

Review



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Targeted Theranostic Strategy for Atherosclerotic Plaques Using Intravascular Multimodal Imaging Techniques

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ABSTRACT

Atherosclerosis, a chronic inflammatory disease, is a leading cause of fatal cardiovascular events including myocardial infarction and stroke, primarily due to plaque rupture. The development of plaques is largely driven by the accumulation of macrophages and lipids within the arterial walls, which are central to the progression of atherosclerotic lesions and have emerged as potential therapeutic targets. However, current therapies cannot accurately target and resolve high-risk inflamed plaques, often leading to off-target damage to healthy vascular cells and increasing complications, such as thrombosis. Additionally, most theranostic strategies, which integrate both diagnostic and therapeutic capabilities, have primarily demonstrated efficacy in murine models, limiting their direct application to human coronary arteries. Recent advancements in targeted drug delivery and photoactivation strategies, combined with customized intravascular structural-molecular imaging, have shown significant promise in overcoming these challenges. Multimodal imaging techniques, such as optical coherence tomography (OCT) and near-infrared fluorescence (NIRF), enable real-time visualization and the precise treatment of plaque inflammation. OCT offers high-resolution imaging of plaque structures, while NIRF detects inflammatory activity, enabling accurate localization of macrophage- and lipid-rich plaques. Following targeted delivery and uptake by plaque macrophages, these theranostic strategies can rapidly resolve plaque inflammation and promote stabilization through orchestrated therapeutic interactions. Accordingly, these clinically relevant theranostic strategies could offer a promising path toward personalized, imaging-guided therapies for human cardiovascular disease, potentially revolutionizing the diagnosis and treatment of atherosclerosis.

Keywords: Atherosclerosis; Inflammation; Macrophage; Multimodal imaging; Precision medicine

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Conflict of Interest

The authors have no conflicts of interest to declare.

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INTRODUCTION

Atherosclerosis is a leading cause of cardiovascular morbidity and mortality worldwide, leading to life-threatening conditions such as myocardial infarction and stroke.¹ Despite advancements in lipid-lowering and anti-inflammatory therapies, atherosclerosis remains a significant clinical challenge because current therapies do not effectively target the underlying cellular and molecular mechanisms responsible for plaque instability, such as macrophage activation.²⁻⁴ Atherosclerosis is characterized by the accumulation of lipids and infiltration of inflammatory cells, particularly macrophages, within the arterial wall; this leads to the formation of unstable plaques that can rupture and cause thrombosis.^{5,6} Therefore, targeting macrophages and lipids is a promising strategy for stabilizing plaques and reducing the risk of cardiovascular events.

Theranostics, an integrated approach that combines diagnostic and therapeutic functionalities, is a novel and promising strategy.⁷ This approach aims to accurately detect diseases and provide immediate intervention with targeted treatment, allowing for instant adjustments if required. Furthermore, theranostic agents can be engineered for high selectivity, enhancing treatment precision and reducing side effects. By providing a multifaceted approach to disease management, theranostics have the potential to personalize treatment regimens and significantly improve patient outcomes, especially in complex diseases, such as atherosclerosis, where precision is crucial.

A key component of theranostic approaches is the use of multimodal intravascular imaging techniques to characterize atherosclerotic lesions and guide targeted interventions. Recent advancements in imaging technologies, such as the development of dual-modality catheters combining optical coherence tomography (OCT) and near-infrared fluorescence (NIRF), have enabled the real-time visualization of plaque structure and inflammatory activity.^{8,12} These innovations provide high-resolution structural data and detailed molecular information, significantly enhancing the identification of high-risk plaques and guiding drug delivery to inflamed areas.

This review explores the recent advancements in intravascular multimodal imaging-assisted theranostic strategies, focusing on targeted approaches for the treatment of high-risk atherosclerotic plaques. The potential of these strategies to provide personalized and minimally invasive treatment options for coronary artery disease will also be discussed, along with translational challenges and future directions in this field.

ROLE OF MACROPHAGES IN PLAQUE PROGRESSION

Macrophages play a critical role in the pathogenesis of atherosclerosis, from the initial development of fatty streaks to the advanced formation of necrotic cores within the plaque.^{13,15} Monocytes recruited from the bloodstream infiltrate the arterial wall under the influence of endothelial cell signals and differentiate into macrophages¹⁶ that ingest oxidized low-density lipoprotein (LDL) to become foam cells.¹⁷ These foam cells are central to plaque progression, as they accumulate lipids and eventually form fatty streaks that evolve into more advanced atherosclerotic lesions.¹⁸ The transformation of monocytes into foam cells is a crucial step triggering a cascade of inflammatory events within the arterial wall.^{19,20} Foam cells store

lipids and release pro-inflammatory cytokines and reactive oxygen species that perpetuate local inflammation and attract additional immune cells, including monocytes and T cells, further amplifying the inflammatory response.^{18,21} Over time, the accumulation of foam cells leads to the development of a lipid-rich necrotic core, a hallmark of vulnerable plaques that are prone to rupture.²² This process is accompanied by the proliferation of smooth muscle cells, which stabilize plaques by forming a fibrous cap.²³ However, the continuous influx of inflammatory cells and resultant oxidative stress weaken the fibrous cap, increasing the risk of plaque rupture and thrombosis formation.²⁴ The inability of macrophages to effectively clear apoptotic cells through efferocytosis further exacerbates the necrotic core, contributing to plaque instability and increasing the risk of acute cardiovascular events.²⁵⁻²⁷

