanomaterials in supporting endothelial repair while simultaneously limiting thrombosis and neointimal hyperplasia.

Endothelial-targeted nanotherapies can be framed as early-intervention or stabilization approaches, aiming to correct barrier dysfunction, reduce leukocyte recruitment, and interrupt inflammatory amplification upstream of plaque expansion. A translationally relevant example is endothelial-directed nanotherapy that focuses on restoring endothelial health and reducing monocyte transmigration, consistent with a prevention-oriented mechanism rather than late-stage lesion debulking.²²⁶ For translation, this category benefits from a clear “indication logic”: such approaches are most defensible when positioned toward early-to-intermediate disease or toward preventing exacerbations in high-risk vascular beds, where improving endothelial function could plausibly shift disease trajectory. In the revised text, it is helpful to explicitly

connect endothelial-targeting strategies to clinical monitoring pathways (eg, endothelial activation biomarkers, imaging of inflammation or permeability surrogates, and vascular function measurements) and to highlight manufacturing and regulatory considerations specific to endothelial ligands or targeting motifs (ligand reproducibility, batch-to-batch consistency, and stability under storage and infusion conditions).

Indication-Oriented Design of Nanomedicines for Atherosclerosis

Atherosclerosis is a chronic, progressive disease with substantial spatial and temporal heterogeneity in lesion composition and dominant pathological drivers. As lesions evolve from early endothelial dysfunction to inflammatory expansion and structural destabilization, the most relevant cellular targets and therapeutic objectives also change. Accordingly, nanomedicine strategies should be designed in an indication-oriented manner, aligning nanomaterial functions with disease stage, plaque phenotype, and clinically meaningful goals rather than being framed as universally applicable solutions.

From an indication-mapping perspective, target selection is best anchored to clinically observable features—particularly imaging phenotypes and hematologic signatures that reflect endothelial activation, inflammatory burden, and structural vulnerability. In early disease dominated by endothelial dysfunction, imaging surrogates of vascular inflammation or barrier disruption together with systemic inflammatory signals support prioritizing endothelium-focused approaches (for example, adhesion-molecule or integrin-directed carriers, and permeability- or ROS-exploiting platforms) over deep-plaque debulking. As plaques become lipid-rich and inflammation-dominant, imaging markers consistent with active inflammation alongside hematologic profiles indicating heightened inflammatory tone favor macrophage-centered delivery that enhances intraplaque uptake, restores cholesterol efflux, or promotes resolution programs such as efferocytosis. In advanced or rupture-prone lesions, indication mapping should become explicitly phenotype-aware for vascular smooth muscle cells (VSMCs): broadly suppressing VSMC proliferation may be counterproductive when fibrous-cap integrity is already compromised, so VSMC-directed strategies should preferentially preserve or re-establish contractile/fibrogenic programs to support cap stability, while plaques with prominent calcific features may warrant prioritizing anti-osteogenic or anti-calcification directions that address osteogenic VSMC switching. Finally, in post-interventional settings, prioritization is defined by the dual requirement of limiting restenosis (synthetic VSMC expansion) while accelerating re-endothelialization to reduce thrombosis risk, which naturally supports localized or site-confined delivery designs that coordinate both processes.

In early-stage atherosclerosis, endothelial activation and dysfunction are initiating events that precede complex plaque architecture. Increased endothelial permeability, upregulation of adhesion molecules (including VCAM-1 and ICAM-1), and disturbed shear stress collectively promote leukocyte recruitment and inflammatory amplification. At this stage, the therapeutic emphasis is prevention-oriented: interrupting disease initiation and slowing lesion progression rather than attempting to debulk established plaques. Endothelial-targeted nanomedicines that restore barrier function, reduce monocyte transmigration, and dampen early inflammatory activation are therefore particularly well matched to the biology and clinical intent of early intervention.²²⁶

