

Natural, Engineered, and Hybrid Platelet Membrane–Based Nanotherapeutics for Inflammatory Diseases

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Abstract: Nanotherapeutics based on platelet membranes represent a new and advanced biomimetic approach in nanomedicine. By covering synthetic nanoparticle cores with natural platelet membranes, these platforms ingeniously combine the multifaceted biointerfacing abilities of platelets, such as long circulation, immune evasion, and targeting of inflamed tissues, with the many functions of engineered cores. This review systematically summarizes recent advances in the design and application of nanotherapeutics, categorizing them into three platforms: those derived from natural platelet membranes, those utilizing engineered platelet membranes for enhanced targeting or drug loading, and those employing hybrid membranes fused with other cell types to combine complementary functionalities. We emphasize their therapeutic efficacy in various inflammatory diseases such as atherosclerosis, ischemic injury (stroke and myocardial infarction), rheumatoid arthritis, microbial infections, and the tumor inflammatory micro-environment. Finally, we discuss the translational potential and current challenges of this technology and provide a critical perspective on its future development in precision medicine.

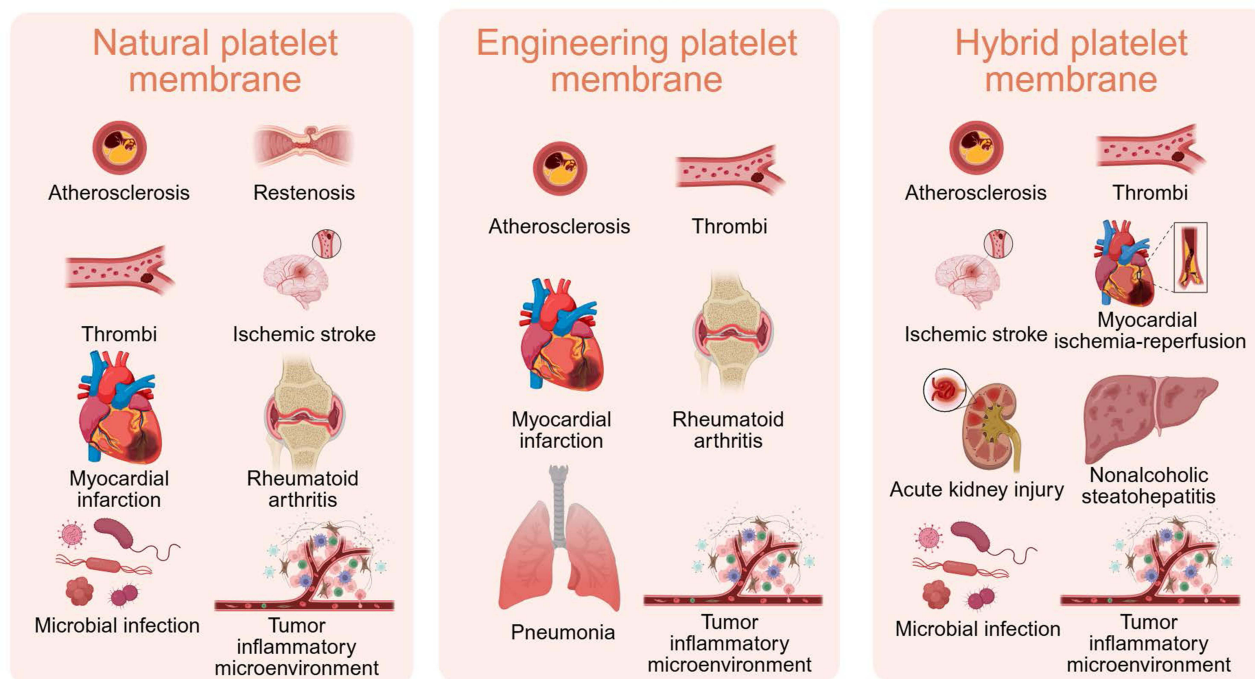
Keywords: platelet membrane, engineered platelet, hybrid membrane, inflammation, nanotherapy

Introduction

Inflammation is a defensive reaction that involves immune cells, blood vessels, and molecular mediators to counteract harmful stimuli such as pathogens, damaged cells, or irritants. It is considered a mechanism of innate immunity that aims to eliminate the initial cause of cell injury, remove necrotic cells and damaged tissues, and initiate tissue repair.¹ During the inflammation process, immune cells such as neutrophils, monocytes, and lymphocytes migrate into the damaged areas to varying extents. Acute inflammation is an essential biological reaction that safeguards against infection, removes harmful substances, and aids in the recovery of injured tissue.² Chronic inflammation can increase the probability of inflammatory harm, as well as infections and other systemic disorders,³ such as arthritis, atherosclerosis, and cancer.^{4,5} There is growing recognition that chronic or uncontrolled inflammation plays a significant role in the onset and advancement of several severe illnesses, including cancer, obesity, type 2 diabetes, atherosclerosis, ischemic disease, systemic inflammatory response syndrome, and even autoimmune disease.⁶ Various pharmacological groups, such as antibiotics, cytotoxic medicines, and hormones, can effectively combat inflammation. However, these treatments have systemic effects, and prolonged usage can lead to significant negative effects.^{7,8} Nanoparticle (NP)-mediated medication-delivery systems incorporating anti-inflammatory medicines are potentially more secure and efficient alternatives.

Graphical Abstract

Platelet Membrane-based Nanotherapeutics for Inflammatory Disease



NP-based drug-delivery systems have shown significant promise in biomedical applications owing to their desirable and adjustable characteristics, such as loading capacity and sufficient protection for drugs, as well as their ability to control drug release, among other benefits.^{9–12} Nevertheless, many challenges remain. Plasma proteins readily opsonize synthetic NPs, leading to their efficient clearance by the immune system.¹³ Under certain circumstances, the NPs can stimulate the immune system to produce antibodies, which in turn hasten their removal from the body.^{14–17} Furthermore, NPs typically lack the ability to aggressively target the disease environment, unlike real cells. As a result, the overall accumulation of NPs is limited. Therefore, utilizing the cell membrane to disguise NPs for active distribution offers a novel opportunity for targeted therapy.¹⁸

The use of cell membrane-based nanotherapeutics has emerged as a highly promising approach for enhancing the transport of therapeutic drugs. This is achieved by combining the biomimetic characteristics of cell membranes with the functional adaptability of nanomaterials.^{19,20} This method involves enveloping artificial nanocarriers with a natural cell membrane, which addresses certain limitations of NPs created using traditional self-assembly techniques, such as poor colloidal stability and nonspecific tissue accumulation.²¹ Cell membrane-coated NPs have the ability to replicate the biological characteristics of the cells from which they are derived. This allows them to persist longer in the circulatory system and target specific diseases.²²

Platelets are tiny, disc-shaped blood cells that lack a nucleus and range in size from 2 to 4 μm . Produced from megakaryocytes in the bone marrow,²³ platelets play a vital role in the process of blood clotting, as they can specifically locate areas of blood vessel damage and ensure proper blood flow.²⁴ Furthermore, platelets participating in the activities and interactions between cells are crucial in inflammatory, immunological, and tumor-development processes.²⁵ Previous studies have shown that platelets, a type of immune cell, are naturally attracted to inflammation and tumors. This

characteristic can be harnessed to deliver drugs with anti-inflammatory and anti-cancer properties.^{26–28} Therefore, platelet membranes and PEVs may be reliable sources of cell membranes for membrane-based nanotherapies.

This paper reviews the use of natural platelet membranes, engineered platelet membranes, or platelet membranes hybridized with other cell membranes as nanotherapies for the treatment of inflammatory illnesses. Herein, we provide a concise overview of the methodologies employed to extract and coat platelet membranes. Next, we discuss the various applications of platelets and their membranes in the treatment of inflammatory illnesses. Finally, we discuss the potential future prospects of this approach.

Preparation and Coating Methods of Platelet Membrane

The commonly employed techniques for producing biomembrane-derived NPs involve the following three stages: extracting the membranes, preparing NP cores, and covering the NP cores with vesicles produced from the membranes (Figures 1 and 2).²⁹ Hu et al fabricated platelet membrane-coated nanoparticles (PNPs) by utilizing a cell membrane

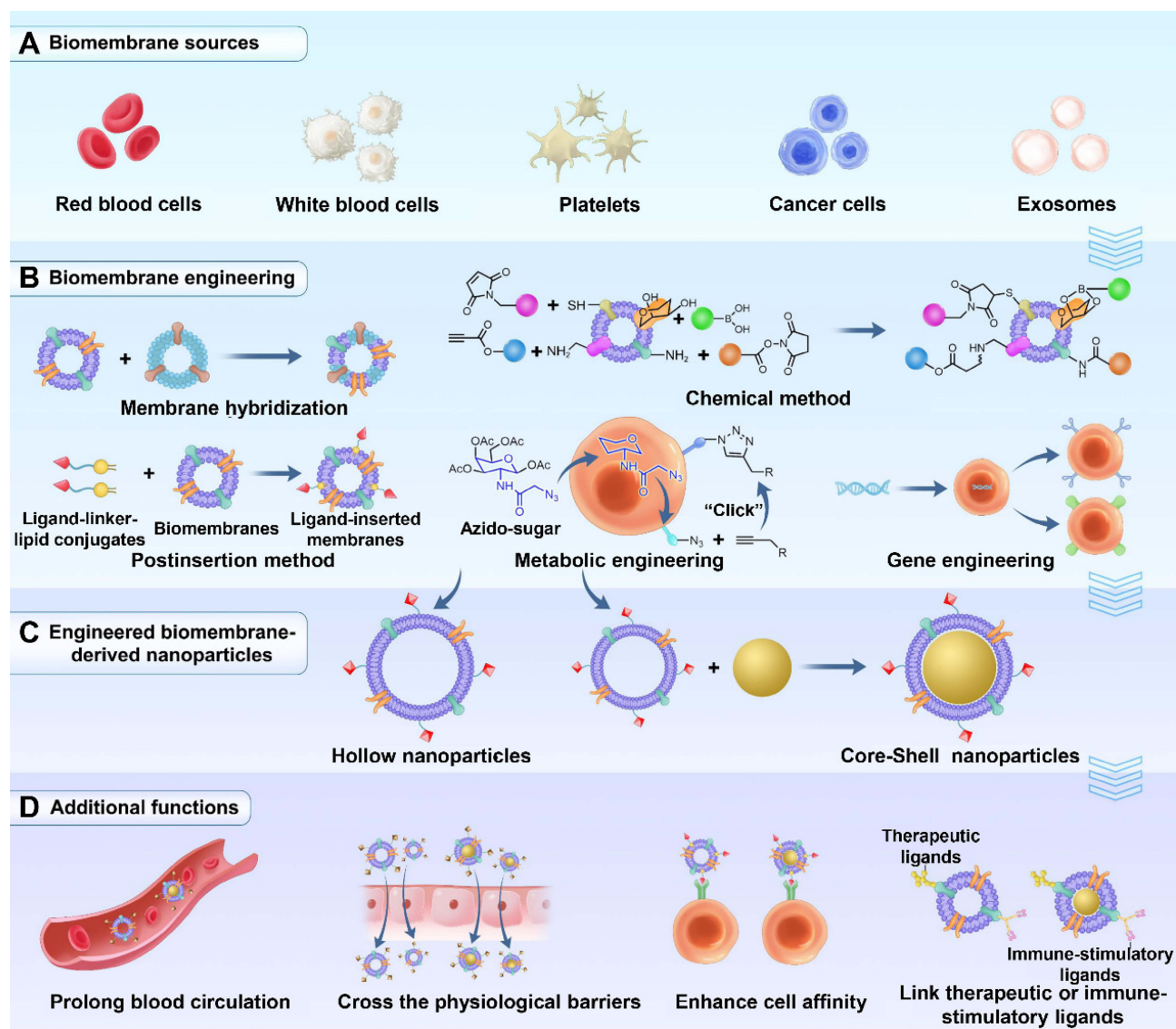


Figure 1 Schematic illustrations of five membrane engineering methods and introduced additional functions. (A) Different types of membrane materials used for engineering. (B) Membrane engineering methods: membrane hybridization, postinsertion method, chemical method, metabolic engineering and gene engineering. (C) Engineering biomembrane-derived nanoparticles: hollow or core-shell types. (D) Additional functions introduced by membrane engineering. Reprinted with permission from Wu Z, Zhang H, Yan J, Wei Y, Su J. Engineered biomembrane-derived nanoparticles for nanoscale therapeutics. *Theranostics*. 2023;13(1):20–39. Copyright 2023 Theranostics.³³

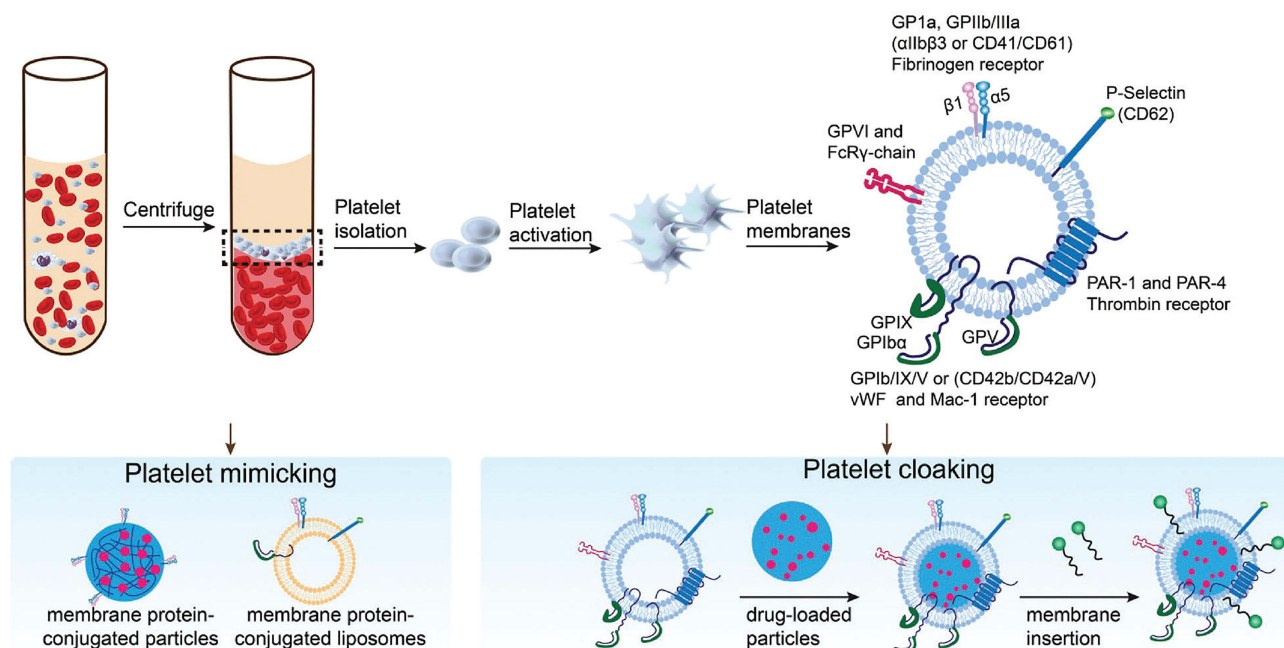


Figure 2 The fabrication of platelet-like nanoparticles for disease treatment. Platelets were collected by centrifugation and activated, and the membranes of the platelets were prepared for further usage. The area within the black dashed box indicates the platelet layer after centrifugation. Reprinted with permission from Li Z, Hu S, Cheng K. Platelets and their biomimetics for regenerative medicine and cancer therapies. *J Mater Chem B*. 2018;6(45):7354–7365. Copyright 2018 Journal of Materials Chemistry B.³⁴

cloaking technique.^{18,30,31} These PNPs are composed of a biodegradable polymeric NP core that is fully protected by the plasma membrane of human platelets.³²

Methods of Platelet Membrane Extraction

Platelets were extracted approximately 30 minutes after blood collection.³² Before collecting the platelets, the blood and plasma samples were combined with ethylenediaminetetraacetic acid (EDTA), which inhibits platelet aggregation by deactivating the fibrinogen-binding integrin α IIb β 3.³⁵ To separate the red and white blood cells, the blood and plasma samples were centrifuged at $100 \times g$ for 20 min at room temperature, resulting in the isolation of platelets. Platelet-rich plasma (PRP) was centrifuged at $100 \times g$ for 20 min to eliminate any residual blood cells. A phosphate buffer solution (PBS) containing EDTA and prostaglandin E1 was introduced into pure PRP to inhibit platelet activation. The platelets were subsequently separated via centrifugation at $800 \times g$ for 20 min at room temperature. The supernatant was then removed, and the platelets were suspended in a solution of PBS containing EDTA. They were then combined with tablets to inhibit the protease enzyme activity. The platelet membrane was obtained using a repetitive freeze–thaw method. The platelet suspensions were initially frozen at -80°C , defrosted at ambient temperature, and then separated by centrifugation at a speed of $4000 \times g$ for a duration of 3 min. After three consecutive washes using a PBS solution containing protease inhibitor tablets, the collected platelet membranes were immersed in water and sonicated in a sealed glass vial for 5 min (Figure 3).³²

Methods for Coating Platelet Membranes onto Nanoparticles

Biomembrane-derived NPs can be created using many techniques, including co-extrusion, sonication, microfluidic electroporation, and cell membrane–templated polymerization. Table 1 summarizes the advantages and disadvantages of different methods for coating platelet membranes with NPs.