NEED FOR THERANOSTICS

1. Limitations of current treatments

Current nonsurgical treatments for atherosclerosis, including lifestyle modifications and pharmacotherapy, primarily focus on reducing overall cardiovascular risk factors, such as hyperlipidemia, hypertension, and smoking. Statins, the cornerstone of pharmacologic therapy, effectively lower LDL cholesterol levels and have anti-inflammatory properties that can stabilize plaques.²⁸⁻³² However, despite their efficacy, statins do not specifically target high-risk plaques. Their systemic effects can lead to side effects such as myopathy, increased risk of diabetes, and even potential liver toxicity in certain patients.^{4,33-35} Moreover, the systemic action of statins reduces lipid levels throughout the entire vasculature; they do not concentrate their effects on the most vulnerable plaques that pose the greatest risk for rupture and subsequent cardiovascular events. Alongside statins, other lipid-lowering agents such as PCSK9 inhibitors, have demonstrated potential in reducing LDL cholesterol levels.³⁶ However, similar to statins, they do not specifically localize their effects to high-risk plaques.³⁷ Additionally, these agents are expensive, limiting their accessibility to a broader patient population. These limitations underscore the need for a more targeted approach that can deliver therapeutic effects directly to unstable plaques while minimizing systemic exposure.

Anti-inflammatory therapy with monoclonal antibodies targeting interleukin (IL)-1 β (e.g., canakinumab) has shown promise in reducing cardiovascular events by mitigating inflammation.³ However, this therapy has significant drawbacks, including an increased risk of infections due to systemic immunosuppression, which can be particularly concerning in patients with comorbidities that predispose them to infections.³ Furthermore, these treatments do not precisely target inflammatory activity within atherosclerotic plaques, which is a key driver of plaque instability. The inability to target high-risk plaques means that the benefits of these treatments are often accompanied by unintended systemic side effects that can be detrimental to vulnerable patients.

Stent implantation is a key interventional approach used during percutaneous coronary intervention to alleviate the symptoms of significant stenosis and restore blood flow in blocked arteries.³⁸ However, although stents effectively widen narrowed arteries and reduce angina, they do not address the underlying plaque vulnerability that can lead to sudden ruptures. Complications including restenosis,³⁹ where the treated artery re-narrows, and stent thrombosis,⁴⁰ where a clot forms at the stent site, pose additional risks following stent

placement. Furthermore, stents do not directly target inflammatory activity or the necrotic core within high-risk plaques, making these plaques vulnerable to rupture. Therefore, there is an urgent need for more localized and targeted treatment approaches to effectively stabilize high-risk plaques.

2. Theranostic approaches in atherosclerosis: diagnostic and therapeutic strategies

Theranostics combine diagnostic and therapeutic modalities,⁷ representing a promising approach for addressing the limitations of current atherosclerosis treatments.⁴¹ In the context of atherosclerosis, theranostic strategies aim to integrate advanced imaging techniques with targeted drug delivery to enable the precise identification and treatment of high-risk plaques. This approach can provide real-time feedback on the strategy's therapeutic efficacy, allowing for more personalized and adaptive treatment regimens.

One significant advantage of theranostic approaches is their ability to personalize treatment based on the specific features of each patient's atherosclerotic plaques.⁴² For instance, molecular imaging modalities, such as NIRF,⁴³⁻⁴⁵ positron emission tomography,^{32,46,47} and magnetic resonance imaging (MRI),⁴⁸⁻⁵¹ have proven useful in characterizing vulnerable plaques, revealing features such as inflammation, matrix remodeling, apoptosis, neoangiogenesis, and calcification. These imaging techniques allow for the identification of plaques at a greater risk of rupture, facilitating targeted therapies that can specifically address these vulnerable regions.

Another promising theranostic strategy involves the use of nanoparticles functionalized with targeting ligands, allowing them to accumulate specifically in inflamed atherosclerotic plaques.^{41,52} Due to their nanoscale size, they can improve the stability, solubility, and targeting efficiency of therapeutic agents, thereby potentially reducing side effects while increasing therapeutic efficacy. Theranostic nanoparticles offer the advantage of combining imaging and treatment using a single platform. These multifunctional capabilities highlight the growing role of nanoparticles as a promising tool for the precise detection, monitoring, and treatment of cardiovascular conditions, such as atherosclerosis (Table 1).

INTRAVASCULAR OCT-NIRF IMAGING

Recent advancements in multimodal imaging have significantly enhanced our ability to assess atherosclerotic plaques at both the structural and molecular levels. The combination of OCT and NIRF imaging is one such advancement that allows for the simultaneous assessment of plaque microstructure and molecular composition.⁸⁴² OCT provides high-resolution images of the arterial wall with an axial resolution of 10–15 μm and limited penetration depth of 1–2 mm,⁵³ enabling the identification of features such as fibrous cap thickness. NIRF imaging can penetrate up to several millimeters into the arterial wall,⁵⁴ providing information regarding the presence of inflammatory markers such as protease activity and lipid accumulation. This dual-modality approach allows for the precise localization of high-risk plaques and provides a valuable tool for guiding targeted therapies. By combining structural and molecular imaging, multimodal techniques offer a more comprehensive understanding of plaque vulnerability and enable effective intervention strategies.