As lesions progress, macrophage accumulation, foam-cell formation, and persistent inflammatory signaling become dominant drivers of plaque expansion and chronicity. In parallel, impaired cholesterol efflux and defective efferocytosis contribute to necrotic core growth and a non-resolving inflammatory milieu. Under these conditions, macrophage-targeted nanomedicines—ranging from ligand-modified nanoparticles and scavenger receptor-recognizing materials to biomimetic platforms such as macrophage membrane-camouflaged systems—can improve intraplaque delivery and cellular uptake, enabling lesion-selective modulation of inflammatory pathways, enhancement of cholesterol efflux, or restoration of pro-resolving functions (including efferocytosis). Translationally, this category is most defensible when framed around lesion-selective immunomodulation that aims to reduce inflammatory burden without systemic immune suppression, and when efficacy readouts are linked to clinically relevant inflammatory signatures.^{203,204}

In advanced or vulnerable plaques, pathological complexity increases substantially, typically featuring large necrotic cores, thinning fibrous caps, and heightened risk of rupture. Here the primary objective shifts from plaque-size reduction to structural stabilization and prevention of acute events. Nanomedicine design in this setting requires particular caution because VSMCs play a dual role: they contribute to lesion growth through maladaptive phenotype switching, yet they also maintain fibrous-cap integrity through collagen production and cap formation. Indication-oriented strategies for

vulnerable plaques should therefore balance inflammation control with preservation or restoration of fibrous-cap structure, prioritizing phenotype-directed VSMC modulation (cap-supporting programs) over indiscriminate anti-proliferative intensity that could inadvertently weaken cap stability.

Post-interventional vascular settings (for example after stent implantation or angioplasty) represent a distinct indication with unique drivers and constraints. Excessive VSMC proliferation contributes to restenosis, while delayed endothelial recovery increases thrombosis risk. In this context, local or site-specific nanomedicine delivery offers clear advantages by enabling spatially confined release, reducing systemic exposure, and coordinating anti-proliferative effects with promotion of endothelial repair. Indication mapping is particularly actionable here because the clinical endpoints are well defined and the delivery route can be engineered to match the intervention site.

Overall, aligning nanomedicine design with stage- and phenotype-specific pathological contexts strengthens interpretability and improves translational plausibility. Although many preclinical studies report substantial therapeutic effects, relatively few explicitly connect nanomaterial design choices (targeting motifs, responsiveness, dosing logic, and safety evaluation) to clinically recognizable plaque phenotypes and risk signatures. Future progress will likely depend on adopting indication-driven principles that integrate imaging- and biomarker-informed stratification with standardized reporting of biodistribution, immune safety, and durability, enabling more rigorous cross-study comparison and a clearer path toward clinically coherent development.

Translational Progress Toward Clinical Application

Building on the indication-oriented framework above, an important question is what “translation” should practically mean for atherosclerosis nanomedicine, and how close current platforms are to a credible clinical path. In cardiovascular disease, the bar is inherently higher than in many acute indications because atherosclerosis is chronic, heterogeneous across vascular beds, and typically managed on top of effective standard-of-care therapies. As a result, a truly translatable nanotherapeutic strategy should be framed with a clear clinical use-case, demonstrate durable benefit under feasible dosing, and generate evidence that aligns with patient-relevant endpoints rather than relying solely on short-term plaque area reduction in early-stage animal models (Table 2).

Clinical benchmarks already cited in this review provide a pragmatic template for translation. First, cholesterol-transport modulation has been tested at scale, exemplified by large, randomized outcome testing of apolipoprotein A-I infusion approaches after acute myocardial infarction. Second, inflammation has been validated as a clinically addressable axis in atherosclerotic disease through outcome trials of anti-inflammatory interventions and post-MI anti-inflammatory therapy. Together, these studies clarify what regulators and clinicians ultimately prioritize: well-defined patient windows (eg, high-risk or post-event populations), standardized clinical endpoints, and a safety profile compatible with long-term cardiovascular care.