- a. Co-extrusion: Co-extrusion involves passing the NP solution and vesicles through polycarbonate porous membranes of varying diameters while simultaneously sonicating them for a few minutes. This process results in the formation of NPs with a consistent cross-sectional profile.³² Extrusion applies a powerful force that can disrupt

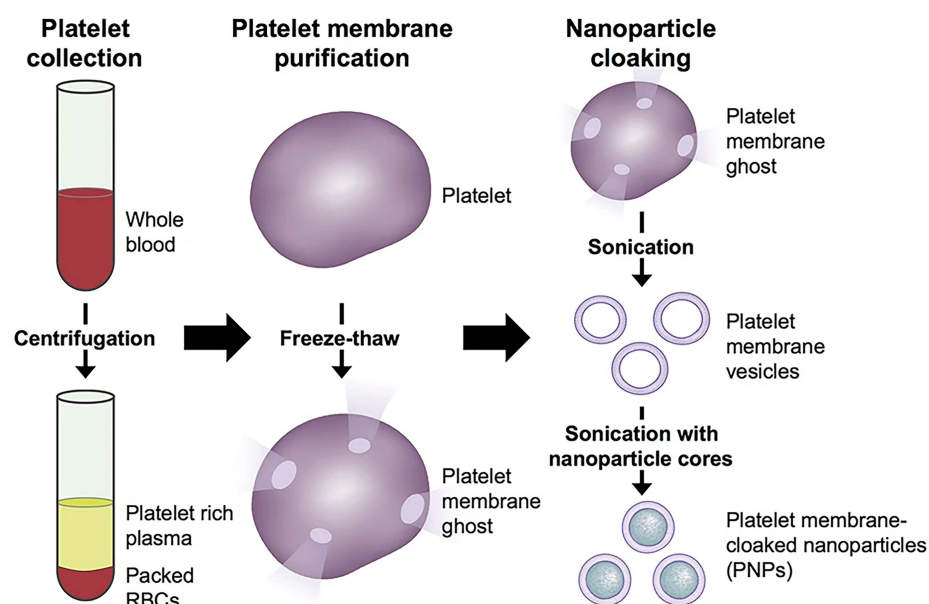


Figure 3 Schematic depicting the process of preparing PNPs. Reprinted with permission from Hu CM, Fang RH, Wang KC, et al. Nanoparticle biointerfacing by platelet membrane cloaking. *Nature*. 2015;526(7571):118–21. Copyright 2015 Nature.³²

the structural integrity of the membrane, allowing it to rebuild around the inner core NP and effectively coat the NP cores.^{18,36,37} Although the extrusion technique shows promise, its use in large-scale production presents obstacles. Therefore, sonication has been demonstrated to be an effective method for fusing NP cores and membrane vesicles.³⁸

- b. **Sonication:** Sonication employs ultrasonic radiation at certain frequencies to merge membranes and nano vehicles³⁹ into core–shell structures, resulting in lower material loss than that caused by co-extrusion.³² The frequency, duration, and amplitude of sonication are the primary factors that determine the effectiveness of the fusion process. During sonication, powerful forces are applied to the NP core and membrane vesicles that are incubated together, resulting in the spontaneous formation of a core–shell structure.³⁸

Table I Comparison of Different Coating Methods for Platelet Membrane–Based Nanoparticles

Method	Principle	Advantages	Limitations	Ref.
Co-extrusion	Co-extruding membrane vesicles and nanoparticle cores through porous polycarbonate membranes using mechanical force to achieve fusion	Simple operation; Allows control over particle size	Difficult to scale up for production; Potential damage to membrane structure	[18,32,36–38]
Sonication	Utilizing ultrasonic energy to physically fuse membrane vesicles and nanoparticle cores in a liquid phase	Applicable to various core materials; low material loss	Requires optimization of sonication parameters; May affect membrane protein activity	[32,38,39]
Microfluidic Electroporation	Applying electric pulses within a microfluidic chip to create temporary pores in membranes, facilitating nanoparticle core entry and coating	High coating efficiency; superior colloidal stability	Complex equipment required; Sensitive to electrical parameters	[33,40]
Cell Membrane-Templated Polymerization	Using the cell membrane as a template to grow a polymeric nanoparticle core in situ through interfacial polymerization.	Excellent control over final nanoparticle size; High coating efficiency and uniformity; Core forms directly within the membrane, ensuring a complete shell	Relatively new and underexplored technique; Requires specialized knowledge of polymerization chemistry; Risk of premature polymerization outside the vesicle	[38]

- c. Microfluidic electroporation: Microfluidic electroporation is a new method that applies an electric pulse between two electrodes to facilitate the coating of nanocores with biomembrane vesicles.³³ Biomembrane-derived NPs, produced using microfluidic procedures, have superior colloidal stability and higher coating effectiveness than those made using standard extrusion methods.⁴⁰ This strategy is gaining popularity because it allows NPs to remain stable while preventing them from clumping together.⁴⁰
- d. Cell membrane-templated polymerization: This technology is new and thus has not yet been extensively studied. It relies on interactions between the cores and cell membranes. The polymeric core is synthesized in situ within the cores to enable effective coating and convenient modification of the NP size. By contrast, the typical process employs prefabricated polymers, which do not allow control over the already produced NPs (Figure 4).³⁸

Natural Platelet Membrane-Based Nanotherapeutics for Inflammatory Diseases

Atherosclerosis

Atherosclerosis is a cardiovascular condition that poses a major hazard to human health. It is characterized by persistent thickening of the arterial walls, an inflammatory reaction, and a disruption in lipid metabolism.^{26,41–44} Inflammatory macrophages have been identified as a crucial element in atherosclerosis development. These macrophages are capable of

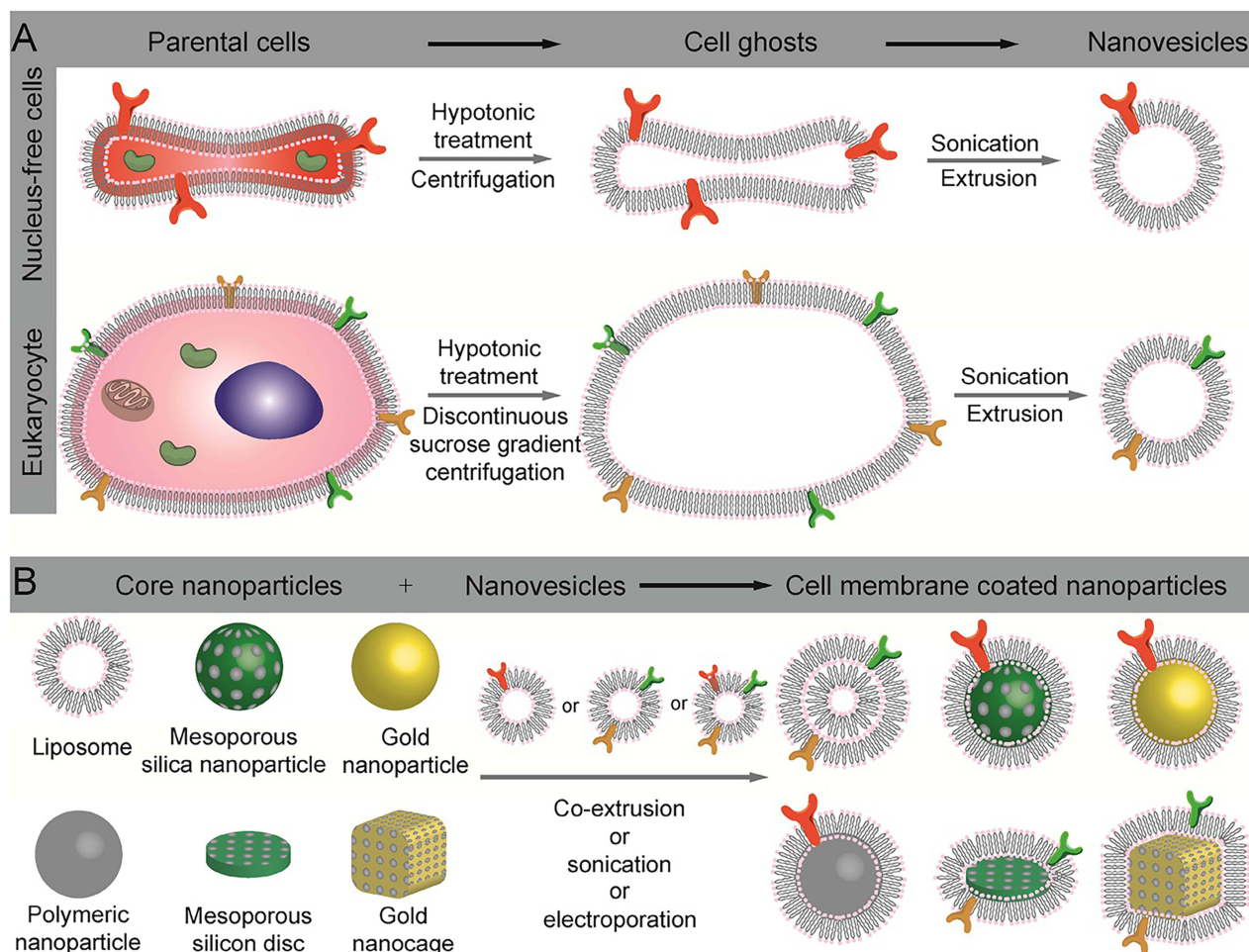


Figure 4 Schematic illustration of the preparation of cell-membrane coated nanoparticles. **(A)** Extract of intact cell ghost from parent cells and further processing into nanovesicles. **(B)** Different types of nanoparticles that have been used as inner cores, and their fusion with nanovesicles to construct cell membrane coated nanoparticles. Reprinted with permission from Zhai Y, Su J, Ran W, et al. Preparation and Application of Cell Membrane-Camouflaged Nanoparticles for Cancer Therapy. *Theranostics*. 2017;7(10):2575–2592. Copyright 2017 Theranostics.³⁶

releasing pro-inflammatory cytokines, which enhance the localized inflammatory reaction at the location of the atherosclerotic plaque, ultimately resulting in the creation of a plaque.^{43,45–47} Biomimetic NPs, created by enveloping a synthetic nanoparticulate core with a platelet membrane, can interact with activated endothelium, foam cells, and collagen. These effects were demonstrated to be specific to platelet membrane-coated NPs. These biomimetic nanocarriers can effectively target both well-established atherosclerotic plaques and subclinical sections of arteries that are prone to plaque formation.⁴⁸ Huang et al effectively created a highly biocompatible Janus mesoporous silicon nanomotor with a drug-loaded platelet membrane bionic structure (MJAMS/PTX/aV). This nanomotor can not only enter the plaque but also be effectively absorbed by stimulated endothelial cells and inflammation-related macrophages upon exposure to near-infrared (NIR) radiation (Figure 5).⁴⁹ Inflammation in the vicinity of atherosclerosis activates endothelial cells, in turn triggering the attachment and clustering of platelets.^{50,51} Wei et al have shown that using platelet membranes as functional coverings for nanocarriers allows for precise targeting of imaging payloads to atherosclerotic sites.⁴⁸ Using rapamycin (RAP) as the model drug and based on platelets' inherent affinity to plaques, Song et al created a platelet-like delivery system to specifically target atherosclerotic plaques. This was achieved by combining platelet membranes with poly (DL-lactide-co-glycolide) NPs (Figure 6). The resulting platelet membrane-coated NPs successfully targeted atherosclerotic plaques, slowed the advancement of atherosclerosis, and stabilized plaques when the NPs were loaded with rapamycin.²⁸ Photodynamic therapy (PDT) triggers cell death through autophagy and controls lipid metabolism in

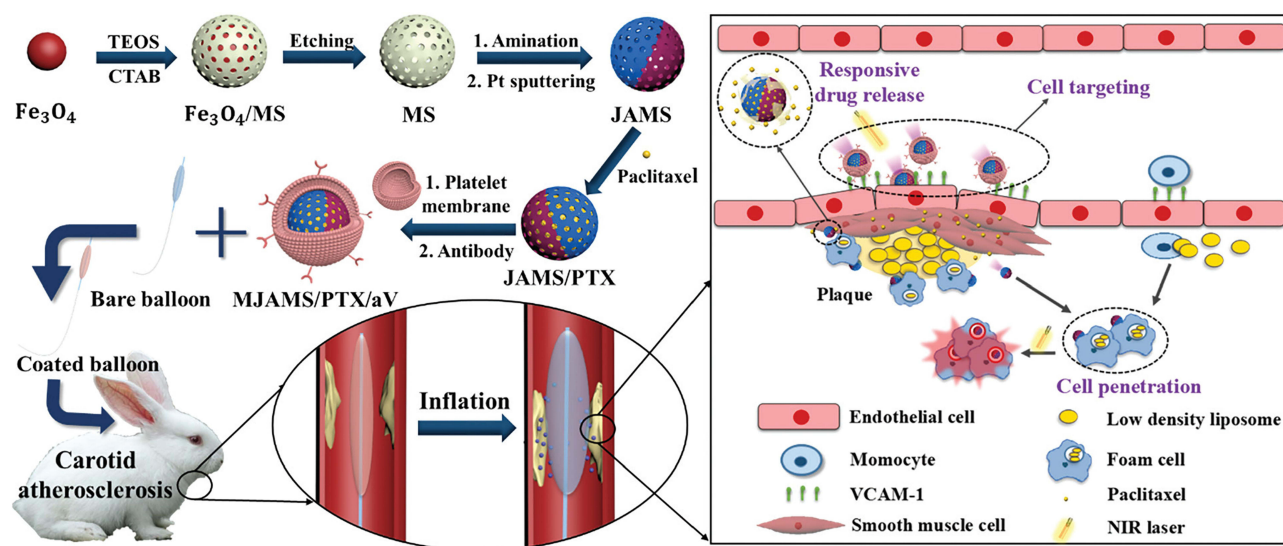


Figure 5 Schematic illustration of the synthesis process of MJAMS/PTX/aV and the mechanism of treatment of atherosclerosis using the MJAMS/PTX/aV coated balloon. Reprinted with permission from Huang Y, Li T, Gao W, et al. Platelet-derived nanomotor coated balloon for atherosclerosis combination therapy. *J Mater Chem B*. 2020;8(26):5765–5775. Copyright 2020 Journal of Materials Chemistry B.⁴⁹