Highly specialized catheter systems are required for catheter-based OCT-NIRF imaging as coronary arteries are narrow and convoluted, with interior diameters ranging from 2–4

Table 1. Effects of theranostics on atherosclerosis

Nanoparticle	Drug	Imaging platform	Animal model	Efficacy	Safety	Potential off-target effects
MMR-Lobe*	Lobeglitazone (PPAR γ agonist)	NIRF	ApoE $^{-/-}$ mice	Effectively reduces plaque burden and inflammation via the activation of PPAR γ pathways in macrophages	No major systemic disturbances	The long-term effect on macrophage plasticity remains uncertain
CCTV NPs-Gd*	Anti-CCR2 peptide	MRI	ApoE $^{-/-}$ mice	Targets CCR2-positive monocytes; reduces inflammation and enables MRI imaging of plaques	No major immune suppression	May impair the immune response to infection
MMR-Lobe-Cy*	Lobeglitazone (PPAR γ agonist)	OCT-NIRF	Rabbit	Robustly induces acute anti-inflammatory effects; shifts the plaque composition to a stable phenotype	Non-toxic up to 50 μ M of lobeglitazone; negligible effects on body weight and hematological, biochemical, and histological profiles	The long-term effect on macrophage plasticity remains uncertain
DS-Ce6 †	Ce6	NIRF	ApoE $^{-/-}$ mice	Reduces plaque burden and inflammation through apoptosis and autophagy	Minimizes damage to nontarget cells; ensures low phototoxicity under nonirradiation	Side effects include colonic mucosal inflammation, thrombocytopenia, and alopecia with high-dose administration
MAN-PEG-Ce6 †	Ce6	NIRF	ApoE $^{-/-}$ mice	Reduces inflammation and induces apoptosis in macrophages	No toxicity up to 20 μ M of Ce6; no hemolytic damage, hepatic or kidney impairments, or tissue damage; low skin phototoxicity	May facilitate long-term immune modulation
FeCNPs †	Ce6	MRI	ApoE $^{-/-}$ mice	Chemically produces singlet oxygen for photodynamic therapy without external light irradiation; combines MRI imaging	Selective accumulation in plaques; avoid external light exposure; Fe $^{3+}$ -catechol complex provides stable and enhanced MRI imaging without major organ damage	High doses may exacerbate atherosclerosis due to iron accumulation and inflammation in plaques
CLIO-THPC †	Ce6	NIRF, MRI	ApoE $^{-/-}$ mice	Selective macrophage ablation and plaque stabilization	Negligible skin phototoxicity; only toxic when activated by the appropriate wavelength of light	Extensive cell death of healthy cells due to increased temperatures
LAM-Ce6 †	Ce6	OCT-NIRF	Rabbit	Promotes inflammation resolution and plaque stabilization	No significant change in the mean body weight; no hepatic or renal toxicity; no damage or impairment to the organs	May not precisely reflect long-term stabilization in human plaques

MMR-Lobe, macrophage mannose receptor-targeted biocompatible nanocarrier loaded with lobeglitazone; PPAR γ , peroxisome proliferator-activated receptor gamma; NIRF, near-infrared fluorescence; CCTV NPs, CC chemokine receptor 2, self-assembled, peptide-conjugated nanoparticle; CCR2, CC chemokine receptor 2; MRI, magnetic resonance imaging; MMR-Lobe-Cy, mannose-polyethylene glycol-glycol chitosan-deoxycholic acid-cyanine 7-lobeglitazone; OCT-NIRF, optical coherence tomography-near-infrared fluorescence; DS-Ce6, dextran sulfate-chlorin e6; Ce6, chlorin e6; MAN-PEG-Ce6, D-mannosamine-polyethylene glycol-Ce6; FeCNP, Fe $^{3+}$ -catechol cross-linked bis(2,4,5-trichloro-6-[pentyloxycarbonyl]phenyl)oxalate-loaded mPEG-Plys-(3,4-dihydroxyphenylacetic acid-Ce6) nanoparticle; CLIO-THPC, crosslinked dextran-coated iron oxide-tetra(hydroxyphenyl)chlorin; LAM-Ce6, laminarin-Ce6.

*Macrophage-targeted drug delivery system; † Macrophage-targeted photoactivation.

mm.⁵⁵ The external diameter of the catheters used for intravascular OCT-NIRF imaging is approximately 0.9–1.2 mm,¹² satisfying this criterion and guaranteeing compatibility with common coronary intervention techniques. These catheters should be thin while maintaining mechanical stability, flexibility, and the capacity to acquire both OCT and NIRF data simultaneously.

VERIFICATION OF THERANOSTIC APPROACHES

1. Macrophage-targeted drug delivery systems

Preclinical studies using murine models have demonstrated the potential of targeted drug delivery systems for treating atherosclerosis (**Fig. 1A**).^{56,57} Nanoparticles functionalized with macrophage mannose receptor (MMR)-targeting^{8,58} ligands have been used to effectively deliver lobeglitazone,^{59,60} a peroxisome proliferator-activated receptor gamma (PPAR γ) agonist, directly to inflamed atherosclerotic plaques (**Fig. 1B**). This targeted system significantly reduced both plaque burden and inflammation, without the systemic side effects often associated with non-targeted PPAR γ therapies. Specifically, the MMR-targeted biocompatible nanocarrier loaded with lobeglitazone increased cholesterol efflux