From a clinical positioning standpoint, most plaque-directed nanotherapies can be framed into a few defensible scenarios. Some are best viewed as early-intervention approaches aiming to normalize endothelial activation and reduce monocyte recruitment upstream of lesion expansion. Others are stabilization-oriented strategies designed for inflammatory, high-risk plaques, where the goal is to suppress local inflammation, restore resolution programs (such as efferocytosis), and reduce features linked to plaque rupture. A third category is intervention-adjacent therapy, where nanomedicines are paired with vascular implants or post-procedure management to limit restenosis while supporting re-endothelialization. Explicitly stating which scenario a given platform targets avoids a common translational pitfall: treating “atherosclerosis” as a single uniform indication and overinterpreting preclinical efficacy without a realistic clinical entry point. Equally important is how therapeutic success is measured. While histology-based endpoints remain essential for mechanism and proof-of-concept, translation benefits from noninvasive, clinically tractable readouts that can be compared across studies—typically imaging-anchored endpoints reflecting plaque biology and stability, complemented by circulating inflammatory and lipid-related biomarkers. For cell-targeted approaches, translational claims should be tied to matched readouts: endothelial-directed systems to barrier function and vascular inflammation, macrophage-directed systems to lesion-selective immunomodulation/resolution, and smooth muscle cell-oriented systems to fibrous-cap biology and stabilization-related features.

Table 2 Comparative Summary of Atherosclerosis Nanotherapies by Cellular Target

Cellular Target	Representative Nano-Platform	Cargo	Advantage	Limitation
VSMCs	Col-IV–targeted pH/ROS dual-responsive nanogel for rapamycin delivery	Rapamycin	Dual-responsive release in acidic/oxidative lesions; lesion-matrix targeting concept supports higher on-site exposure and reduced systemic spillover.	Evidence base is preclinical and model-dependent (often injury/restenosis-adjacent settings); translation will require clearer chronic dosing feasibility and long-term safety characterization.
	miR-145 micelles	miR-145	Directly “reprograms” VSMC phenotype toward a contractile program; includes human-cell relevance in the study design, strengthening translational plausibility.	Nucleic-acid delivery typically faces durability/dosing questions (how often to dose, how stable in vivo); larger-animal and long follow-up data are usually needed before clinical framing.
	CuS–TRPV1 photothermal switch	Photothermal activation of TRPV1	Spatiotemporal controllability (light-triggered), integrates imaging and therapy; authors report plaque attenuation in ApoE ^{−/−} mice without “obvious long-term toxicity” in that study context.	Requires external irradiation/device workflow and sufficient light delivery; general photothermal constraints include penetration depth and protocol standardization across vascular beds.
	CD68-targeted Ce6 liposomes (PDT)	Chlorin e6 (Ce6)	Lesion-cell–directed PDT concept can localize oxidative bursts and modulate VSMC behaviors (migration/foam-cell–related processes) with reduced systemic exposure compared to free photosensitizer.	PDT feasibility depends on light access and dose control; photosensitivity and off-target phototoxicity are common translational considerations for PDT-based strategies.
Macrophages	TRAF6i-HDL “nanobiologic” inhibiting CD40–TRAF6 signaling	Small-molecule inhibitor (CD40–TRAF6 interaction)	Targets an upstream inflammatory signaling node in myeloid cells; short-course dosing design directly addresses feasibility (treatment schedule rather than single-dose-only proof).	Clinical translation will hinge on scalable HDL-like manufacturing, batch consistency, and ensuring immune modulation stays lesion-selective without impairing host defense.
	Leukocyte-membrane-coated rapamycin NP (Leuko-Rapa)	Rapamycin	Biomimetic coating aims to enhance lesion homing; study reports reduced macrophage proliferation/inflammatory readouts with targeted rapamycin delivery.	Cell-membrane coating adds CMC complexity (source material control, sterility/viral safety, reproducibility); immunogenicity and storage stability are typical hurdles for membrane-camouflaged systems.
	Platelet-membrane-wrapped porous silica NP carrying anti-CD47 (aCD47@PMSN)	Anti-CD47 antibody	Reactivates efferocytosis (“don’t-eat-me” blockade) and links mechanistically to necrotic core reduction/plaque stabilization endpoints.	CD47 blockade is systemically sensitive (on-target effects beyond plaque are a known concern in the CD47 field); targeted delivery helps but safety windows must be tightly defined.
	S2P-targeted siRNA NP against CaMKII γ (S2P-siCamk2g)	siRNA (Camk2g)	Directly rescues an efferocytosis-relevant pathway and ties to structural plaque endpoints (cap thickness/necrosis) in the study.	siRNA therapies often need repeated dosing and careful off-target /innate immune activation monitoring; peptide-targeting motifs add another reproducibility variable for CMC.