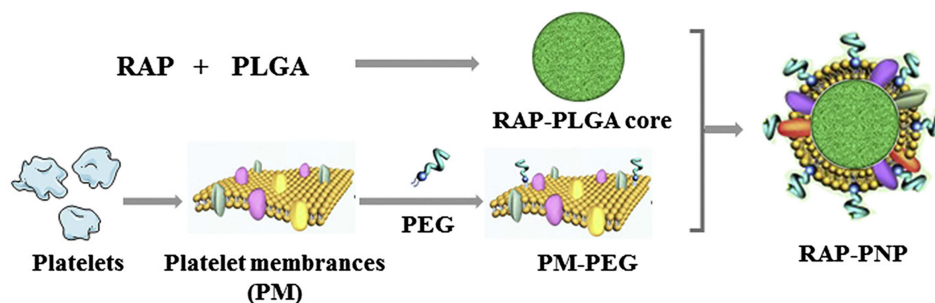


Figure 6 Schematic design of RAP-loaded PNP. Reprinted with permission from Song Y, Huang Z, Liu X, et al. Platelet membrane-coated nanoparticle-mediated targeting delivery of Rapamycin blocks atherosclerotic plaque development and stabilizes plaque in apolipoprotein E-deficient (ApoE^{-/-}) mice. *Nanomedicine*. 2019;15(1):13–24. Reproduced with permission from. Copyright 2019 Nanomedicine.²⁸

foam cells produced from macrophages.⁵² Ma et al effectively developed a delivery system that mimics platelets. This technology allows for the precise targeting and noninvasive PDT of atherosclerotic plaques. In addition, SPECT/CT-guided PDT effectively mitigates the advancement of atherosclerosis by modulating lipid metabolism and diminishing inflammation.⁵³ Zhang et al developed a bionic nano-delivery platform that used platelet membranes (PMs) to cover black phosphorus nanosheets (BPNSs) and specifically target macrophages in atherosclerotic plaques. The NPs were used to insert small interfering RNA into macrophages that inhibit Ca^{2+} /calmodulin-dependent protein kinase γ (CaMKII γ). Moreover, macrophage efferocytosis was reestablished by inhibiting CaMKII γ and enhancing the expression of MerTK, a cytosolic receptor, thereby facilitating the removal of apoptotic cells from plaques.⁵⁴ Chen et al created a biomimetic platelet membrane-coated polyphenol-cerium dioxide nanozyme complex that worked as a broad-spectrum antioxidant by eliminating superoxide anions, H_2O_2 , and intracellular reactive oxygen species (ROS) while also boosting the activities of hepatic superoxide dismutase (SOD) and glutathione (GSH). This complex specifically targets atherosclerotic plaques and is highly effective at reducing oxidative stress, preventing lipid uptake and accumulation, controlling cholesterol efflux, and stopping the release of inflammatory factors.⁵⁵

Restenosis

Postoperative restenosis has emerged as a significant limitation of interventional endovascular therapy for cardiovascular conditions and significantly affects the long-term prognosis and quality of life of patients.^{56,57} The onset and advancement of this phenomenon are highly intricate, and a sequence of reactions, such as an inflammatory response, thrombus, and intimal hyperplasia (IH), typically occurs following initial damage to endothelial cells. These processes pose significant challenges for the development of effective anti-restenosis strategies.^{58,59} Hao et al developed a pH-responsive NP (RM/JQ1/PM) to encapsulate JQ1 (a multi-effect endothelium-protective epigenetic inhibitor) for targeted drug delivery with controlled release. The NPs were camouflaged using PMs. This system demonstrated a notable anti-inflammatory effect by impeding the nuclear factor- κB (NF- κB) signaling pathway and the release of pro-inflammatory cytokines from macrophages (Figure 7).⁶⁰

Ischemic Disease

Thrombi

Vascular diseases such as myocardial infarction, stroke, and peripheral artery disease are significant contributors to both morbidity and mortality worldwide.⁶¹ A common clinical manifestation in these diseases is the development of occlusive clots (thrombi) in blood vessels, which impede blood flow to vital organs.⁶² ROS, originating from activated platelets and disrupted endothelial cells, are widely recognized for their significant contributions to the formation of blood clots. They achieve this by facilitating platelet-endothelium interactions and causing malfunction in the endothelium.⁶³⁻⁶⁶ Surplus ROS also provokes the development of pro-inflammatory cytokines on the endothelium and promotes vascular blockage.^{67,68} Pawlowski et al created platelet microparticle (PMP)-inspired nanovesicles (PMINs) that can safeguard thrombolytic medications by enclosing them, preventing unintended absorption and effects. These nanovesicles can attach to blood clots using PMP-relevant molecular mechanisms and release the drugs when triggered by enzymes relevant to blood clots, which could also be an efficient delivery platform for other therapeutic payloads in the vascular compartment.⁶⁹ Zhao et al produced H_2O_2 -responsive platelet membrane-cloaked argatroban-loaded polymeric NPs (PNPArg). These NPs were designed for thrombus therapy, taking advantage of the abundance of H_2O_2 and the thrombus-targeting properties of platelets. PNPArg efficiently and specifically targeted blocked blood arteries and effectively inhibited the formation of blood clots. Additionally, they reduced the levels of H_2O_2 and inflammatory cytokines produced by ferric chloride in a mouse model of carotid artery thrombosis.⁷⁰

Ischemic Stroke

Ischemic stroke, which accounts for 80% of all stroke cases,^{71,72} is recognized as a leading cause of death worldwide.^{73,74} At present, the first-line treatments for stroke patients are thrombolysis⁷⁵ and antiplatelet therapy⁷⁶ to improve cerebral circulation. The FDA approved the early use of recombinant tissue plasminogen activator (rtPA) as an exclusive and efficacious thrombolytic treatment for acute ischemic stroke (AIS).⁷⁷⁻⁷⁹ Enclosing melanin nanoparticles (MNPs) and tissue plasminogen

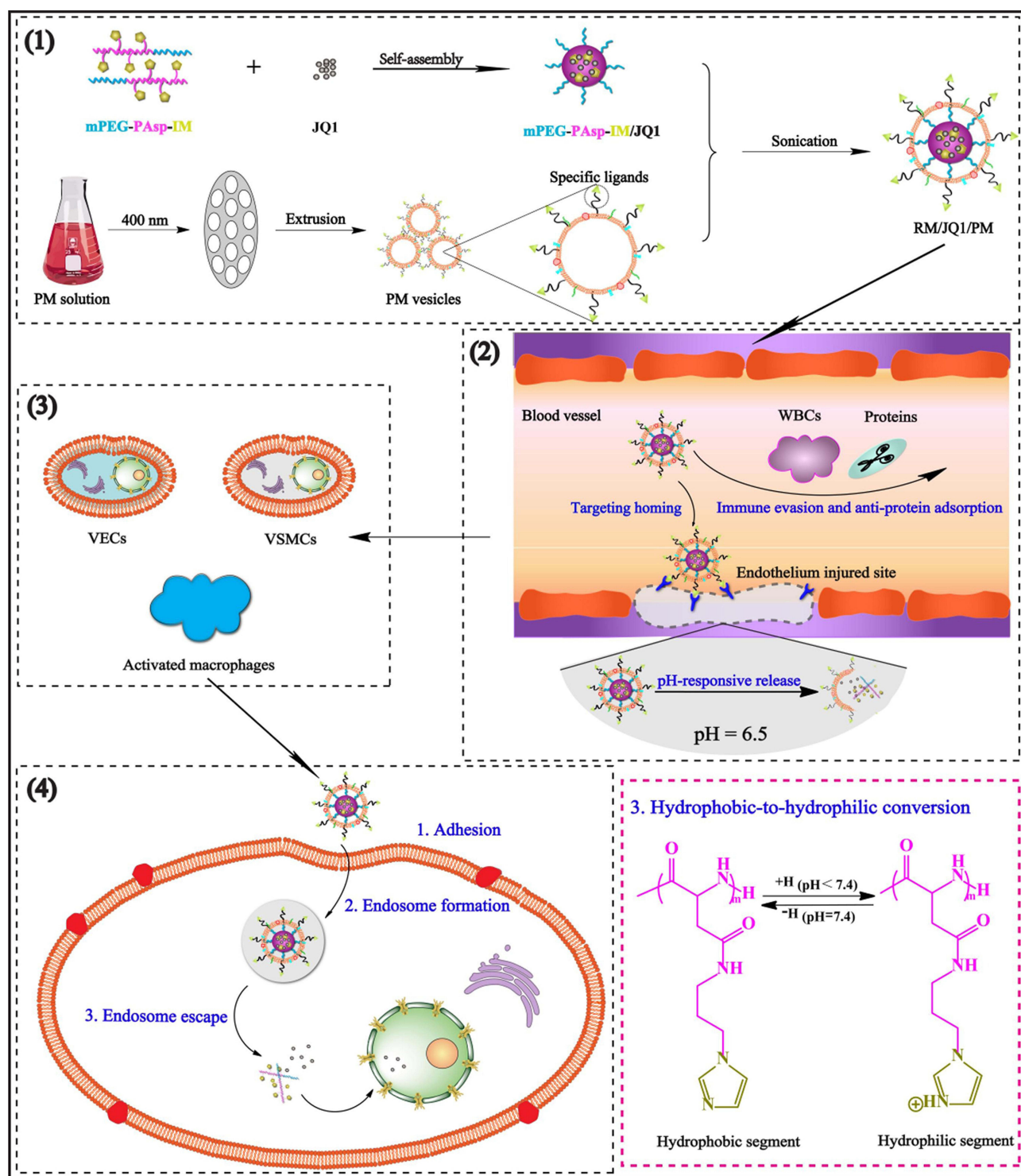


Figure 7 Process of RM/JQ1/PM preparation (1), targeting homing to injured vascular endothelium site (2), selectivity for different cells including VECs, VSMCs and activated macrophages (3) and cellular drug delivery in VSMCs as well as pH-responsive JQ1 release (4). Reprinted with permission from Hao X, Gai W, Ji F, et al. Biomimetic and responsive nanoparticles loading JQ1 for dual-targeting treatment of vascular restenosis via multiple actions. *Chemical Engineering Journal*. 2022; 431:133452. Copyright 2022 Chemical Engineering Journal.⁶⁰

activator (tPA) with vesicles derived from platelet membranes (PMs), Yu et al created a biomimetic nanovesicle called tPA/MNP@PM. These nanovesicles combine the thrombus-targeting ability of PM, photothermal conversion capabilities, and the ability to scavenge the free radicals of natural melanin. Site-specifically released MNPs, when combined with hemoperfusion, can cross the blood-brain barrier (BBB) and gather at the site of cerebral ischemia. It acts by removing different types of

harmful free radicals and reduces damage caused by inflammation and immunological responses, thus providing neuroprotection following thrombolysis.⁸⁰

Neutrophils (NEs) are the first and most prevalent inflammatory cells that emerge during microvascular reactions to ischemic stroke. By contrast, monocytes/macrophages move to the cerebral ischemic areas throughout the acute phase of inflammation.^{81–83} The excessive infiltration of NEs is linked to increased levels of ROS and inflammatory mediators, which exacerbate the damage to ischemic tissue.^{84–87} Tang et al presented platelet-mimetic nanoparticles (PTNPs) that can accurately detect inflammatory NEs in cerebral ischemic regions, enter cells by exploiting the specific attraction between platelets and polarized NEs, and deliver drugs to intervene with NEs, resulting in a significant decrease in infiltrating NEs in cerebral ischemic regions. This study showed that the combination of PTNPs, piceatannol (a selective inhibitor of splenic tyrosine kinase), and superparamagnetic iron oxide (a contrast agent for T2 imaging) effectively identified adherent NEs by coating the platelet membranes. The loaded piceatannol may be transported to attached NEs and released into the circulatory system, thereby diminishing NE infiltration and decreasing infarct size (Figure 8).⁸⁸

Cerebral ischemic damage significantly affects the prognosis of AIS.^{89–92} During cerebral ischemic injury, neuronal death occurs in the vicinity of the affected area. The injury induces a low-pH environment, a strong neuroinflammatory reaction, and alterations in the activity of immune cells, resulting in the disruption of the BBB.^{93,94} During ischemic injury, microglia are activated into two different polarized phenotypes: the M1 phenotype, characterized by its pro-inflammatory properties, and the M2 phenotype, which is anti-inflammatory.^{95–97} The transition of microglia from M1 to M2 has the potential to protect neurons and decrease apoptosis. MiRNA-Let-7c mitigated ischemia injury by modulating neuronal survival and altering microglial phenotypes. Zhao et al created NPs that camouflaged with platelet membranes and had multiple functions. These NPs were specifically designed to target the brain and treat cerebral ischemic injuries. Their main purpose was to transport MiRNA-Let-7c, which aids in reducing brain cell apoptosis and controlling the

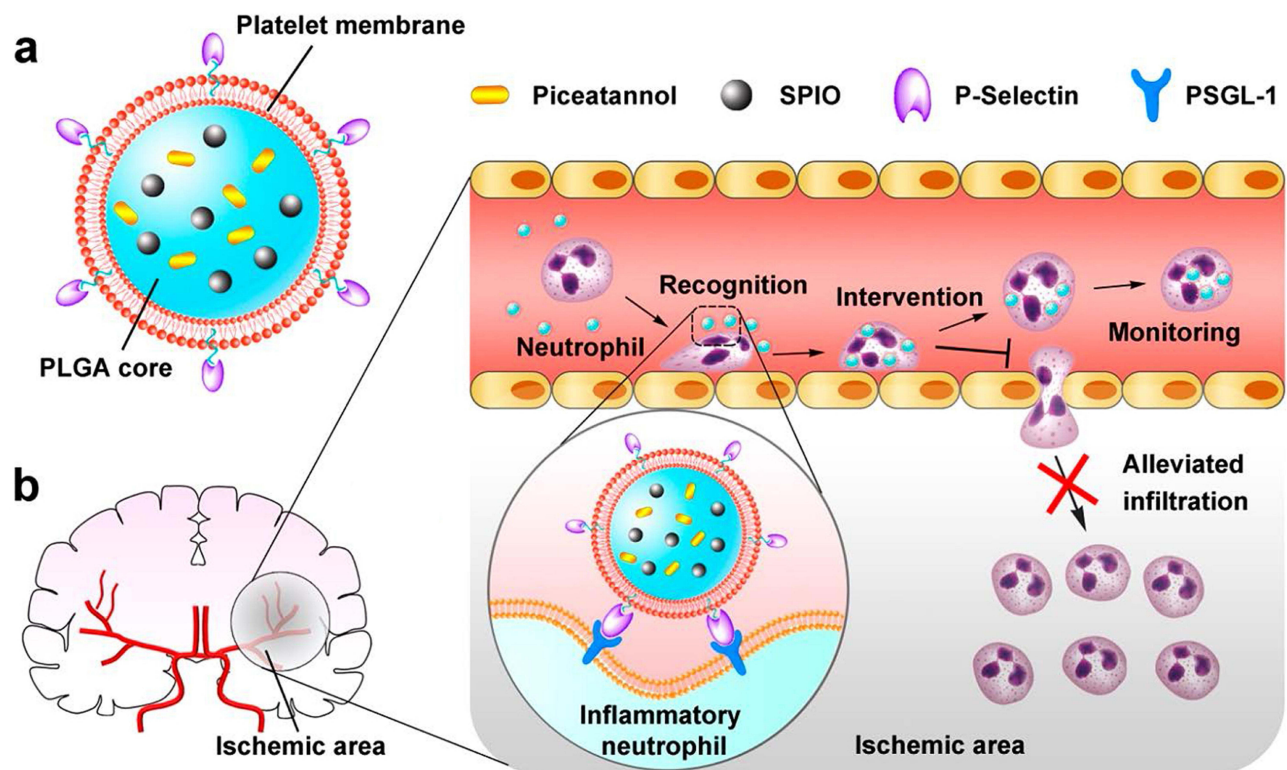


Figure 8 Effective recognition, intervention, and monitoring of inflammatory neutrophils by PTNPs for the treatment of AIS. (a) A diagram of the main components of PTNPs, including the SPIO and piceatannol co-loaded PLGA core and the platelet membrane coating shell. (b) The recognition, intervention, and monitoring of inflammatory neutrophils by PTNPs, along with the reduction in neutrophil infiltration. The red cross indicates the alleviated effect of PTNPs on neutrophil infiltration. Reprinted with permission from Tang C, Wang C, Zhang Y, et al. Recognition, Intervention, and Monitoring of Neutrophils in Acute Ischemic Stroke. *Nano Lett.* 2019;19(7):4470–4477. Copyright 2019 Nano Letters.⁸⁸

transformation of microglial cells from the M1 to the M2 phenotype. This regulation was achieved through the activation of the Notch1 cell signaling pathway (Figure 9).⁹⁸ Li et al described a thrombo-inflammatory cascade-targeted biomimetic nanobubble created by gas-liquid interfacial modular assembly of platelet membranes and the immunomodulator fingolimod (FTY720). Molecular dynamics simulations revealed a gas-liquid interfacial self-organization mechanism that governs the ordered spatial arrangement of platelet membrane lipid rafts and amphiphilic FTY720, facilitating the formation of platelet membrane-coated FTY720 nanobubbles. This type of modularly assembled nanobubble can improve the function of targeted proteins and drug molecules at the biointerface. This facilitates the targeting of lesions in a precise order, BBB crossing, and the drug uptake of microglial cells, greatly improving drug-delivery efficiency and reducing damage to brain tissue.⁹⁹