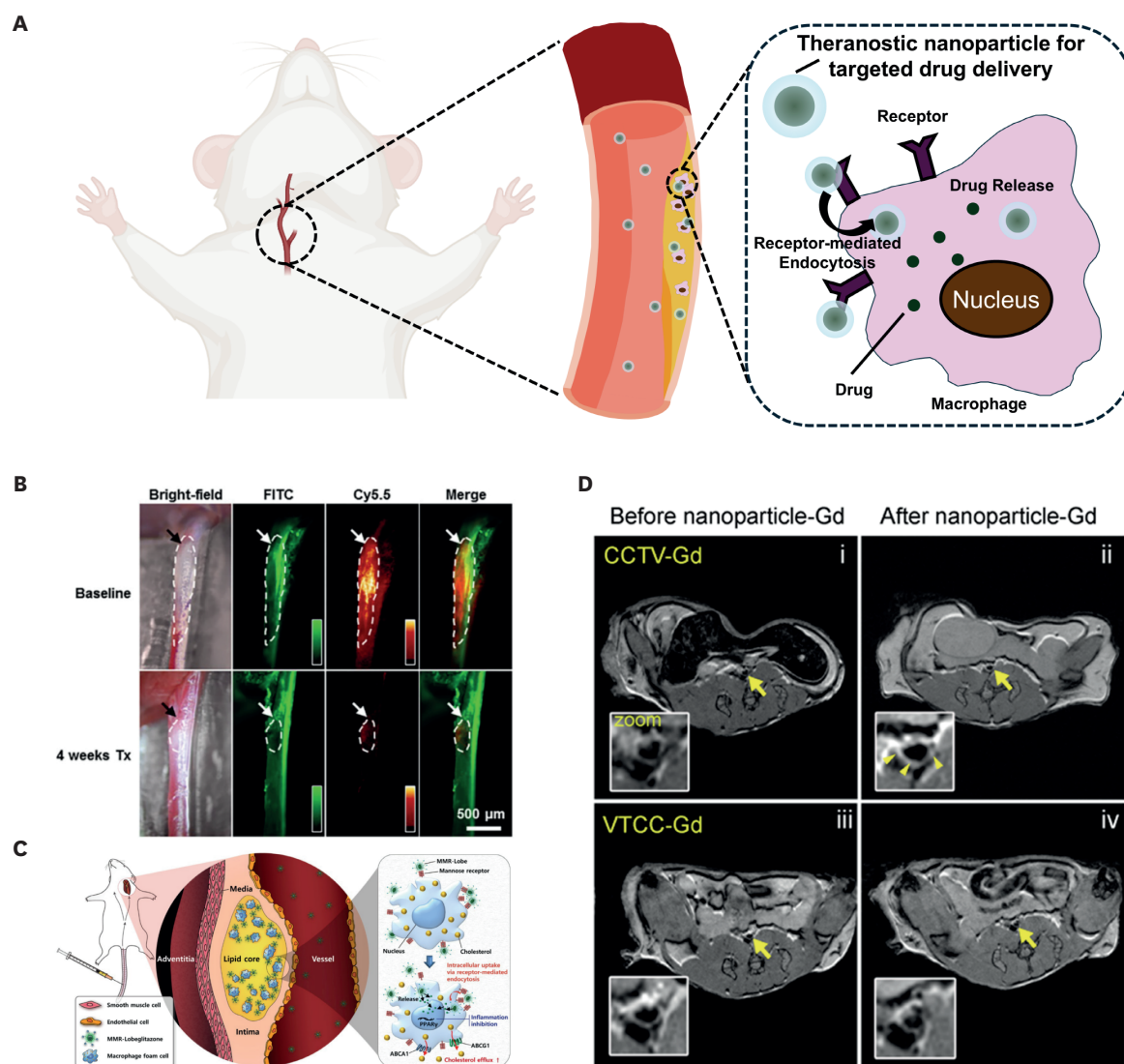


Fig. 1. Macrophage-targeted theranostic drug delivery system. (A) Schematic overview of the macrophage-targeted drug delivery system. (B) *In vivo* serial imaging using MMR-Lobe in ApoE^{-/-} mice. (C) Schematic illustration of MMR-Lobe effects. (D) Representative magnetic resonance imaging of an atherosclerotic plaque with CCTV-Gd and a VTCC-Gd. The inset is a zoomed-in area of the Gd-enhanced plaque. Figures were adapted from the following sources: (B, C) Choi et al.,⁵⁶ CC-BY-NC-4.0; (D) Mog et al.,⁵⁷ CC-BY-4.0.

FITC, fluorescein isothiocyanate; MMR-Lobe, macrophage mannose receptor-targeted biocompatible nanocarrier loaded with lobeglitazone; PPAR γ , peroxisome proliferator-activated receptor gamma; CCTV, CC chemokine receptor 2, self-assembled, peptide-conjugated nanoparticle; VTCC, CCTV mirror-analog nanoparticle.

via the activation of ABCA1, ABCG1, and LXR α pathways and decreased the expression of inflammatory markers, such as tumor necrosis factor (TNF)- α , IL-6, and matrix metalloproteinase-9 (**Fig. 1C**). These effects were clearly observed *in vivo*, where serial imaging demonstrated a marked reduction in plaque size and inflammatory burden in treated murine models.