ECs	VCAM-I–targeted pBAE NP (VHPK) delivering anti-miR-712	anti-miR-712	Clear ligand–receptor targeting logic (VCAM-I on inflamed ECs); study links miR modulation to TIMP3 preservation and anti-atherosclerotic effects.	Endothelial activation is heterogeneous across vascular beds and disease stages; targeting performance and dosing windows may vary substantially, so indication framing matters.
	VCAM-I–targeted cationic liposome (VHPK-CCL-anti-miR-712)	anti-miR-712	Demonstrates a “lower-dose vs naked oligo” principle, supporting the translational argument that delivery efficiency can reduce treatment burden.	Cationic systems can face tolerability constraints (complement/infusion reactions are common considerations); thorough immunotoxicity panels are usually expected for IV cationic carriers.
	Neutrophil-membrane–camouflaged ZIF-8 delivering anti-miR-155 (AM@ZIF@NM)	anti-miR-155	Biomimetic membrane approach supports EC targeting within plaques (ICAM-I–related interactions) and intracellular delivery of antisense cargo.	Membrane-derived systems raise scale-up/standardization issues; MOF-like cores also require careful biodegradation/long-term accumulation assessment.
	Monocyte-membrane NP delivering verteporfin (YAP/TAZ inhibition)	Verteporfin	Targets a mechanotransduction/inflammatory transcription axis in endothelium (YAP/TAZ), aligning with an “upstream barrier + inflammation” rationale.	Verteporfin has photoreactivity history; even when used as a small-molecule inhibitor, safety/PK and off-target exposure need careful translational mapping.
ECs/Stent interface	VEGF Hep/PLL nanoparticles immobilized on 316L SS	VEGF	Surface-bound nano-reservoir supports re-endothelialization while reducing platelet adhesion and VSMC proliferation in the reported setup.	Growth-factor coatings can raise concerns about dose control, stability during storage/implantation, and potential pro-angiogenic side effects depending on context.
ECs/Valve scaffold	VEGF-loaded NPs on decellularized porcine aortic valves	VEGF	Builds a regenerative interface to promote endothelial coverage on biologic scaffolds, matching device-related translational pathways.	Complex product category (combination of biologic scaffold + NP + VEGF) increases regulatory/CMC burden; durability and immunologic compatibility become central endpoints.
ECs (gene)	REDV peptide + ZNF580 plasmid delivery to accelerate endothelialization	ZNF580 gene	Pro-endothelialization gene strategy with the added appeal (as reported) of simultaneously restraining VSMC proliferation—useful for restenosis-prone scenarios.	Gene delivery raises persistence/safety questions (expression control, vector-related inflammation); clinical translation generally needs more stringent long-term vascular safety readouts.

Dosing feasibility and treatment burden are often underappreciated barriers. Because atherosclerosis management is long-term, platforms that require frequent intravenous administration, complex logistics, or narrow safety margins will struggle to compete with existing therapies even if preclinical efficacy is strong. Translation therefore favors designs that provide sustained local activity after limited administrations or can be integrated into routine clinical workflows, supported by repeat-dosing tolerance and durability assessments in clinically relevant treatment windows.

Manufacturability and quality consistency should also be treated as design variables rather than afterthoughts. Platforms relying on highly complex assemblies or poorly defined biological components may face hurdles in scale-up, stability, and batch reproducibility. More analytically tractable materials and standardized reporting of key attributes (eg, size, surface chemistry, ligand presentation) paired with harmonized pharmacokinetic/biodistribution readouts will strengthen cross-platform comparability and accelerate credible clinical development.

Finally, translation must be discussed alongside cardiovascular safety expectations. Many candidates will be developed for patients already receiving multiple long-term therapies and who are sensitive to off-target immune effects, coagulation perturbations, or organ accumulation. This motivates a “risk-by-design” translational pathway—prioritizing lesion-selective activity, anticipating liver–spleen exposure, and embedding safety monitoring early—which naturally leads to the next section on risks, mitigation strategies, and regulatory/manufacturing requirements.