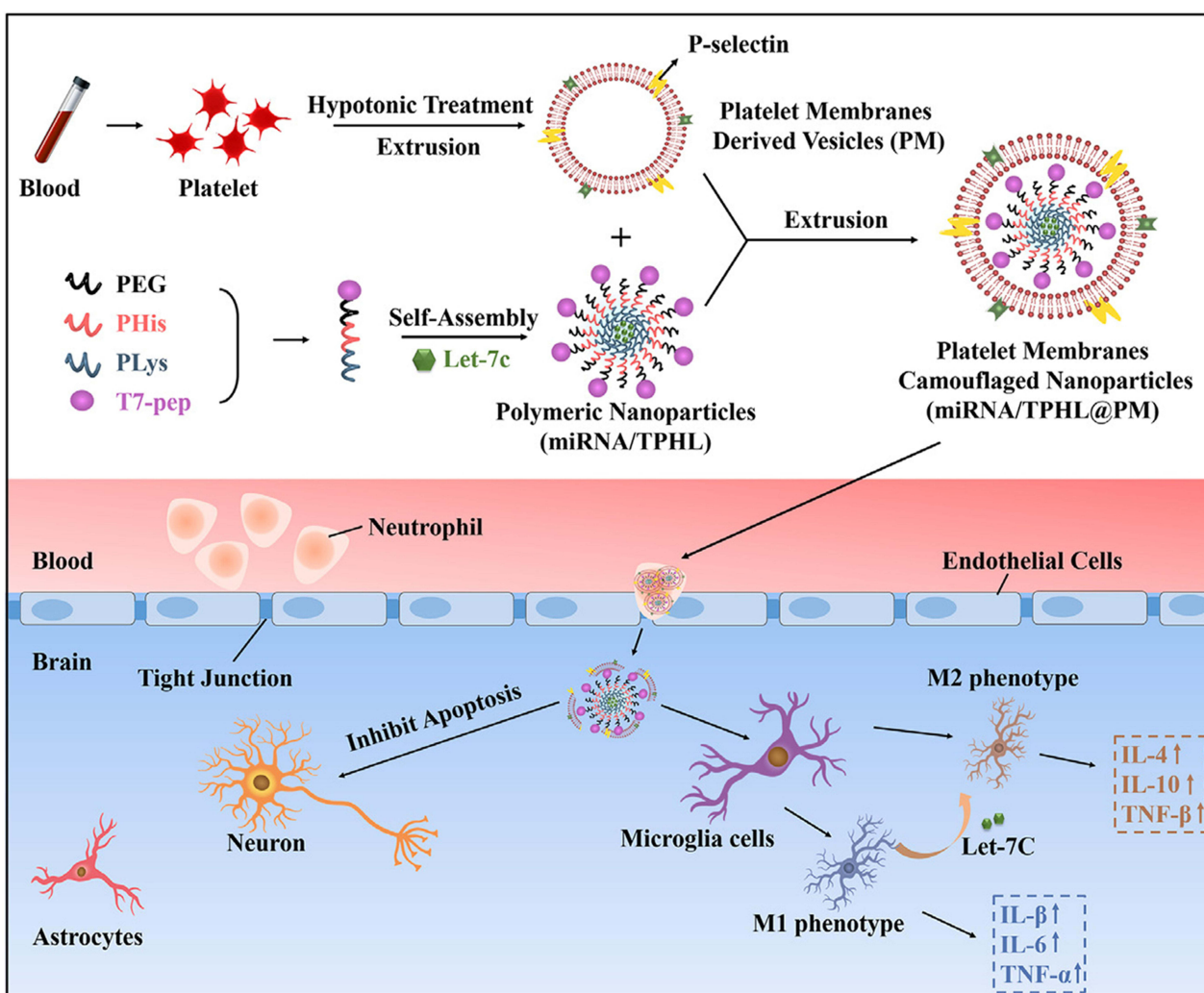


Figure 9 Schematic of the delivery of miRNA through platelet membrane-camouflaged nanoparticles to the site of the brain lesion to reduce apoptosis of neurons and regulate the phenotype of microglia in ischemia/reperfusion (I/R) injury. Schematic illustration of the constructed miRNA/TPHL@PM. In I/R injury, the miRNA/TPHL@PM is bound to neutrophils that can cross the blood-brain barrier via chemotaxis and deliver the miRNA to the site of the lesion. The brown and blue upward arrows indicate upregulation of the corresponding elements. Reprinted with permission from Zhao C, Chen Q, Li W, Zhang J, Yang C, Chen D. Multi-functional platelet membrane-camouflaged nanoparticles reduce neuronal apoptosis and regulate microglial phenotype during ischemic injury. *Applied Materials Today*. 2022; 27:101412. Copyright 2022 Applied Materials Today.⁹⁸

Myocardial Infarction

A significant number of patients develop congestive heart failure (CHF) after myocardial infarction (MI). Survivors of an initial ischemic attack experience post-infarction inflammation and fibrosis, leading to chronic weakening of the heart.^{100,101} Importantly, after infarction, splenic monocytes contribute to the demise of cardiomyocytes that have survived the ischemia phase by generating ROS and secreting matrix metalloproteinases, exacerbating cardiac remodeling.⁴ In postinfarction, abundant monocytes from the spleen are attracted to the heart and engage with platelets while circulating. Cheng et al developed platelet-like proteoliposomes (PLPs) that exploit the interactions between platelets and circulating monocytes. Mimicking the typical behavior of platelets, PLPs exhibit a high affinity for monocytes but do not attach strongly to endothelial cells *in vitro*. Notably, PLPs augment the anti-inflammatory cobalt protoporphyrin to specifically target the heart in a manner independent of enhanced permeability and retention (EPR). This has led to improved therapeutic results.¹⁰² Yang et al fabricated ROS-responsive biomimetic NPs by placing niobium carbide MXenes (Nb₂C) on mesoporous silicon nanoparticles (MSNs) that were already covered in the platelet membrane. During the acute phase of MI, these NPs are injected into the infarcted heart intravenously. The MSN mesoporous structure improves the ability of Nb₂C to eliminate ROS from the infarction and mitigates oxidative stress. Silicon ions released from MSN further stimulate angiogenesis in the infarcted area.¹⁰³

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a prevalent, long-lasting autoimmune inflammatory condition that leads to ongoing inflammation and damage to joints, cartilage, and bones. It can lead to the loss of joint function and significant disability.¹⁰⁴ Research has demonstrated that the submicron “gaps” between endothelial cells are also present in the vasculature of the synovium in RA. This results in increased permeability of the affected joint.¹⁰⁵ NPs have the potential to be extensively utilized for drug delivery in RA owing to their ability to efficiently penetrate the “gaps” and target the inflamed joints.¹⁰⁶ Platelets can enhance inflammation in RA by producing pro-inflammatory microparticles. By promoting the production of interleukin-1, these microparticles can stimulate fibroblast-like synoviocytes (FLS) to produce cytokines.¹⁰⁷ In addition to passive leaking, the intermolecular interactions between activated platelets and inflammatory synovial tissues contribute significantly to the buildup of platelet components in the inflamed joint in RA.⁷² He et al created poly lactic-*co*-glycolic acid (PLGA) NPs coated with platelet membranes to deliver drugs specifically to RA, taking inspiration from the natural connection between platelets and RA (Figure 10).¹⁰⁶ The NPs were stabilized and their circulation improved by coating with platelet membranes, resulting in a passive targeting advantage.¹⁰⁶ The study presents a novel biomimetic targeted technique that has significant promise for RA treatment.¹⁰⁶

Microbial Infection

The emergence of antimicrobial resistance (AMR) and multidrug resistance (MDR) has become a significant health problem and a major challenge in recent years.¹⁰⁸ The prevalence of MDR bacteria has led to an increase in the morbidity and mortality rates associated with bacterial infections.^{109,110} Consequently, it is imperative to develop efficient techniques for quickly diagnosing bacteria¹¹¹ and treatments that can bypass bacterial resistance mechanisms,^{112,113} and enhance the effectiveness of current antibiotics. Nanotechnology is a valuable tool for achieving these goals.¹¹⁴ Recent data have shown that platelets play a crucial role as sentinel effector cells in infectious illnesses.^{115–117} The innate immune response to invading pathogens is significantly affected by the crosstalk with platelets. Platelets have the ability to detect and respond to danger signals and can direct leukocytes to locations where injury, inflammation, or pathogen invasion has occurred.^{118–121} Kim et al investigated the application of human platelet membrane-cloaked nanoparticles (PNPs) as a biomimetic decoy technique to counteract *S. aureus* toxins and maintain the defensive activities of host cells.¹²² The PNPs prevented platelet damage caused by toxins released by *S. aureus*, thereby promoting platelet activation and bactericidal action.¹²² In addition, the PNPs prevented damage to macrophages caused by toxins generated by *S. aureus*. This helped enhance the macrophage oxidative burst, production of nitric oxide, and killing of bacteria. Furthermore, it reduced the release of neutrophil extracellular traps triggered by methicillin-resistant strains.¹²² Using ultrasound, Wu et al developed a potent adjuvant-like biomimetic nanovesicle to store meropenem-loaded polyamidoamine (PAMAM) in platelet membrane vesicles. This nanovesicle has the ability to effectively

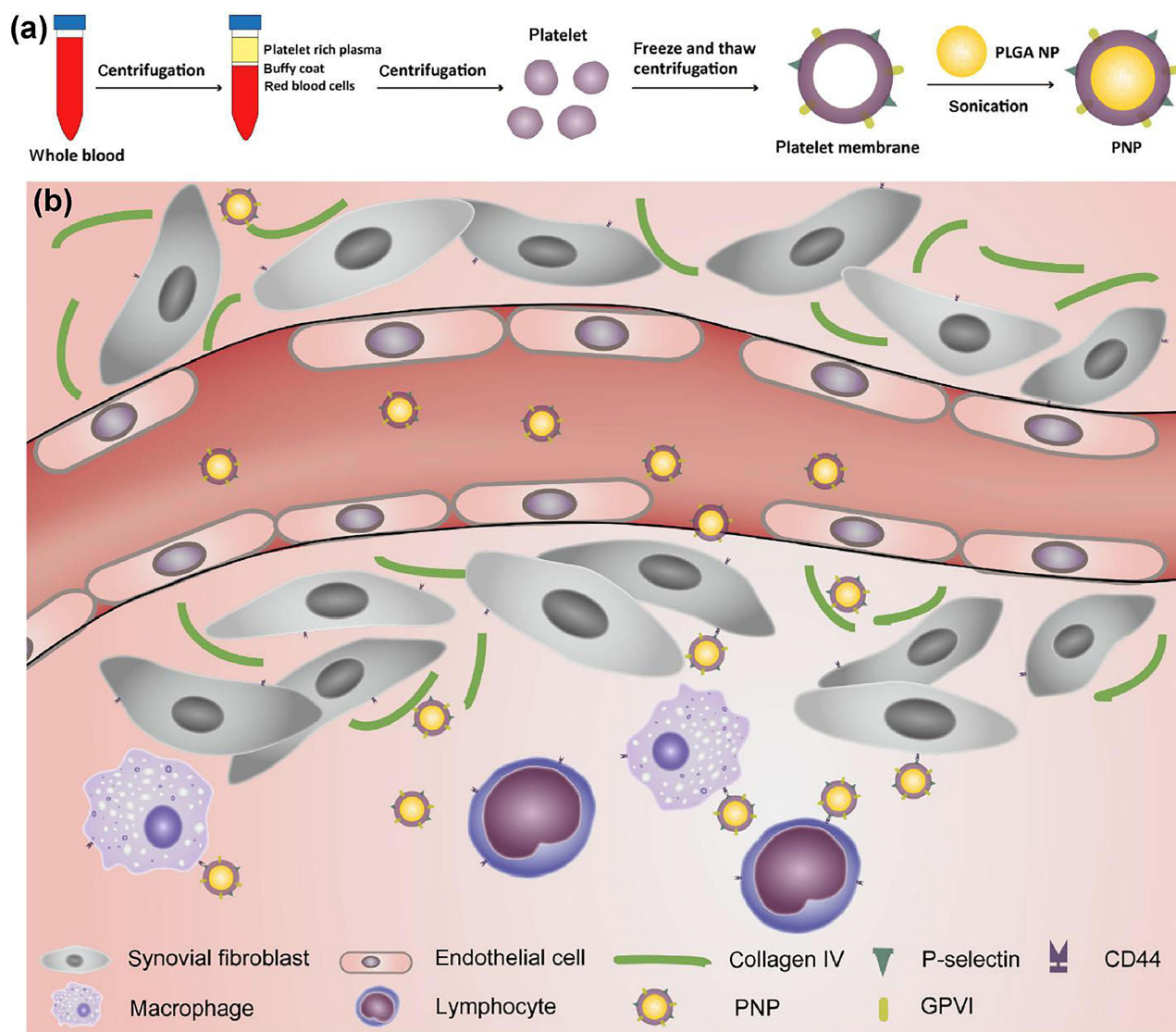


Figure 10 Schematic illustration of the targeted delivery of PNPs to the inflamed joint in RA. (a) Process used for the preparation of platelet membrane-coated PLGA nanoparticles. (b) Targeted delivery of PNPs in the inflamed joint via enhanced permeability and specific binding of PNPs to collagen and overexpressed CD44 on some cells of the inflamed joint tissue. Reprinted with permission from He Y, Li R, Liang J, et al. Drug targeting through platelet membrane-coated nanoparticles for the treatment of rheumatoid arthritis. *Nano Research*. 2018;11(11):6086–6101. Copyright 2018 Nano Research.¹⁰⁶

overcome carbapenem resistance in New Delhi metallo β -lactamase-producing clinical isolates and treat severe bacterial infections.¹²³ The nanovesicles effectively target bacterial infection sites and deliver PAMAM and meropenem drugs. They also rapidly release inflammatory microenvironment-powered drugs that help reduce the development of resistance to pathogens. This approach can be used to successfully treat various bacterial infections without systemic toxicity.¹²³

Tumor Inflammatory Microenvironment

Over the past decade, cancer has been one of the primary causes of mortality worldwide.¹²⁴ Chemotherapy, a widely used approach for cancer treatment, is hindered by its limited capacity to specifically target cancer cells and its significant side effects.^{125,126} To address these issues, extensive research and development has focused on targeted drug-delivery systems (TDDS), particularly those based on NPs.¹²⁷ NPs offer several benefits, including a large capacity for drug loading, tunable physiochemical properties, and flexible modification. These properties make NPs suitable for encapsulating anti-cancer medications, which may then be modified in terms of solubility, stability, and in vivo behavior.¹²⁸ Furthermore, the surface modification of NPs could prolong their presence in the bloodstream and enable precise targeting, thereby

enhancing their effectiveness while reducing adverse effects.^{129,130} Recent studies have demonstrated that platelets play a critical role in promoting the metastatic progression of cancer through various mechanisms. These include facilitating tumor angiogenesis, aiding tumor survival in the bloodstream, and promoting the interaction between tumor cells and blood vessels.¹³¹ Researchers have created bionic methods for targeted drug delivery, considering the intimate interplay between platelets and tumor metastasis. Mai et al created platelet membranes (PMs) to serve as nanocarriers for the simultaneous encapsulation of metformin and IR780.¹³² These nanocarriers successfully corrected tumor hypoxia by inhibiting mitochondrial respiration. The attachment between the PM and tumor cells causes a prolonged circulation lifetime and higher accumulation of IR780 and Met in tumors.¹³² Shang et al developed a nanoplatform consisting of black phosphorus quantum dots (BPQDs) disguised with a platelet (PLT) membrane containing hederagenin (HED), named PLT@BPQDs-HED.¹³³ PLTm vesicles act as a protective covering to encapsulate many drug-loaded nanocores. These nanocores can specifically target tumor locations and greatly enhance antitumor activity.¹³³ The platform markedly decreased the survival of tumor cells and the mitochondrial membrane potential (MMP), while simultaneously enhancing the generation of intracellular ROS.¹³³ Li et al developed NPs called MSN@PM-C-A by coating mesoporous silicon nanoparticles (MSNs) with platelet membranes. These NPs were designed to simultaneously deliver a vascular disruption agent, combretastatin A4 (CA4), and an anti-angiogenic drug, apatinib (Apa), for the combination treatment of tumors (Figure 11).¹³⁴ The customized NPs gathered in tumor tissues by specifically adhering to damaged vessel sites through the platelet membrane surface. This leads to a notable disruption of blood vessels and the effective prevention of new blood vessel formation in animal models.¹³⁴