The development of nanoparticles to target CC chemokine receptor 2 (CCR2), self-assembled, peptide-conjugated nanoparticles (CCTVs), has significantly contributed to the focused alleviation of macrophage-mediated inflammation within atherosclerotic plaques.⁵⁷ The CCTVs, composed of a 4-mer peptide conjugated to a lipid nanoparticle, selectively target overexpressed CCR2 in inflammatory monocytes and macrophages. *In vivo* studies illustrate that CCTVs facilitate an MRI-sensitive diagnosis of plaque inflammation while

further antagonizing the inflammatory response by blocking CCR2 (**Fig. 1D**). This therapeutic diagnosis imaging paradigm indicates that simple nanoparticles, like CCTVs which have a ligand of some type on their surface to either carry imaging agents or exert therapeutic effects, have great potential in targeting high-risk or inflammatory atherosclerotic lesions. CCTVs also offer the advantage of being more targeted than typical systemic mutagenic immunosuppressive drugs, which treat the whole body.

2. Macrophage-targeted photoactivation

Photoactivation-targeting macrophages have emerged as a promising theranostic approach for treating atherosclerosis (**Fig. 2A**).⁶¹⁻⁶⁴ In murine models, photoactivatable agents such as chlorin e6 (Ce6)-based compounds have selectively targeted and eliminated macrophages within atherosclerotic plaques. These agents including dextran sulfate-Ce6 (DS-Ce6)⁶¹ and D-mannosamine-polyethylene glycol-Ce6 (MAN-PEG-Ce6)⁶² are activated by near-infrared light that can penetrate the arterial wall and induce reactive oxygen species production within macrophages,⁶⁵ leading to their apoptosis,⁶⁶ thereby reducing the plaque burden⁶⁷ (**Fig. 2B and C**).

In addition to promoting macrophage apoptosis, photoactivation has been shown to enhance autophagy⁶⁵ within plaques, a critical process that contributes to inflammation resolution and plaque stabilization. DS-Ce6 photoactivation triggers apoptosis as well as induces autophagy, leading to enhanced clearance of apoptotic cells (efferocytosis) via Mer tyrosine-protein kinase upregulation. This multifaceted approach reduces inflammatory activity within plaques and supports the remodeling and stabilization of atherosclerotic lesions. Similarly, MAN-PEG-Ce6 specifically targeted mannose receptor-positive macrophages, which are abundant in inflamed atherosclerotic plaques. Upon activation by laser irradiation, MAN-PEG-Ce6 generates singlet oxygen, significantly reducing macrophage-mediated inflammatory responses without causing collateral damage to surrounding tissues.

Recent advances include the development of magnetofluorescent nanoparticles, such as Fe³⁺-catechol cross-linked bis(2,4,5-trichloro-6-[pentyloxycarbonyl]phenyl)oxalate-loaded mPEG-Plys-(3,4-dihydroxyphenylacetic acid-Ce6) nanoparticles (FeCNPs)⁶³ and crosslinked dextran-coated iron oxide-tetra(hydroxyphenyl)chlorin (CLIO-THPC).⁶⁴ These nanoparticles integrate MRI capabilities and allow for the combined imaging and treatment of atherosclerosis. FeCNPs have shown efficacy in noninvasively targeting macrophage-rich atherosclerotic lesions using chemically excited photodynamic therapy (**Fig. 2D**). This system eliminates the need for external light irradiation and relies on the chemical reaction between hydrogen peroxide and a high-energy compound to excite the photosensitizers, resulting in the production of singlet oxygen. This chemiexcited approach effectively reduces the inflammatory burden of plaques, as evidenced by decreases in CD68, monocyte chemoattractant protein-1, and TNF- α expression levels after treatment.

Moreover, a study using CLIO-THPC, a light-activated theranostic nanoagent, confirmed the efficacy of such treatments in murine models. *In vivo* imaging confirmed the significant localization of CLIO-THPC to macrophage-rich atherosclerotic lesions (**Fig. 2E**), with subsequent light irradiation leading to effective macrophage ablation, which promoted plaque stabilization without excessive off-target effects. Importantly, CLIO-THPC reduced skin phototoxicity compared with conventional Ce6-based agents, indicating a favorable safety profile.