Potential Risks, Mitigation Strategies and Regulatory Considerations

Immunotoxicity and Long-Term Accumulation

Although nanomedicines can improve lesion targeting and reduce systemic exposure compared with free drugs, immunotoxicity and long-term tissue accumulation remain central translational bottlenecks, particularly for atherosclerosis where patients may require repeated dosing and long-term management. A major acute safety concern is complementing activation–related pseudoallergy (CARPA) and other infusion reactions, which have been reported across multiple nanoparticle classes and can be triggered by particle surface chemistry, protein corona formation, and interactions with circulating complement proteins.²²⁷ In addition, nanoparticles are frequently cleared by the mononuclear phagocyte system, leading to preferential uptake in the liver and spleen; while this may be acceptable for single-dose settings, it becomes a key concern for chronic cardiovascular indications because slow clearance may translate into cumulative burden, chronic inflammation, or organ-specific toxicity.²²⁸

These risks are especially relevant for “complex” or biomimetic systems where multiple components are introduced (eg, membranes, targeting ligands, immune-modulatory cargos), because each added element can alter immunogenicity and biodistribution. Therefore, manuscripts intended to inform clinical translation should explicitly discuss: (i) the likelihood of complement activation and hypersensitivity, (ii) the probability of reticuloendothelial sequestration and chronic retention, and (iii) how these risks were evaluated (eg, complement assays, cytokine panels, repeat-dose toxicology, and longer follow-up windows).²²⁹

Off-Target Effects and Haemostatic Risks

Atherosclerosis is uniquely sensitive to haemostatic perturbations, because patients often have concomitant antiplatelet/anticoagulant therapy and a high baseline risk of thrombosis. Consequently, nanomedicines that interact with platelets, endothelium, or coagulation pathways must be discussed in terms of both intended benefits and unintended risks. In particular, platelet-membrane–based biomimetic designs, while attractive for vascular targeting and immune evasion, warrant careful consideration regarding platelet activation, procoagulant activity, or unanticipated interactions with thrombi and inflamed endothelium.²³⁰ Similarly, strategies that promote angiogenesis or aggressively remodel lesion microenvironments may carry theoretical risks related to neovessel fragility, intraplaque hemorrhage, or altered vascular permeability, emphasizing the need to balance lesion remodeling with vascular safety.²³¹

From an evaluation perspective, haemostatic risk discussion should go beyond a generic “hemolysis test.” For cardiovascular translation, it is more convincing to specify a minimal haemocompatibility package that includes platelet activation/aggregation markers, coagulation parameters, complement–coagulation crosstalk where relevant, and thrombotic/bleeding tendency assessment *in vivo* when the design plausibly engages these pathways.²³²

Manufacturing and Quality Control

Even when atherosclerosis nanomedicines show compelling preclinical efficacy, translation frequently stalls at manufacturing, quality control, and reproducibility. Regulatory and industrial experience consistently highlights that nanoscale systems are highly sensitive to process conditions, and small changes in mixing, solvent removal, shear, temperature, or raw material attributes can alter critical quality attributes (CQAs) such as particle size distribution, PDI, surface charge, cargo encapsulation, free-drug fraction, and stability.²³³ In practice, this means that “successful laboratory formulation” does not automatically imply a product is developable under GMP; rather, the formulation must be compatible with scalable unit operations and robust in-process controls that ensure batch-to-batch consistency and clinically reproducible exposure.²³⁴

For complex or biomimetic constructs, additional CMC challenges arise, including quantifying ligand density or membrane coating completeness, controlling biological raw-material variability, ensuring sterility/endotoxin compliance, and validating long-term storage stability. Because these factors directly influence both safety (eg, immunogenicity, infusion reactions) and efficacy (eg, targeting and release), a translationally oriented review should explicitly emphasize that future studies need to report manufacturing-relevant parameters and QC-readouts in a standardized manner, rather than only demonstrating a one-off “proof-of-concept” batch.²³⁵