Engineering Platelet Membrane–Based Nanotherapeutics for Inflammatory Diseases

Atherosclerosis

Cardiovascular diseases (CVDs) are the primary cause of mortality worldwide.^{135,136} Atherosclerosis is the primary aetiology of CVDs, characterized by the gradual accumulation of plaque in the arteries, resulting in the constriction of the artery and ultimately leading to life-threatening complications.^{137,138} Recent findings indicate that the approach to treating atherosclerosis has changed to focus more on anti-inflammatory medication.^{139,140} There is strong evidence that vascular inflammation is intimately linked to the worsening of problems related to atherosclerosis.^{141,142} Platelets, a type of immune cell, have an innate affinity to sites of inflammation, such as atherosclerotic plaques, making them suitable for delivering anti-inflammatory medicines.^{26–28} MCC950, an NLRP3-inflammasome inhibitor that prevents the production of Interleukin-1 β (IL-1 β) caused by NLRP3 activator,¹⁴³ has been shown to decrease the formation of atherosclerotic lesions and alleviate inflammation.^{144–146} Ma et al produced nanosized MCC950 loaded platelet-derived extracellular vesicles (MCC950-PEVs) by introducing MCC950 onto platelet extracellular vesicles (PEVs) and subsequently activating them.¹⁴⁷ Administering MCC950-PEVs intravenously can effectively decrease the development of atherosclerotic plaques, decrease inflammation in the affected area, and hinder the proliferation of macrophages and T cells at the location of the plaque.¹⁴⁷

Ischemic Disease

Thrombi

Thrombotic events, specifically cardiovascular-related illnesses,⁶² ischemic stroke,¹⁴⁸ and pulmonary embolism (PE),¹⁴⁹ are the primary causes of illness and death globally.¹⁵⁰ Thrombus formation at specific locations can cause a sudden blockage of blood vessels, resulting in significant harm to tissues and potentially leading to organ failure, which can be life-threatening.¹⁵¹ Platelets preserve the structural integrity of blood vessels under normal circumstances and participate in the development of blood clots in abnormal situations. Platelets and platelet-like bionanoparticles have the potential for stroke detection, atherosclerosis treatment, and targeted thrombolysis owing to their roles in thrombus targeting and immune evasion.^{32,48,152} Xu et al created polymeric NPs coated with platelet membranes and attached rtPA to the surface. This design, called PNPPA, aims to deliver clot-targeted thrombolytic therapy.¹⁵³ The engineered nanoplatelets effectively gather at the blood clots in mice, resulting in a notable enhancement in thrombolytic activity when compared

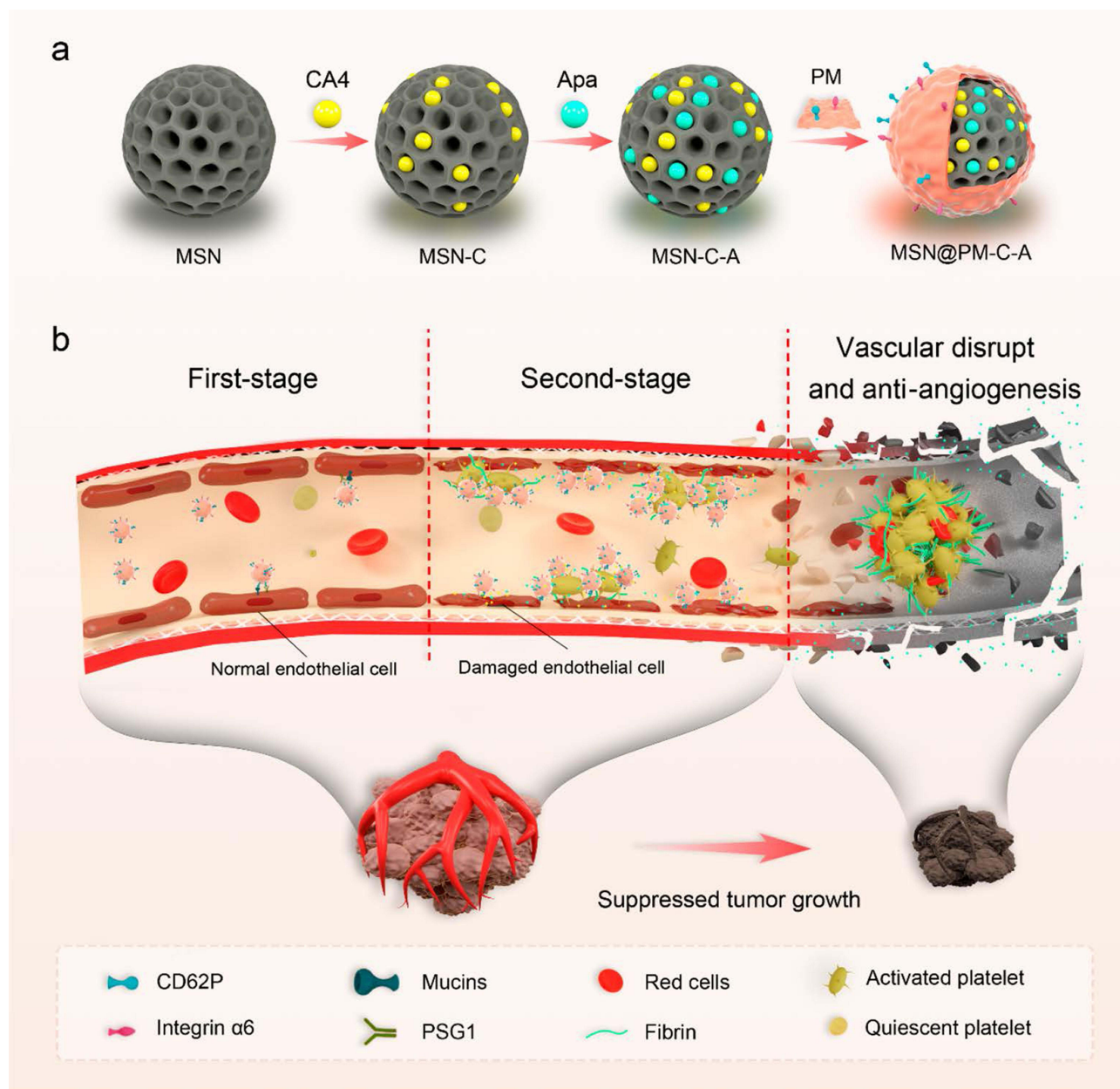


Figure 11 Illustration of the design principles and proposed action mechanism of MSN@PM-C-A in tumor vessels. (a) The preparation of MSN@PM-C-A containing blank MSN (mesoporous silica nanoparticle) synthesis, drug loading, and platelet membrane coating. (b) Proposed antitumor mechanism of MSN@PM-C-A in the tumor-bearing mouse model. The platelet membrane camouflage endows nanoparticles with the ability to escape early systemic clearance as well as tumor targeting realized by receptor–ligand interactions between platelet membranes and vasculature endothelial cells (first-stage); the more platelet-membrane-camouflaged nanoparticles have a tropism for damaged vascular endothelium (disrupted vessels) and secondary microthrombosis induced by CA4, with release of Apa drugs (second stage). Therefore, in the tumor sites, the nanoparticles locally impaired the vascular endothelium and the more nanoparticles are persistently recruited to the sites of vasculature damages, engendering a mutually facilitated intratumoral vascular disruption and anti-angiogenesis, consequently exerting their antitumor effects by shutting off tumor blood supply. Reprinted with permission from Li B, Chu T, Wei J, et al. Platelet-Membrane-Coated Nanoparticles Enable Vascular Disrupting Agent Combining Anti-Angiogenic Drug for Improved Tumor Vessel Impairment. *Nano Lett.* 2021;21(6):2588–2595. Copyright 2021 Nano Letters.¹³⁴

with free rt-PA.¹⁵³ Wang et al developed a platelet-based delivery system that combined urokinase (uPA) and arginine (Arg) to specifically dissolve blood clots and prevent their reformation. This approach involves attaching thrombolytic medicines to the surface of platelets using specialized engineering techniques.¹⁵⁴ This engineered platelet-based drug-delivery system precisely delivers uPA to blood clots, extends the circulation of uPA in the bloodstream, and prevents the recurrence of blood clots while minimizing the risk of bleeding.¹⁵⁴

Myocardial Infarction

Acute myocardial infarction (AMI), primarily resulting from the blockage of a coronary artery, is a significant global cause of mortality and impairment.¹⁵⁵ An AMI triggers a sterile inflammatory reaction that promotes additional damage to the heart and contributes to negative changes in cardiac structure and function.¹⁵⁶ IL-1 β is a key factor in the sterile inflammatory response caused by AMI.¹⁵⁶ Li et al created platelet microparticles (PMs) equipped with anti-IL-1 β to counteract the effects of IL-1 β during AMI and hinder unfavorable cardiac remodeling.¹⁵⁶ Their findings indicate that the infarct-targeting PMs have the ability to attach to the damaged heart, enhancing the concentration of anti-IL-1 β antibodies in that area. The anti-IL-1 β platelet microparticles (IL1-PMs) protect the cardiomyocytes against apoptosis by neutralizing IL-1 β and reducing the activity of caspase-3, which is driven by IL-1 β .¹⁵⁶

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory condition characterized by inflammation of the synovial membrane and damage to the joints.^{157,158} Biological products and kinase inhibition drugs have significantly enhanced the effectiveness of RA treatment.¹⁵⁹ However, their efficacy in treating chronic synovial inflammation and joint deterioration must be improved.^{160,161} Synovial fibroblasts, which are stromal cells located in the synovium, play a crucial role in controlling the advancement of RA by generating several disease-causing proteins.^{162,163} Platelet microparticles (PMPs) are generated by activated platelets and have a significant impact on inflammatory disorders.¹⁶⁴ Joints affected by arthritis and blood samples of patients with RA have revealed abundant PMPs.¹⁶⁵ PMPs enhance inflammation of the synovial tissue by releasing interleukin-1 (IL-1) after attaching to RA synovial fibroblasts (RASFs).¹⁶⁷ The results indicate that PMPs have a strong attraction to areas of inflammation and synovial fibroblasts in individuals with RA. All-*trans* retinoic acid (ATRA) is a vitamin A derivative that has been demonstrated to have anti-inflammatory effects in many animal models of RA.¹⁶⁶ Furthermore, ATRA has the capability to disrupt the Golgi apparatus.¹⁶⁷ Research has shown that specifically targeting the Golgi organelles of target cells with ATRA can successfully damage this organelle, leading to a decrease in protein secretion and expression.^{168–170} A peptide that targets the Golgi apparatus and contains the SXYQRL sequence can precisely localize to the Golgi apparatus.¹⁷¹ Deng et al hypothesized that modifying the Golgi-targeting peptide could result in the localization of PMP membrane (PMM)-camouflaged NPs in the Golgi of RASFs.¹⁷² The researchers developed Golgi-targeting PMM-camouflaged nanoparticles (Gol-PMMNPs) to specifically deliver ATRA to the Golgi organelles of RASFs in arthritic joints (Figure 12).¹⁷² The ATRA-Gol-PMMNPs significantly decreased the accumulation of harmful proteins in RASFs by damaging the Golgi organelles. This reduced the level of inflammation in synovial tissue and prevented damage to arthritic joint cartilage in rats with collagen-induced arthritis (CIA).¹⁷²

Pneumonia

Acute pneumonia is a severe respiratory tract infection caused by viruses, bacteria, fungi, or other pathogens. It is a leading cause of death globally.¹⁷³ Mounting data indicates that individuals with severe pneumonia experience cytokine storm syndrome, a condition in which the immune system's response results in unregulated inflammation of the lung tissue.¹⁷⁴ Previous studies and clinical findings have demonstrated that despite the total eradication of the germs responsible for pneumonia using antibiotics or antiviral medications, individuals with severe pneumonia are still at high risk of succumbing to a cytokine storm in the lungs.¹⁷⁵ Suppressing the cytokine storm could potentially be pivotal in preserving the lives of individuals suffering from severe pneumonia caused by a highly virulent strain such as SARS-Cov-2.^{176–179} Cellular delivery technologies have garnered significant attention owing to their exceptional biocompatibility and distinctive delivery characteristics.^{180–184} Platelets are inherently attracted to the site of inflammation.^{26–28} They have the ability to attach to the activated or inflamed vascular walls by interacting with several receptor patterns, such as CD40L, glycoproteins Iba, aIIb, and VI, as well as P-selectin.^{26–28} 5-(*p*-Fluorophenyl)-2-ureido thiophene-3-carboxamide (TPCA-1) is a powerful and specific inhibitor of I κ Bkinases (IKK) in the NF- κ B pathway. It has the ability to prevent the generation of TNF- α , IL-6, and IL-8 from human monocytes.^{185,186} Ma et al developed PEVs specifically designed for delivering target drugs to treat pneumonia.¹⁸⁷ The TPCA-1 was loaded onto the platelets, which was followed by platelet activation in order to produce the TPCA-1-PEVs.¹⁸⁷ The engineered PEVs have the ability to selectively target the inflamed lung tissue. Through injection, the nanosized PEVs are able to cross the vasculature and target the damaged area. This is achieved by exploiting the transient dilation and increased

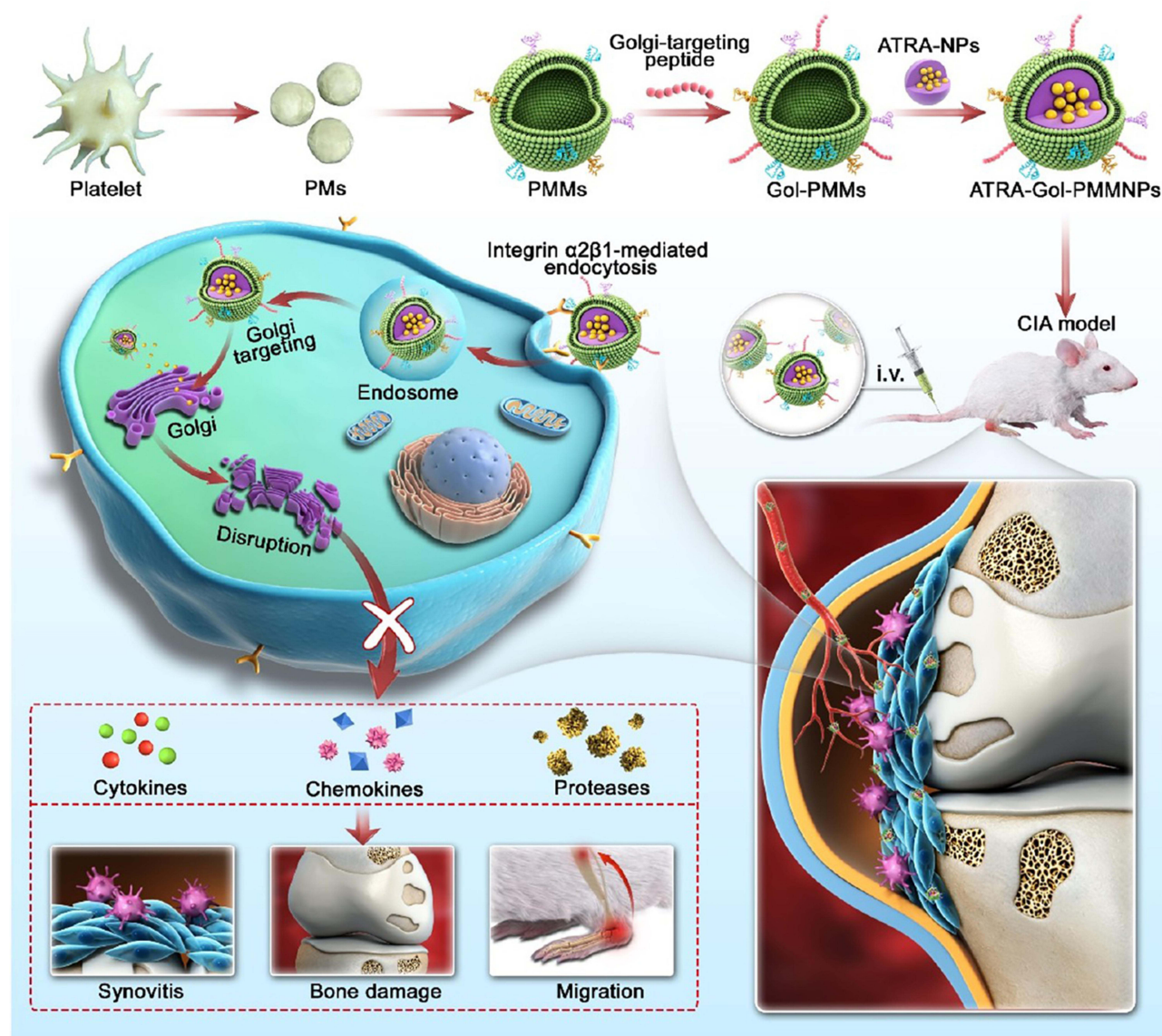


Figure 12 Schematic representation of ATRA-Gol-PMMNPs targeting the multiple pathogenic mediators produced by RASFs via integrin $\alpha2\beta1$ -mediated endocytosis and retrograde transport from endosomes to the Golgi apparatus. The white cross signifies the blockade of pathogenic proteins, chemokines, and cytokines expression in RASFs by ATRA-Gol-PMMNPs, consequently alleviating synovial inflammation, bone destruction and inflammatory migration in the arthritic joints of CIA rats. Reprinted with permission from Deng C, Zhao X, Chen Y, et al. Engineered Platelet Microparticle-Membrane Camouflaged Nanoparticles for Targeting the Golgi Apparatus of Synovial Fibroblasts to Attenuate Rheumatoid Arthritis. *ACS Nano*. 2022;16(11):18430–18447. Copyright 2022 ACS Nano.¹⁷²