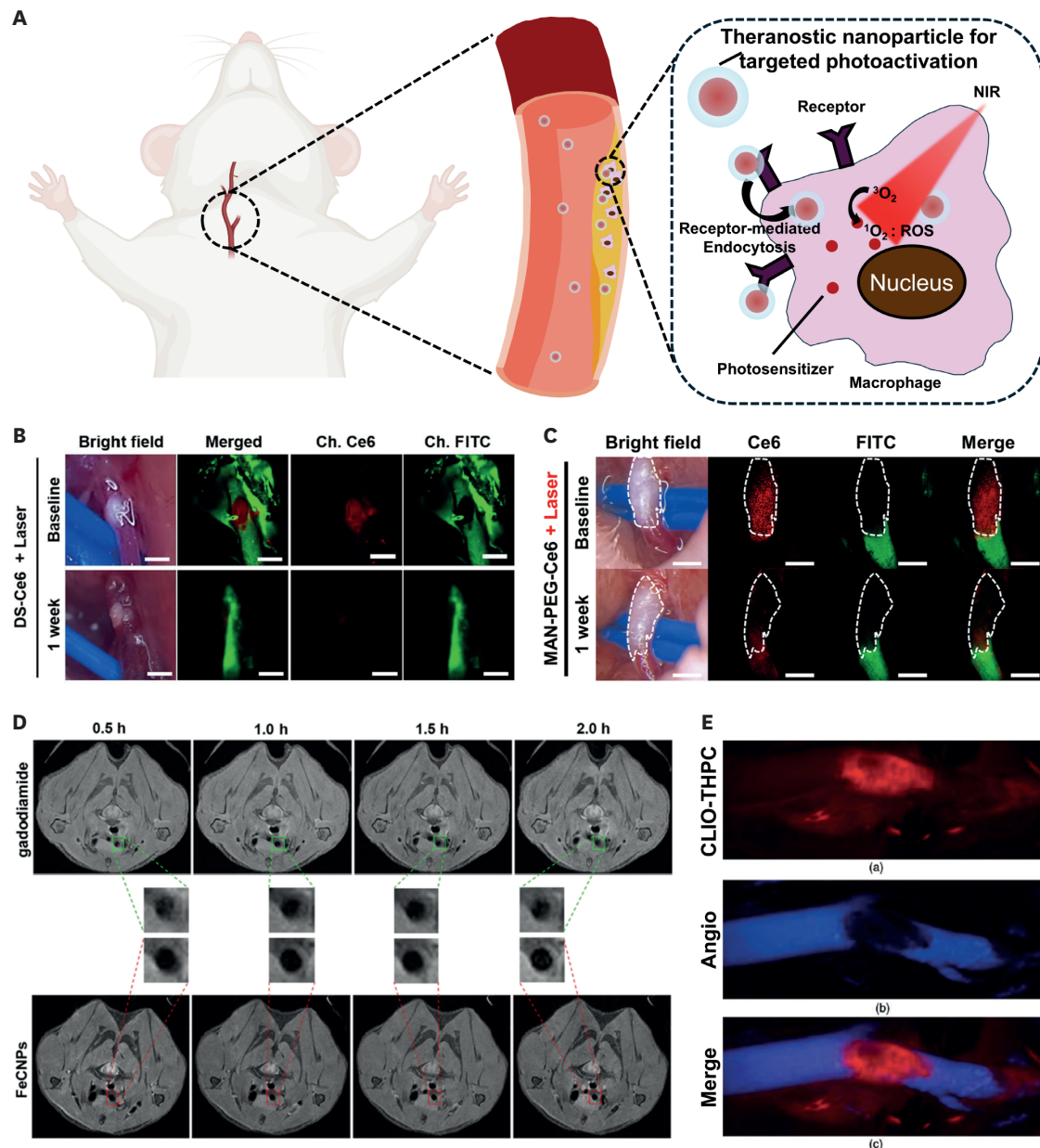


Fig. 2. Macrophage-targeted phototheranostic strategy. (A) Schematic overview of macrophage-targeted photoactivation. (B) Serial *in vivo* plaque imaging using DS-Ce6. (C) Serial *in vivo* plaque imaging using MAN-PEG-Ce6. (D) T_1 -magnetic resonance imaging of brachiocephalic artery of ApoE^{-/-} mouse treated with FeCNPs. (E) *In vivo* localization of CLIO-THPC using intravital fluorescence microscopy. Figures were adapted from the following sources: (B) Song et al.,⁶¹ CC-BY-4.0; (C) Lee et al.⁶² with permission from Elsevier; (D) Mu et al.,⁶³ *Int J Nanomedicine* 2022;17:2353-2366 Originally published by and used with permission from Dove Medical Press Ltd. Copyright remains with the authors and Dove Medical Press Limited; (E) JR McCarthy et al.⁶⁴ with permission from John Wiley and Sons. NIR, near-infrared; ROS, reactive oxygen species; DS-Ce6, dextran sulfate-chlorin e6; Ce6, chlorin e6; FITC, fluorescein isothiocyanate; MAN-PEG-Ce6, D-mannosamine-polyethylene glycol-Ce6; FeCNP, Fe3+-catechol cross-linked bis(2,4,5-trichloro-6-[pentyloxycarbonyl]phenyl)oxalate-loaded mPEG-Plys-(3,4-dihydroxyphenylacetic acid-Ce6) nanoparticle; CLIO-THPC, crosslinked dextran-coated iron oxide-tetra(hydroxyphenyl)chlorin.

Collectively, these findings suggest that macrophage-targeted imaging-guided photoactivation is a highly promising approach for the treatment of atherosclerosis, providing both diagnostic and therapeutic functionalities in a single nanoplatform. The ability to visualize and directly treat inflamed plaques could significantly advance the current treatment modalities for high-risk patients.