Mitigation Strategies and Evaluation Frameworks

A practical way to advance atherosclerosis nanomedicine is to adopt a risk-by-design mindset: safety and developability should be treated as design constraints from the earliest stages rather than post hoc add-ons. First, to reduce immunotoxicity, designs may prioritize biocompatible and/or biodegradable materials, avoid excessively cationic surfaces, minimize unnecessary formulation complexity (“minimal effective complexity”), and incorporate rational surface engineering to mitigate complement activation and nonspecific opsonization.^{227,236} Second, to address long-term accumulation, platforms should consider clearance pathways explicitly (eg, renal-clearable or metabolizable components where feasible) and adopt repeat-dose designs only when supported by chronic safety data and biodistribution evidence.²³⁷ Third, to manage haemostatic risk—especially for platelet- or thrombus-interacting systems—evaluation should include coagulation/platelet panels and context-specific models, recognizing that cardiovascular patients often receive concomitant antithrombotics.²³⁰

Finally, the field would benefit from a more standardized evaluation and reporting framework that improves cross-study comparability and regulatory readiness. In this regard, structured assay panels developed by national characterization initiatives illustrate how systematic physicochemical, immunological, toxicological, and pharmacokinetic characterization can be operationalized for nanotechnology products.²³⁸ For atherosclerosis nanomedicines, we recommend that future preclinical studies routinely report (at minimum) size/PDI, surface chemistry or coating completeness, cargo loading and free fraction, stability under storage and in serum, quantitative biodistribution, repeat-dose immune safety (including complement activation), and haemocompatibility endpoints when designs plausibly interact with coagulation. Such systematic reporting will accelerate the transition from “promising lesion-level efficacy” toward formulations that are clinically testable, manufacturable at scale, and acceptable under regulatory review.

Future Perspectives

AS is a chronic inflammatory disease. Modern medicine’s treatment strategies for AS are based on early lipid-lowering therapy and late stent implantation. The emergence of nanomaterials provides a promising strategy for AS treatment. Nanomaterials offer numerous advanced strategies and innovative research pathways for treating patients with AS disease by utilizing their small size, high drug loading rate, and excellent targeting ability. Targeted nanotherapies enable passive or active targeting through surface modification and bionic mimicry, delivering small molecule therapeutic agents precisely to the atherosclerotic plaque site, and exerting highly effective therapeutic effects against different cells and molecules in the progression of AS. A complex microenvironment is formed inside the atherosclerotic plaques, which is characterized by a variety of cell types, cholesterol enrichment, inflammation, and excess ROS. Therefore, targeted nanotherapies need to be characterized by (i) the ability to evade MPS; (ii) the ability to target AS plaques; (iii) precise release of loaded drugs; and (iv) high biosafety.

Although there are few clinically approved nanotherapeutics for use, there have been several clinical studies that are exploring the possibility of targeted nanotherapies for the treatment of human AS diseases (NCT04616872; NCT04148833; NCT03473223; NCT01270139). However, before targeted nanotherapies can be formally introduced into the clinic, their biosafety, biodistribution, and clearance need to be evaluated in detail. Some studies have found that nanomaterials may cause inflammatory responses and abnormal activation of immune cells.^{239–242} The chronic inflammatory nature of the disease characteristic of AS requires long-term administration, and the cumulative effect of nanomaterials may introduce toxicity that cannot be noticed with short-term administration, which is related to the size, shape, and indicated properties of the nanomaterials.^{243–246} Therefore, the development of targeted nanomedicine-based therapies as treatments for use in clinical practice requires their continuous optimization and medically based testing. In addition, the low consistency of nanomaterials during production and harsh storage conditions are limiting their clinical applications. This requires systematic industrial production of nanomaterials to ensure batch-to-batch reproducibility.

Currently, targeted nanotherapies in AS have shown promising applications. The next research should focus on improving the therapeutic efficiency of these targeted nanomaterials and reducing their side effects and systemic production. Although there are still many directions that need to be explored and improved in the future, targeted nanotherapies have the potential to open up a series of innovative research areas in the treatment of AS.

Data Sharing Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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