permeability of blood vessels generated by histamine in response to injury.¹⁸⁸ In comparison to the free-drug-treated group, the PEVs significantly enhance treatment efficacy by inhibiting the infiltration of inflammatory cells in the lungs and mitigating the cytokine storm through the delivery of anti-inflammatory medications such as TPCA-1, which can decrease the generation of inflammatory components.¹⁸⁷ Dexamethasone (DEX), a corticosteroid with anti-inflammatory properties, is commonly employed in clinical settings to mitigate inflammatory reactions.¹⁸⁹ Nevertheless, the conventional method of administering DEX through direct injection is linked to numerous adverse effects, including hepatotoxicity and immunosuppression.¹⁹⁰ Ma et al created a platform that specifically targets acute pneumonia using PEVs to deliver DEX.¹⁹¹ DEX can be readily loaded onto PEVs through hydrophobic interactions, forming DEX-loaded PEVs (DEX-PEVs).¹⁹¹ DEX-PEVs have the potential to significantly enhance the therapeutic effects of DEX by boosting the amount of the drug delivered to the inflammation site.¹⁹¹ The method reduced not only the occurrence of adverse effects but also the required dosage of DEX to a significant extent.¹⁹¹

Tumor Inflammatory Microenvironment

Surgery is the primary therapeutic approach for most solid tumors. Although surgical procedures have been consistently improving, the presence of persistent microtumors and/or circulating tumor cells (CTCs) following tumor removal continues to be a difficult problem.^{192–194} Cancer immunotherapy seeks to activate the immune system to fight cancer cells. This approach has garnered significant interest and has yielded remarkable results in clinical treatment.^{195,196} Tumor immunotherapy shows considerable potential in reducing the growth of primary tumors and tumor metastasis by utilizing the abilities of activated immune cells to recognize and eliminate cancer cells.^{197–199} Scientists are using platelets as effective delivery platforms in tumor immunotherapy.²⁰⁰ Engineered platelets possess significant promise to enhance the antitumor effects of immunotherapy and broaden their therapeutic uses.²⁰⁰ Wang et al attached anti-PDL1 (engineered monoclonal antibodies that target programmed-death ligand 1) to platelets to provide a preventive therapy for post-surgical cancer recurrence.²⁰¹ They proposed that platelets can assist in transporting anti-PDL1 to remaining microtumors at the surgical site, as well as to CTCs in the bloodstream.²⁰¹ Platelet activation resulted in the formation of a T-cell–inflamed tumor microenvironment, in turn leading to an upregulation of PDL1 expression at the tumor site.²⁰¹ The release of Anti-PDL1 was successful following platelet activation, resulting in a blocking of PDL1 on both cancer cells and antigen-presenting cells (APCs).²⁰¹ Fan et al developed an engineered platelet loaded with anti-CD47 to serve as a natural carrier for delivering anti-CD47 to tumors for macrophage immunotherapy. These NPs have a specific affinity for bacteria-treated tumors.²⁰² Anti-CD47 were attached to purified blood platelets via a click reaction.²⁰³ Following the induction of rapid and extensive blood coagulation and inflammation in tumor tissues by *Escherichia coli* TOP10, the macrophages that are recruited are mostly polarized towards the antitumor M1-like phenotype by lipopolysaccharide in the bacterial wall.²⁰² Anti-CD47 inhibits the interaction of CD47 and signal regulatory protein- α (SIRP- α) in M1-like phenotype macrophages, enhancing the digestion of polarized M1-like phenotype macrophages for tumor cells.²⁰²

Hybrid Platelet Membrane–Based Nanotherapeutics for Inflammatory Diseases

Atherosclerosis

Atherosclerosis, a persistent inflammatory condition characterized by the narrowing of blood arteries and the consequent limitation of blood circulation, is the primary cause of cardiovascular disorders and accounts for approximately one-third of global mortality.¹³⁶ It is characterized by damage to endothelial cells, accumulation of lipids, and aggregation of inflammatory cells.²⁰⁴ Macrophages are the predominant leukocyte subset seen in plaques and have crucial functions in both the onset and advancement of atherosclerosis.²⁰⁵ During the initial stage of atherosclerosis, monocytes are drawn towards the damaged vascular cells and migrate to the arterial wall. Once there, they differentiate into pro-inflammatory macrophages.²⁰⁶ The macrophages with inflammatory properties secrete significant amounts of inflammatory-related cytokines, chemokines, and ROS, intensifying oxidative stress within the plaques.²⁰⁷ Macrophages constantly consume copious amounts of cholesterol derived from low-density lipoprotein (LDL), resulting in their transformation into foam cells. This transformation initiates a chronic inflammatory state associated with atherosclerosis.²⁰⁸ Under normal physiological conditions, platelets primarily circulate in close proximity to the walls of blood vessels without interacting with endothelial cells (ECs). Platelets quickly adhere to the damaged endothelium when the integrity of the endothelial layer is compromised.^{209,210} Mounting research has demonstrated that mesenchymal stem cells (MSCs) provide protection throughout all phases of atherosclerosis.²¹¹ MSCs have the ability to minimize endothelial dysfunction,²¹² polarize macrophages into anti-inflammatory phenotypes to decrease inflammation, and reduce the generation of foam cells.^{213,214} These actions help prevent the development of atherosclerosis and improve the stability of advanced atherosclerotic lesions.²¹⁵ Li et al created platelet mimetic MSC-EVs (P-EVs) by adorning extracellular vesicles with platelet membranes to specifically treat atherosclerosis. P-EVs possess the inherent potential to target plaques, similar to platelets, and also exhibit the therapeutic benefits of MSC-EVs.²¹⁶ Following this, the P-EVs conveyed miRNAs to the cytoplasm of macrophages by escaping from lysosomes. This process ultimately slows the development of arterial plaque buildup by transforming the macrophages into an anti-inflammatory phenotype, removing excessive ROS and decreasing lipid accumulation in the lesional macrophages (Figure 13).²¹⁶ Song et al created biomimetic

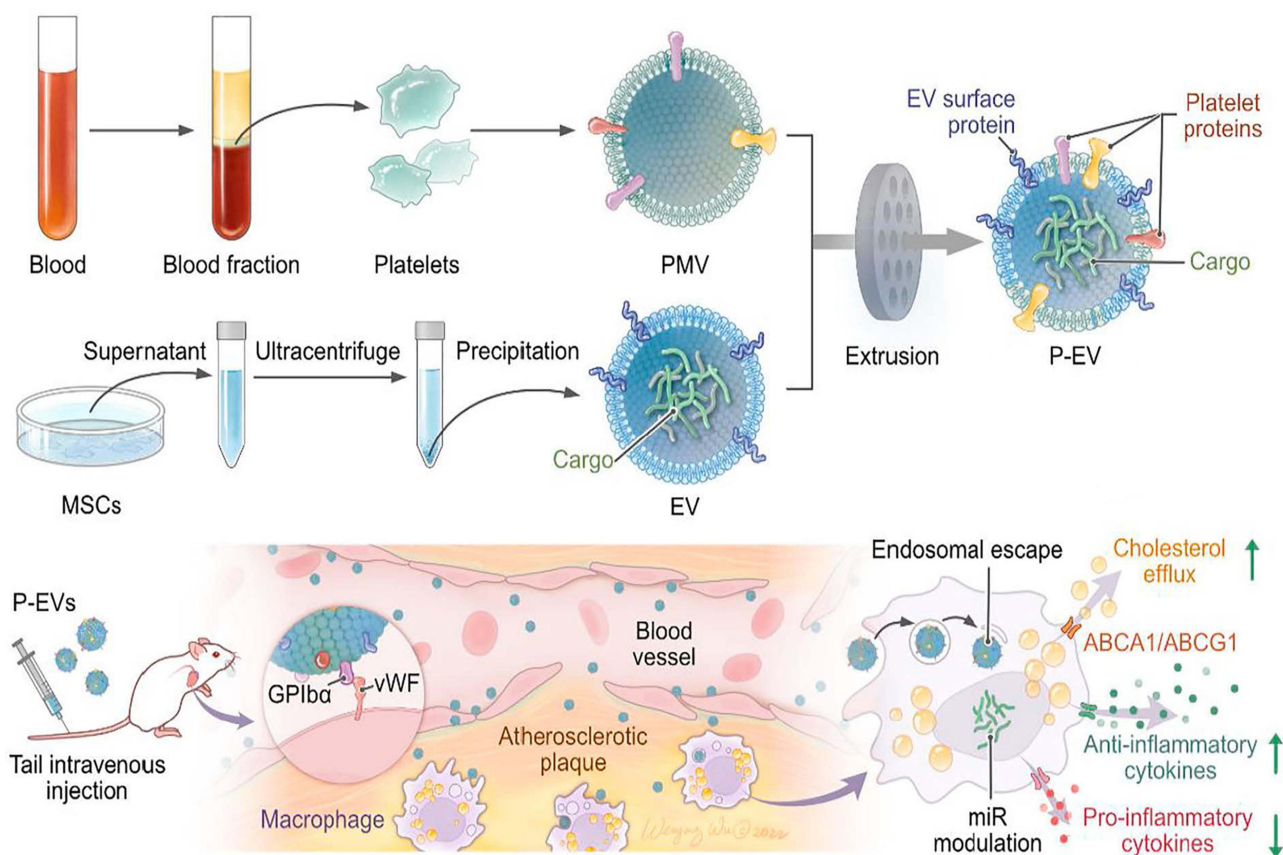


Figure 13 Schematic diagram of targeted delivery of P-EVs to plaques for the treatment on atherosclerosis. The green upward arrow indicates upregulation of the relevant process or factor expression, while the green downward arrow represents downregulation. Reprinted with permission from Li Q, Huang Z, Pang Z, et al. Targeted delivery of platelet membrane modified extracellular vesicles into atherosclerotic plaque to regress atherosclerosis. *Chemical Engineering Journal*. 2023; 452:138992. Copyright 2023 Chemical Engineering Journal.²¹⁶

liposomes (P-Lipo) by hybridizing artificial liposomes with platelet membranes. This design is influenced by the manner in which platelet membrane components engage with atherosclerotic plaques, and the goal is to target atherosclerosis.²¹⁷ The extrusion method is used to fuse natural platelet membranes with artificial lipid membranes, resulting in the formation of hybrid nanovesicles. These nanovesicles are believed to possess the targeted abilities of platelets as well as the physicochemical and pharmaceutical attributes of liposomes.²¹⁷ Because the lipid bilayer of liposomes is easily fused with other bilayers, such as cell membranes, and owing to their highly fluid and dynamic features,²¹⁸ P-Lipo can be scaled up and effectively maximize the utilization efficiency of platelet membranes.²¹⁷ P-Lipo offers a secure and effective alternative for treating atherosclerosis and various other disorders associated with platelet involvement.²¹⁷

Ischemic Disease

Thrombi

Blood vessels can be suddenly blocked owing to thrombus formation at certain locations. This can result in significant tissue damage and even organ failure, a potentially fatal condition.¹⁵¹ The pathological interaction between oxidative stress, inflammation, and thrombosis induced by endothelial injury establishes a self-reinforcing cycle that compromises standard thrombolytic treatments. Jiang et al developed near-infrared (NIR) light-responsive nanomotors by combining thylakoid and platelet membranes with strontium-doped mesoporous polydopamine NPs. This allowed for the simultaneous dissolution of thrombi and restoration of the vascular microenvironment. After intravenous administration, the nanomotors preferentially gathered in the thrombi and were taken up by the damaged endothelial cells. Simultaneously, the thylakoid-embedded catalase converted hydrogen peroxide into oxygen. This not only prevents oxidative damage and platelet-endothelium interactions but also causes self-propulsive forces through gas propulsion, which helps the nanomotors penetrate the thrombus. Local NIR

irradiation caused a small amount of photothermal conversion in the nanomotors, which softened the fibrin networks, facilitating intrathrombus infiltration, and accelerated localized thrombolysis.²¹⁹

Ischemic Stroke

Stroke ranks as the second most prevalent cause of mortality on a global scale.^{220,221} Vascular occlusion leads to neuronal apoptosis, breakdown of the BBB, and necrosis of cerebral tissue, causing significant functional impairment in patients.²²² Microglia is a form of neuroglia found throughout the central nervous system (CNS).²²³ As the first cells to be activated upon CNS damage, microglia are crucial for host defense, inflammatory modulation, neurodegeneration, and tissue repair.²²⁴ During ischemia/reperfusion injury, two distinct polarized phenotypes of microglia are prevalent: the classical M1 (pro-inflammatory) and the alternative M2 (anti-inflammatory).²²⁵ These phenotypes have specific roles in the injury process. M1 microglia increase the expression of pro-inflammatory cytokines, which worsen neuronal damage and hinder cellular repair. On the other hand, the M2 phenotype provides neuroprotection and supports brain recovery by producing anti-inflammatory cytokines.²²⁶ Li et al created a platelet hybrid microglia platform that can specifically polarize microglia into an anti-inflammatory phenotype using ultrasound irradiation. This platform is designed for targeted healing of the cerebrum following a stroke (Figure 14).²²⁷ The engineered microglia exhibit robust adhesion to damaged cerebral blood arteries through fusion with platelet membranes and achieve targeted anti-inflammatory polarization with ultrasound-responsive IL-4 liposome decoration.²²⁷ The microglial platform, when injected intravenously and subjected to insonation, exhibits anti-inflammatory polarization at the site of stroke. This