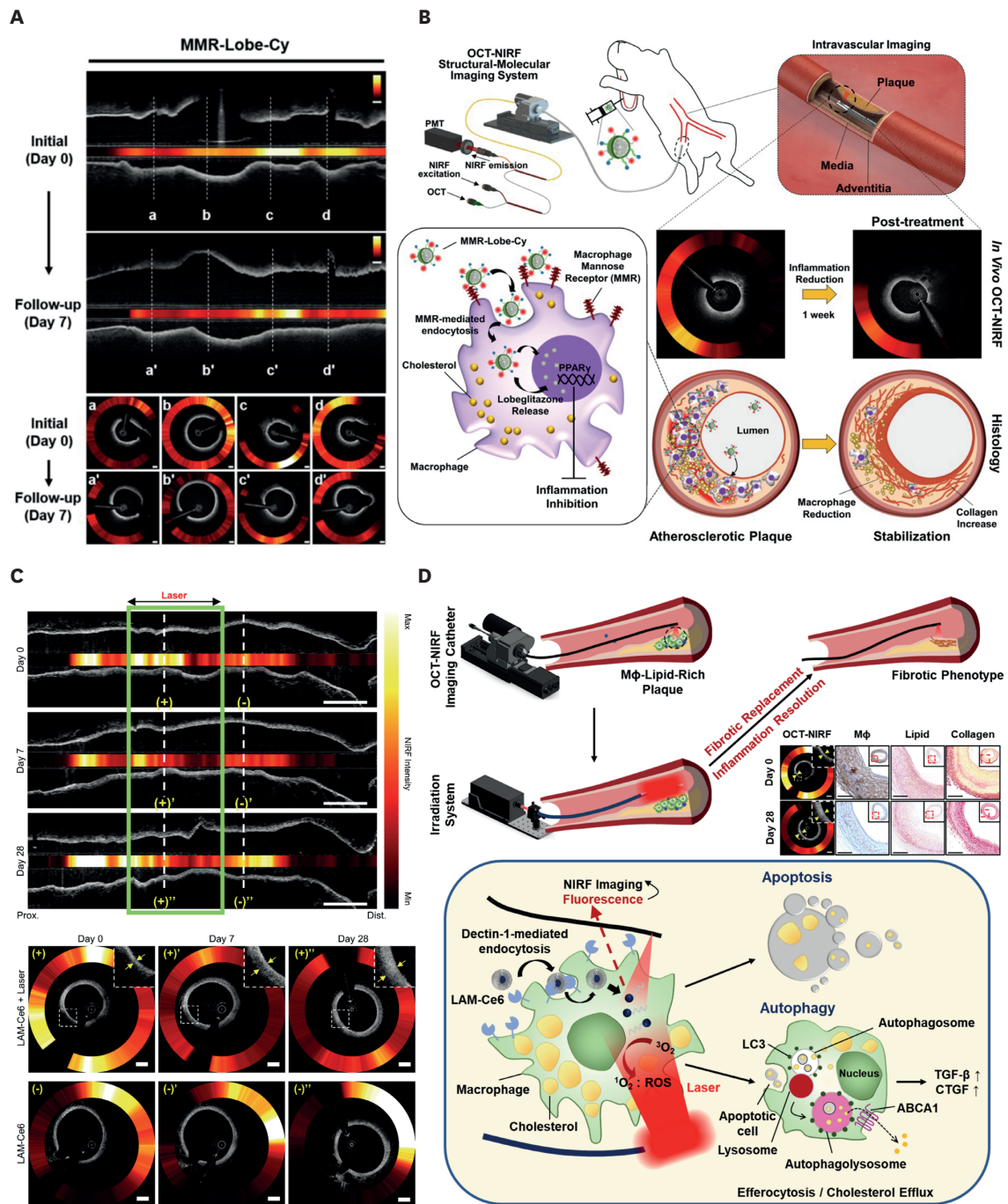


Fig. 3. Intravascular multimodal imaging-assisted theranostics. (A) *In vivo* serial longitudinal and axial OCT-NIRF images of an atheromatous rabbit treated with MMR-Lobe-Cy. (B) Schematic overview of *in vivo* OCT-NIRF imaging for theranostic drug delivery. (C) *In vivo* serial longitudinal and axial OCT-NIRF images of an atheromatous rabbit phototreated with LAM-Ce6. (D) Schematic overview of the *in vivo* OCT-NIRF imaging-guided photoactivation strategy. Figures were adapted from the following sources: (A) and (B) Song et al.,⁶⁸ CC-BY-4.0; (C) and (D) Kim et al.⁶⁹ with permission from Wolters Kluwer Health, Inc. MMR-Lobe-Cy, mannose-polyethylene glycol-glycol chitosan-deoxycholic acid-cyanine 7-lobeglitazone; OCT-NIRF, optical coherence tomography-near-infrared fluorescence; PMT, photomultiplier tube; NIRF, near-infrared fluorescence; MMR, macrophage mannose receptor; PPAR γ , peroxisome proliferator-activated receptor gamma; LAM-Ce6, laminarin-chlorin e6; ROS, reactive oxygen species; LC3, light chain 3; TGF- β , transforming growth factor β ; CTGF, connective tissue growth factor.

INTRAVASCULAR IMAGING-GUIDED THERANOSTIC STRATEGIES

1. Macrophage-targeted drug delivery system

Intravascular imaging-guided targeted drug delivery systems represent significant advancements in the management of high-risk atherosclerotic plaques (**Fig. 3A and B**). By utilizing imaging modalities, such as OCT-NIRF, it is possible to precisely identify plaques with high inflammatory activity and deliver therapeutic agents specifically to these sites. This targeted approach not only enhances treatment efficacy but also minimizes the risk of systemic side effects. In preclinical studies involving rabbit models, the use of OCT-NIRF-guided drug delivery systems demonstrated a significant reduction in plaque inflammation and stabilization of high-risk plaques. MMR-targeted nanodrugs, including mannose-polyethylene glycol-glycol chitosan-deoxycholic acid-cyanine 7-lobeglitazone, were loaded with the PPAR γ agonist lobeglitazone and precisely delivered to inflamed regions within the plaques.⁶⁸ This resulted in reduced macrophage content and increased fibrous cap thickness, both indicators of plaque stabilization. Moreover, the use of intravascular OCT-NIRF imaging allowed for real-time visualization of dynamic changes in inflammatory activity and rapid stabilization of coronary-sized arteries within just 1 week of treatment. This theranostic approach, which integrates diagnostic imaging and therapeutic interventions, is a promising tool to reduce the risk of acute coronary events by effectively targeting and stabilizing vulnerable atherosclerotic plaques.