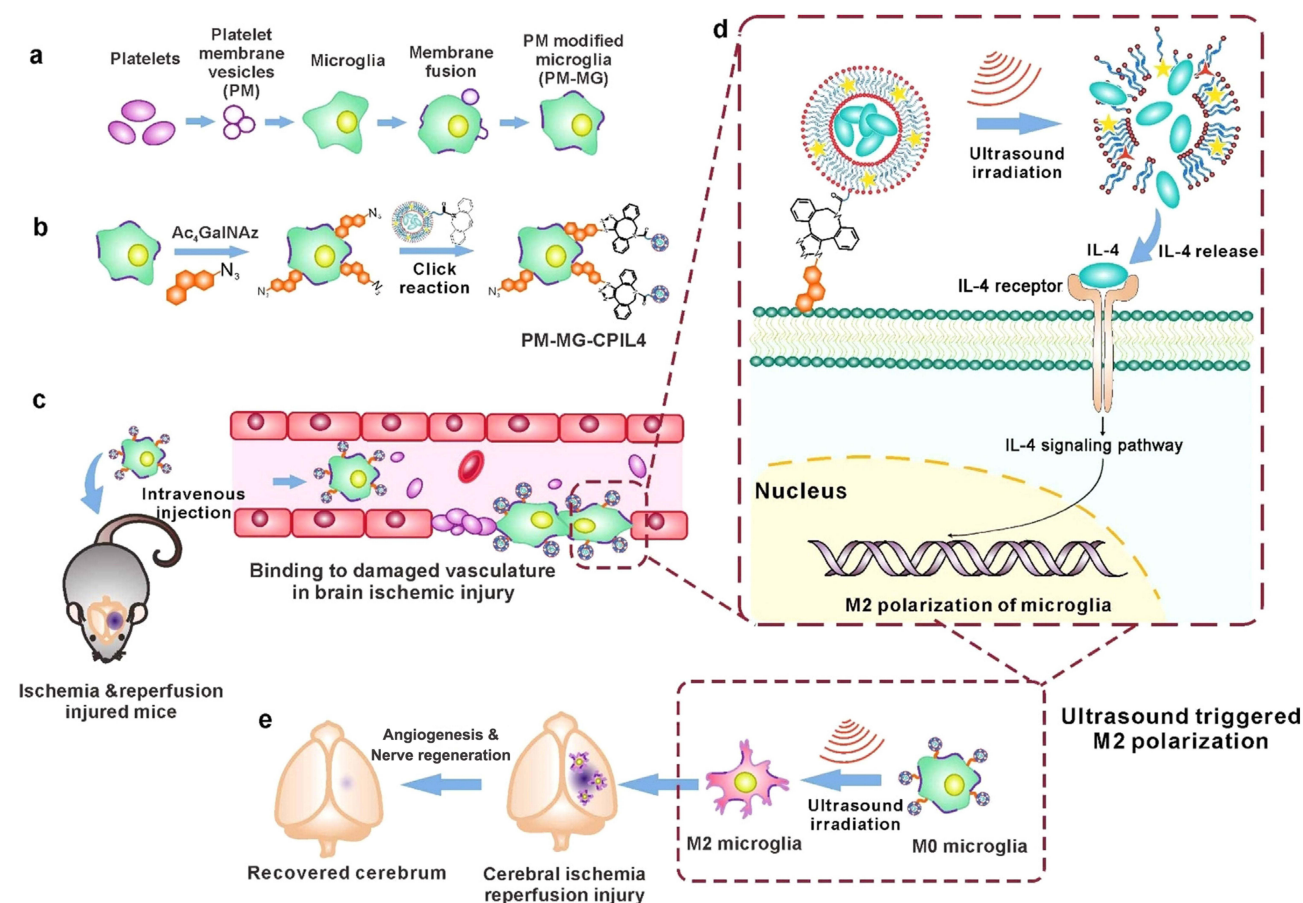


Figure 14 Schematic illustration of ultrasound triggered polarization of platelet fused microglia for targeted treatment of ischemia-reperfusion injury post stroke. (a) Platelet membrane vesicle generation and decoration on M0 microglia (MG) to form PM decorated MG (PM-MG) by membrane fusion. (b) Ultrasound responsive liposome coated IL-4 (CPIL4) is conjugated to PM-MG via click reaction to form PM-MG-CPIL4. (c) Tail vein injected PM-MG-CPIL4 can anchor to the injured cerebrovascular for targeted repair. (d) Upon ultrasound irradiation, IL-4 directly releases from the CPIL4 and subsequently binds to the IL-4 receptor on the cell surface to initiate M2 polarization of microglia through IL-4 signaling pathway. (e) M2 polarized microglia contribute to the angiogenesis and nerve regeneration of the injured brain post ischemic stroke and reperfusion injury. Reprinted with permission from Li Y, Teng X, Yang C, et al. Ultrasound Controlled Anti-Inflammatory Polarization of Platelet Decorated Microglia for Targeted Ischemic Stroke Therapy. *Angew Chem Int Ed Engl.* 2021;60(10):5083–5090. Copyright 2021. *Angew Chem Int Ed Engl.*²²⁷

platform has the ability to specifically polarize towards the desired phenotype for brain tissue regeneration and to accelerate M2 polarization of the endogenous microglia. This polarization process promotes the formation of vascular and neuronal structures, leading to improved behavior in mice affected by stroke.²²⁷

Myocardial Ischemia Reperfusion

Ischemic cardiocerebrovascular disease, which includes MI and stroke, has significantly contributed to mortality rates over the last two decades. Even though prompt blood-flow restoration has greatly decreased immediate mortality, reperfusion does not seem to be risk-free, and some patients with MI and stroke either do not improve or worsen after reperfusion owing to reperfusion injury.^{228,229} Microcirculation in the body's tissues is particularly vulnerable to the consequences of reperfusion, resulting in microvascular dysfunction. This dysfunction includes the breakdown of the endothelial barrier with hemorrhage, as well as impaired capillary perfusion (no-flow).²³⁰ Immediately following ischemia reperfusion, VE-cadherin, a highly important intercellular connection, rapidly disassembles and degrades. Meanwhile, endothelial cells experience significant damage as a result of the increased accumulation of ROS.²³¹ These two factors work together shortly after the beginning of ischemia reperfusion, leading to impaired barrier function, which causes increased infiltration of proteins and cells and triggers severe bleeding and inflammation.²¹⁰ Gao et al developed biomimetic NPs fused with the platelet membrane, which combine angiopoietin-like 4 (ANGPTL4) with liposomes encapsulating a thrombin-responsive peptide and Fe₃O₄. These NPs were designed to exploit the natural tendency of platelets to migrate to the injured endothelium and locally activate thrombin. Its purpose was to deliver both ANGPTL4 and Fe₃O₄, which act as ROS scavengers, to the damaged endothelium in the heart, which is affected by myocardial ischemia-reperfusion (MI/R).²¹⁰ The NP effectively reached the endothelial cells as a result of platelet-mimetic adhesion, which was created by merging platelet membranes and lipid membranes.²¹⁰ After the damaged endothelium causes thrombin-responsive peptide cleavage, ANGPTL4 attaches to endothelial cell receptors to prevent VE-cadherin junction rupture. In addition, endo-lysosomal escape of Fe₃O₄ to cytosol effectively scavenged ROS and prevented apoptosis in endothelial cells.²¹⁰ The preservation of VE-Cadherin and the rescue of cells effectively maintained the integrity of the endothelial barrier, resulting in a reduction in leukocyte extravasation and intracardial hemorrhage.²¹⁰ This action also reduced cardiomyocyte apoptosis and ultimately improved cardiac function.²¹⁰ Zhou et al produced biomimetic nanocomplexes based on inflammation-sheddable cloaking using a platelet-macrophage hybrid membrane in order to effectively transfer Sav1 siRNA into cardiomyocytes and block the Hippo pathway while promoting cardiomyocyte regeneration.²³² To mitigate MI/R injury after coronary recanalization in MI-affected hearts, He et al engineered NPs inspired by stromal-platelet membranes. These NPs feature a poly (lactic-co-glycolic acid) (PLGA) core, adorned with a dual membrane coating: a platelet membrane for precise adhesion to the compromised endothelial region and a stromal cell membrane to augment receptor-ligand interactions and confer immune evasion. This unique dual-membrane configuration reduces fibrosis and inflammation while encouraging angiomyogenesis.²³³

The strong inflammatory cascade that follows MI/R injury is a crucial step in the process of cardiac remodeling.²³⁴ Early after injury, inflammatory macrophages (M1) penetrate the damaged area and release a variety of cytokines along with phagocyte debris.^{235,236} Multiple investigations have shown that the timely transition to a reparative phenotype (M2) is essential for resolving inflammation.²³⁶⁻²³⁹ Tan et al created platelet-like fusogenic liposomes (PLPs) by drawing inspiration from the increase in circulating platelet-monocyte aggregates in patients after MI/R. They chose fusogenic liposomes for their ability to effectively carry their contents to the cytoplasm of target cells. Mesoporous silica nanospheres containing miR-21, an anti-inflammatory drug, can be targeted to inflammatory monocytes in the bloodstream of MI/R-induced mice by means of coating with PLPs.²⁴⁰ Subsequently, they undergo membrane fusion to enter the cytoplasm of monocytes, leading to reparative reprogramming of the inflammatory macrophages formed from it.²⁴⁰

Sepsis-Induced Acute Kidney Injury

Sepsis-induced acute kidney injury (SAKI) is a prevalent complication observed in critically ill patients and is characterized by rapid deterioration in renal function. It accounts for 60% of severe sepsis cases.^{241,242} Patients with SAKI have a considerably greater mortality risk than those with acute kidney injury (AKI) alone.^{243,244} Although the precise mechanisms of SAKI remain incompletely understood, they mostly contribute to microcirculation disturbances,

immunological reactions, and cellular malfunctions.²⁴⁵ Microcirculatory dysfunction can be caused by various mechanisms, including endothelial injury, autonomic nervous system reaction, shedding of the glycocalyx, and activation of the coagulation cascade.²⁴⁶ During sepsis, toxins in the bloodstream affect the vascular endothelium, causing a decrease in microcirculatory blood flow and the release of several inflammatory substances. This leads to damage to the microvascular endothelial barrier and loss of the glycocalyx.²⁴⁷ Yang et al developed a new form of hybrid microbubble by coating platelet membranes (Pla-MBs), considering the characteristics of endothelial injury in the early stage of SAKI and the quick adhesion of platelets to the damaged endothelium layer (Figure 15).²⁴⁷ Pla-MBs were created using ultrasound to recombine liposomes and platelets, which contained the natural platelet membrane obtained from isolated platelets. Pla-MBs were given different adhesive receptors, including integrin α Ib β 3, by applying a platelet membrane coating. This allows them to selectively adhere to the injured endothelium in SAKI.²⁴⁷ By utilizing the inherent properties of the platelet membrane, molecular ultrasound imaging, and quantitative analysis, Pla-MBs can specifically identify microbubble signals that bind to damaged blood vessels, enabling the early detection of SAKI in rats. Bedside

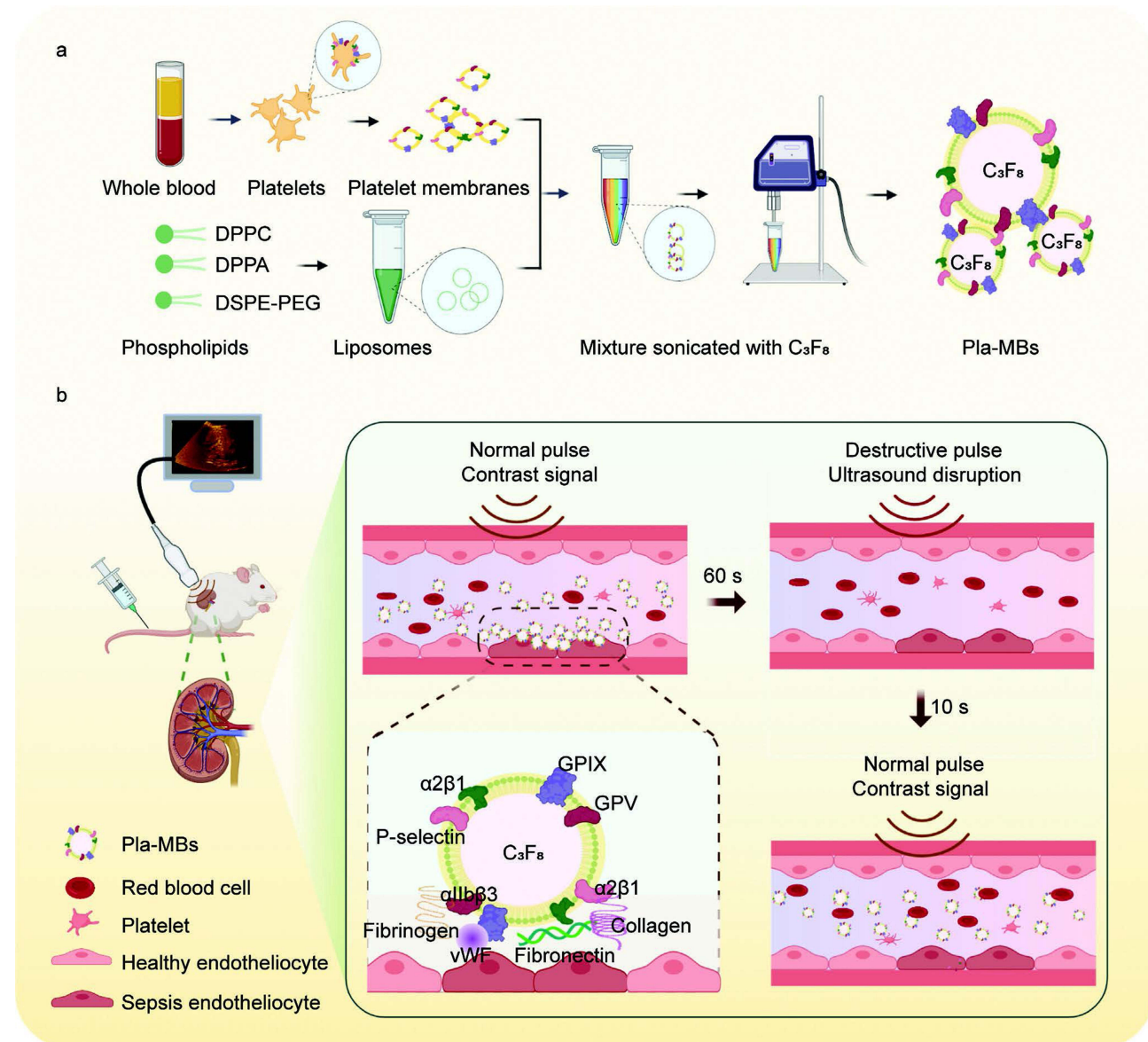


Figure 15 Schematic diagram of the preparation of Pla-MBs and kidney-targeted molecular ultrasound imaging in vivo. (a) Preparation of Pla-MBs. (b) Molecular ultrasound imaging of sepsis-induced acute kidney injury via Pla-MBs. Reprinted with permission from Yang J, Miao X, Guan Y, et al. Microbubble Functionalization with Platelet Membrane Enables Targeting and Early Detection of Sepsis-Induced Acute Kidney Injury. *Adv Healthc Mater.* 2021;10(23): e2101628. Copyright 2021 Adv. Healthcare Mater.²⁴⁷

sonographic devices may offer a sensitive and specific technique for the early detection of SAKI, which can help prevent and control SAKI and reduce mortality in septic patients.²⁴⁷ Zhang et al created a PM hybrid rapamycin liposome that not only facilitates rapamycin delivery but also harnesses the ability of PM to make long-lasting repairs. The intravenous administration of the NPs demonstrated their dual properties, including swift anti-inflammatory effects and enduring tissue-repair capabilities. Mechanistic studies have demonstrated that the NPs significantly contribute to the activation of autophagy and polarization of macrophages, consequently decreasing renal cell apoptosis and lowering pro-inflammatory cytokine levels after ischemia-reperfusion injury (IRI). Hybridization with PM seems to help reshape damaged nephron units by encouraging the recruitment and differentiation of CD34⁺ cells.²⁴⁸

Nonalcoholic Steatohepatitis

Nonalcoholic fatty liver disease (NAFLD) is a prevalent liver condition that affects approximately 30% of adults globally and 80% of individuals with obesity or diabetes.^{249,250} NAFLD encompasses a spectrum of conditions ranging from mild steatosis to more severe nonalcoholic steatohepatitis (NASH), which can progress to varying levels of liver fibrosis. While individuals with mild steatosis may not always acquire a more severe condition, NASH has the potential to advance to cirrhosis or even liver cancer.²⁵¹ NASH is distinguished by the presence of insulin resistance, steatosis, and necroinflammation, which may or may not be accompanied by centrilobular fibrosis.²⁵² Xie et al developed a novel drug delivery system utilizing a hybrid membrane composed of platelet membranes and neutrophil membranes that were coated with gelatin NPs containing vitamin E and pioglitazone (PNM-G).²⁵³ Pioglitazone effectively enhances insulin resistance and liver histology in patients diagnosed with NASH.²⁵⁴ Vitamin E can interact with free radicals, eliminating a significant amount of ROS in the liver. It also hinders the oxidation of unsaturated fatty acids by blocking this process. Additionally, vitamin E can enhance the mitochondrial membrane potential, which in turn inhibits the generation of ROS in the mitochondria. This protective action effectively safeguards liver cells and reduces the harmful effects of the second hit. Vitamin E alleviates steatosis, inflammation, ballooning, and steatohepatitis in individuals diagnosed with NASH.^{255–259} Functionalizing the biomimetic surfaces of gelatin NPs with PNM-G can improve their ability to target inflammatory areas and enrich the liver tissue.²⁵³ PNM-G possesses immune-escape capabilities and dual NASH-targeting functionality.²⁵³ PNM-G presents a promising therapeutic alternative to NASH by utilizing an innovative method of administering medication.