2. Macrophage-targeted photoactivation

Macrophage-targeted photoactivation guided by intravascular imaging has demonstrated considerable potential in the treatment of atherosclerosis (**Fig. 3C and D**).⁶⁹ By combining OCT-NIRF imaging with a catheter-based light diffuser, researchers have successfully applied localized photoactivation to atherosclerotic plaques *in vivo* within coronary-sized vessels. This approach allows for the real-time monitoring of therapeutic effects, enabling adaptive adjustments to optimize outcomes.

Laminarin-Ce6 (LAM-Ce6)⁶⁹ was fabricated via chemical conjugation with the dectin-1 ligand laminarin and Ce6. Using OCT-NIRF imaging guidance, LAM-Ce6 was selectively delivered to macrophage-rich regions and subsequently activated using intravascular laser irradiation. This localized photoactivation led to macrophage apoptosis and enhanced autophagy within the plaques, thereby reducing the inflammatory burden. Moreover, LAM-Ce6 photoactivation triggered a phenotypic shift in plaques toward more stable, fibrous, and transforming growth factor β -dependent collagen deposition. This resulted in an increased collagen content and decreased lipid levels in the plaques, indicating a more stable plaque phenotype.

These findings suggest that intravascular imaging-guided photoactivation may serve as a valuable tool for the treatment of high-risk atherosclerotic plaques, particularly in patients who are not candidates for more invasive interventions. The combination of precise imaging guidance, targeted agent delivery, and real-time adaptability offers an innovative theranostic approach with a high translational potential for reducing cardiovascular events linked to plaque rupture.

KEY OBSTACLES AND CHALLENGES OF CLINICAL TRANSLATION

Despite the promising preclinical test results obtained in small-animal models, integrating theranostic approaches into real-world applications has several substantial barriers.^{70,71} Among those challenges is the requirement to conduct large-scale studies in larger animals to ensure safety and effectiveness in conditions more closely resembling those in humans. While small-animal models are suitable and serve their purpose for initial proof of concept studies, they are woefully deficient in capturing the anatomical and physiological complexity of human coronary arteries. Studies with larger animals, especially pigs and some nonhuman primates, provide invaluable information on the pharmacokinetics, biodistribution, and long-term safety of new drugs, which is critical for the clinical application of nanoparticle-based therapies.

Obtaining regulatory approval poses yet another challenge. The U.S. Food and Drug Administration and European Medicines Agency conduct rigorous validation of nanoparticle-based therapies, including long-term toxicity studies, immunogenicity evaluations, and batch-to-batch consistency checks for reproducibility and patient safety. All these must comply with Good Manufacturing Practice requirements to reduce variability in the production process. Another interesting problem is the cost and scalability of nanoparticle production. Nanoparticle synthesis and functionalization, as well as targeting ligands and enhanced imaging agents, are relatively expensive and difficult to scale up for clinical applications, highlighting barriers in bringing therapeutic solutions to a wider population. New cost-effective techniques for producing numerous nanoparticles are required to increase accessibility to broader patient populations.

The overall cost of manufacturing can be massively reduced via cheap synthesis with automatic processes and more productive manufacturing. A coordinated group of clinicians, biomedical engineers, regulatory specialists, and industry partners will be key to overcoming these obstacles. Such a collaborative approach will optimize production processes, improve regulatory compliance, and accelerate the clinical translation of theranostic strategies.

CONCLUSION

Macrophages have been identified as crucial players in promoting plaque progression and vulnerability; thus, there is an urgent need for new approaches that directly address the underlying mechanisms of their action. A theranostic strategy that combines advanced imaging diagnostics with targeted therapy may provide the most promising solution to these challenges. The combination of state-of-the-art multimodal imaging techniques including but not limited to OCT and NIRF along with targeted drug delivery and macrophage-specific interventions, can facilitate a highly tailored, personalized, and minimally invasive approach for stabilizing high-risk atherosclerotic plaques.

Recent advances in dual-modality imaging catheters and nanoparticle-based drug delivery have shown great promise for enhancing the specificity of atherosclerosis therapy. Targeted drug delivery and photoactivation have resulted in significant decreases in plaque inflammation, as evidenced by preclinical studies in murine and rabbit models, leading to improved plaque stability without the systemic side effects associated with traditional

therapies. In addition to providing high-resolution visualization of vulnerable plaques, these theranostic approaches allow for real-time adaptive interventions that may reduce the risk of acute cardiovascular events.

While these results are encouraging, significant hurdles remain in translating intravascular imaging-assisted theranostic strategies into clinical practice. Key challenges include the need for extensive validation in large animal models and human trials and addressing major questions related to safety, cost, and scalability. Cost-effective synthesis and the large-scale production of nanoparticles are essential for accurate clinical translation. Additionally, ensuring regulatory compliance with Good Manufacturing Practice standards is essential. Establishing robust quality control measures will be crucial in guaranteeing the safety and efficacy of these therapies in clinical settings.

Future studies should focus on optimizing nanoparticle formulations and validating these approaches in large-animal models. Bridging the gap between preclinical success and clinical application will require collaboration across disciplines to address safety, regulatory, and economic challenges. Given these novel approaches, theranostics may play a central role in reducing the burden of cardiovascular disease and improving patient outcomes in the near future.

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