Microbial Infection

The use of NPs for treating infections is intriguing owing to treatment failures resulting from antimicrobial resistance and the dearth of new medications currently being developed. Furthermore, access to drugs is hampered by the fact that many infections occur inside cells in either active or latent form.^{260–262} NPs provide a viable solution for addressing these issues. Currently, there is a strong focus on their use as antimicrobial agents to combat various diseases, including bacteria, viruses, fungi, and parasites.¹¹⁰ Jin et al created a biomimetic phage-platelet hybrid nanoparticle (PPHN) by physically attaching the BCP1-BGL virus to platelet membrane NPs. BCP1-BGL phages and PPHNs were subjected to a range of trials to investigate their prolonged circulation and antibacterial abilities.²⁶³ Esteban-Fernández de Ávila et al published a study on the development of biomimetic nanorobots propelled by ultrasound. These nanorobots are composed of gold nanowires coated with a mixture of red blood cell (RBC) membranes and platelet (PLT) membranes. The purpose of these nanorobots is to perform multiple tasks, including biodegradation and concurrent elimination of pathogenic bacteria and toxins.²⁶⁴

Tumor Inflammatory Microenvironment

Cancer therapies have long faced challenges in effectively targeting tumors and penetrating them at the intratumoral level.²⁶⁵ In order to optimize the accuracy of drug accumulation specifically at tumor locations, numerous delivery systems have been created to take advantage of the enhanced permeability and retention (EPR) effect, with a particular focus on nanoscale vectors.^{266,267} Biomimetic particles obtained from biological sources have garnered growing interest owing to their distinct benefits, such as enhanced biocompatibility, the ability to reduce immunogenicity, and the capability for active targeting.^{268,269} Platelets play a crucial role in the advancement and spread of cancer, particularly by recognizing and interacting with circulating tumor cells (CTCs) in the bloodstream.^{270,271}

Platelets have the ability to specifically target cancers by attaching specific cognate signaling molecules on the surface of tumor cells and accumulating in them.^{272–274} These inherent physiological characteristics support the utilization of platelets as a feasible approach for designing targeted drug delivery to tumors and improving the ability of drugs to penetrate the tumor.²⁷⁵ Kim et al fabricated gold nanostars coated with red blood cells (RBC) and platelet membranes loaded with curcumin (named R/P-cGNS). This study showed that R/P-cGNS effectively transported medicines to their intended location, thereby improving anti-cancer efficacy. Additionally, R/P-cGNSs prevented macrophage phagocytosis and exhibited anti-inflammatory effects on macrophages.²⁷⁶ Hao et al initially synthesized gold nanocages (AuNCs) co-loaded with DOX and indocyanine green (ICG). Subsequently, the AuNC surface was decorated with a hybrid cell membrane derived from platelets and neutrophils, resulting in the formation of nanokillers (NSKs).²⁷⁷ NSKs exhibited enhanced cellular uptake, deeper infiltration into tumors, and increased toxicity towards tumor cells. They captured and eliminated circulating tumor cells (CTCs) and exosomes through high-affinity membrane adhesion receptors. This process effectively severed communication between immune cells and exosomes.²⁷⁷ In their study, Liu et al demonstrated that polypyrrole nanoparticles (PPy NPs) coated with fused RBC and PLT membranes could eliminate tumor cells when exposed directly to NIR irradiation. The resulting PPy NPs possessed the combined characteristics of RBC and PLT. They could circulate throughout the body for a lengthy period and demonstrated self-targeting properties.²⁷⁸ Zhang et al developed a biomimetic nanoplatform using a combination of a leukocyte/platelet hybrid membrane (LPHM) and dendritic large-pore mesoporous silicon nanoparticles (DLMSNs). This approach successfully combined photothermal therapy (PTT), photodynamic therapy (PDT), and chemotherapy to target triple-negative breast cancer (TNBC) and achieved synergistic effects.²⁷⁹ The large pores of the DLMSNs were used to co-load a NIR fluorescent dye, IR780, with DOX. This resulted in the formation of DLMSN@DOX/IR780 (DDI) NPs. These NPs were then coated with LPHM to create LPHM@DDI NPs (Figure 16).²⁷⁹ When exposed to a NIR laser, the LPHM@DDI NPs demonstrated a combined impact of synergistic cytotoxicity and apoptosis-inducing activity in TNBC cells. Additionally, they significantly inhibited tumor development and recurrence in TNBC mice by destroying the tumor and preventing the formation of new blood vessels.²⁷⁹

Conclusions and Prospects

This paper reviews the applications of nanotherapy based on natural platelet membranes, engineered platelet membranes, and platelet membranes hybridized with other cell membranes in the treatment of different inflammatory diseases. Bionic cell-membrane strategies have made significant progress in the field of nanomedicine. Disguised by a cell membrane, biomimetic NPs exhibit the characteristics of the cell membrane and the functional adaptability of the core nanomaterial. Unlike other carrier systems, natural cell membranes do not elicit immune responses. Moreover, surface constituents can engage with receptors on specific cells, enabling the accurate targeting and regulation of cargo release at the site of inflammation. By tailoring the origin of the membrane and the composition of the NP core, bionic NPs with distinct capabilities can be generated.

However, to turn this promising technology into a clinical therapy, we still need to define and overcome a series of challenges.

First, we face challenges related to the scale of production and associated costs. Achieving large-scale, low-cost production of platelet membrane-based nanomaterials that meet commercial and regulatory standards is a major bottleneck. This solution requires the development of simpler, more economical, and process-robust manufacturing techniques to ensure consistency across product batches.

Secondly, biocompatibility and long-term safety issues arise. Before introducing this membrane-coated system containing artificial and biological components into the human body, biocompatibility and safety must be ensured. This will involve a comprehensive assessment of the immunogenicity, potential toxicity, and metabolic pathways in the body.

Thirdly, issues related to membrane stability and functional integrity exist. The inherently low stability and degradability of platelets and their derived biological membranes pose challenges for maintaining their functions during transportation and storage. Therefore, preserving these biological materials for a long time without compromising membrane protein activity and function is crucial.

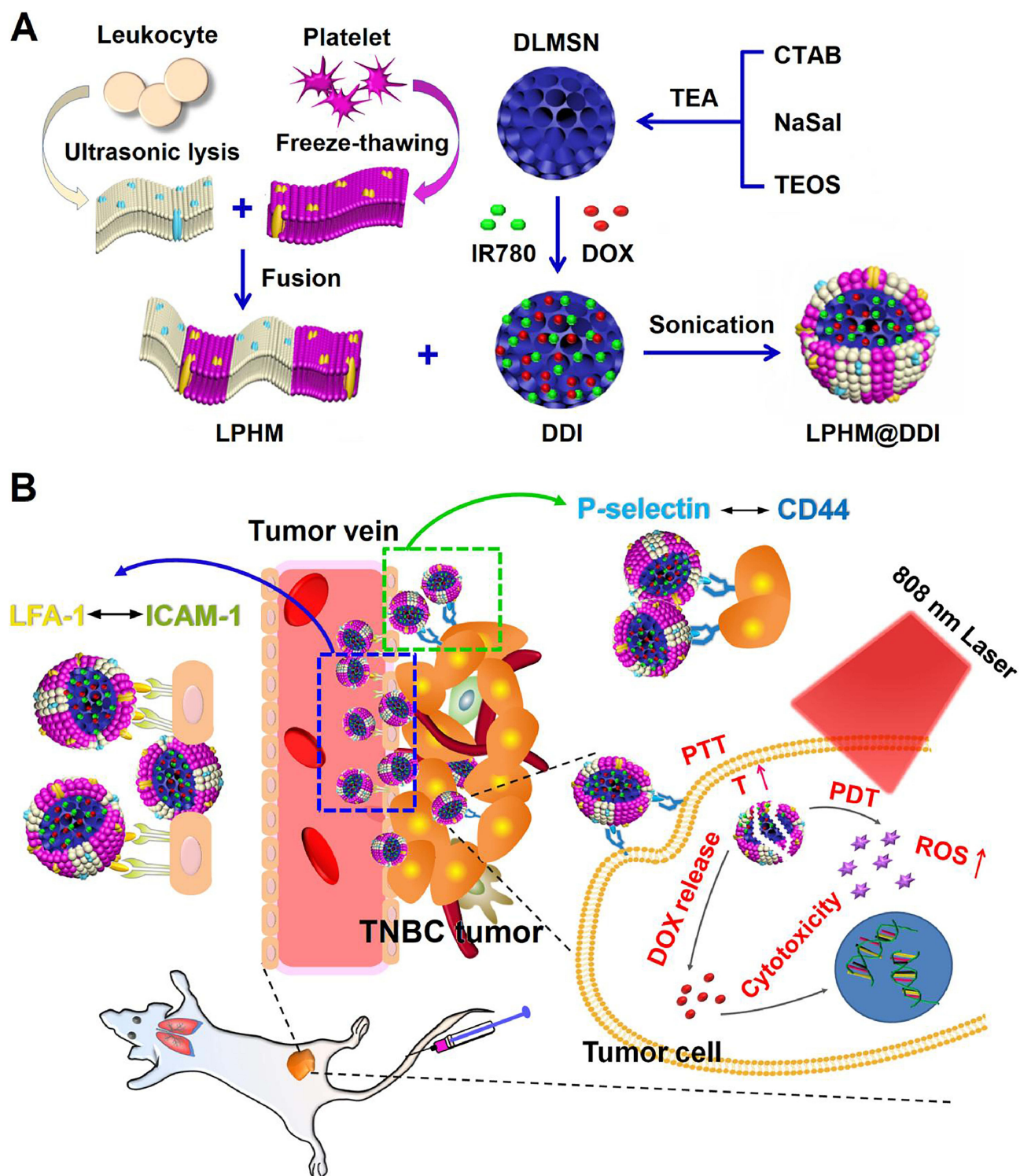


Figure 16 Schematic illustrations for preparation method of LPHM@DDI NPs (**A**) and their synergistic effects in TNBC treatment via combining PTT/PDT with chemotherapy (**B**). Blue dashed box: NPs target tumor vascular and enhance vascular permeability through activation of the LFA-1/ICAM-1 adhesion pathway. Green dashed box: Following extravasation, NPs specifically target to tumor cells via P-selectin/CD44 interactions. The red text "T" stands for temperature. The red upward arrow indicates upregulation of the corresponding elements. Reprinted with permission from Zhang T, Liu H, Li L, et al. Leukocyte/platelet hybrid membrane-camouflaged dendritic large pore mesoporous silica nanoparticles co-loaded with photo/chemotherapeutic agents for triple negative breast cancer combination treatment. *Bioact Mater.* 2021;6(11):3865–3878. Copyright 2021 Bioactive Materials.²⁷⁹

Finally, the targeted precision of platelets and their potential risks should be considered. Platelets and their biological membranes tend to aggregate in blood vessels, which presents a dual challenge. This tendency not only forms the basis of its targeted nature but may also limit its application in nonvascular-related inflammation and increase the risk of accidental accumulation at non-targeted vascular sites.

In the future, development in this field should focus on the following directions:

Precise engineering of membrane functions: In the future, we should not be satisfied with a simple membrane coating. Instead, through methods such as genetic engineering, chemical modification, or metabolic labeling, we should refine the engineering of membranes to enhance their targeting ability and loading capacity, or introduce environmentally responsive release mechanisms.

Developing intelligent hybrid membrane systems: Hybridizing the membranes of platelets with those of other cells (such as stem cells, immune cells, and red blood cells) is an effective strategy for enhancing the circulation time, active targeting ability, and additional therapeutic functions (such as immunomodulation and tissue repair) of biomimetic NPs. The key lies in optimizing the fusion process and preserving the functional integrity of each component of the cell membrane as much as possible.

Deepening translational medical research: To accelerate clinical translation, prioritizing research that conforms to translational standards is necessary. This includes systematically evaluating the pharmacokinetics, safety, and efficacy of drugs in larger animal models that are closer to clinical settings and actively collaborating with regulatory agencies to establish quality standards for such complex products.

Expanding application boundaries: In addition to their role as drug-delivery carriers, we should actively explore the use of platelet membrane NPs in diagnostic imaging (eg, as an imaging agent targeting inflammation) and immunomodulation (eg, as an “attractant” to neutralize inflammatory factors), among other applications.

In conclusion, nanotherapeutic technology based on platelet membranes has enormous potential for the treatment of inflammatory diseases. By focusing on addressing the challenges it faces in terms of large-scale production, safety, stability, and targeting, and by conducting in-depth studies on the aforementioned future directions, we can reasonably anticipate that platelet-based delivery systems are likely to evolve into next-generation intelligent drug carriers that meet various medical needs.

Abbreviations

AIS, acute ischemic stroke; AKI, acute kidney injury; AMI, Acute myocardial infarction; AMR, antimicrobial resistance; ANGPTL4, angiopoietin-like 4; Apa, apatinib; APC, antigen-presenting cell; ApoE(−/−) mice, Apolipoprotein E-deficient mice; Arg, arginine; ATRA, All-trans retinoic acid; AuNC, gold nanocage; BBB, blood-brain barrier; BPNS, black phosphorus nanosheet; BPQD, black phosphorus quantum dot; CA4, combretastatin A4; CaMKII γ , Ca²⁺/calmodulin-dependent protein kinase γ ; CHF, congestive heart failure; CIA, collagen-induced arthritis; CNS, central nervous system; CPIL4, liposome coated IL-4; CTAB, cetyl trimethyl ammonium bromide; CTC, circulating tumor cell; CVD, Cardiovascular disease; DDI, DLMSN@DOX/IR780; DEX, Dexamethasone; Dex-PEV, DEX-Loaded-PEV; DLMSN, dendritic large pore mesoporous silicon nanoparticle; DOX, doxorubicin; EC, endothelial cell; EDTA, Ethylenediaminetetraacetic acid; EPR, enhanced permeability and retention; EV, extracellular vesicle; FLS, fibroblast-like synoviocyte; FTY720, fingolimod; Gol-PMM, Golgi-targeting peptide modified PMM; Gol-PMMNP, Golgi-targeting PMM-camouflaged nanoparticle; GSH, glutathione; HED, hederagenin; ICAM-1, intercellular adhesion molecule-1; ICG, indocyanine green; IH, intimal hyperplasia; IKK, I κ Bkinases; IL-1, interleukin-1; IL1-PM, IL-1 β platelet microparticle; IL-1 β , interleukin-1 β ; I/R, ischemia/reperfusion; IRI, ischemia-reperfusion injury; i.v., intravenous injection; JAMS, Janus aminated mesoporous silica; LDL, low density lipoprotein; LFA-1, Integrin lymphocyte function-associated antigen-1; LPHM, leukocyte/platelet hybrid membrane; MCC950-PEV, MCC950 loaded platelet-derived extracellular vesicle; MDR, multidrug resistance; MG, microglia; MI, myocardial infarction; MI/R, myocardial ischemia-reperfusion; MMP, mitochondrial membrane potential; MNP, melanin nanoparticles; MSC, mesenchymal stem cell; MSN, mesoporous silicon nanoparticle; NAFLD, Nonalcoholic fatty liver disease; NaSal, sodium salicylate; NASH, nonalcoholic steatohepatitis; Nb2C, niobium carbide MXenes; NE, Neutrophil; NF- κ B, Nuclear factor- κ B; NIR, near-infrared radiation; NP, nanoparticle; NSK, nanokiller; PAMAM, polyamidoamine; PBS, phosphate buffer solution; PDT,

Photodynamic therapy; PE, pulmonary embolism; PEV, platelets extracellular vesicle; Pla-MB, hybrid microbubble by coating platelet membrane; PLGA, poly lactic-co-glycolic acid; PLP, splatelet-like proteoliposomes; PLP, platelet-like fusogenic liposome; PLT, platelet; PM, platelet membranes; PMIN, PMP -inspired nanovesicle; PMM, PMPs membrane; PMP, platelet microparticle; PM-MG, PM decorated MG; PNPArg, platelet membrane-cloaked argatroban-loaded polymeric nanoparticle; PNP, platelet membrane-cloaked nanoparticle; PPHN, phage-platelet hybrid nanoparticle; PPy NP, polypyrrole nanoparticle; PRP, platelet-rich plasma; PTNP, platelet-mimetic nanoparticle; PTT, photothermal therapy; P-EV, platelet mimetic MSC-EV; P-Lipo, biomimetic liposomes; RA, Rheumatoid arthritis; RAP, Rapamycin; RASF, RA synovial fibroblast; RBC, red blood cell; ROS, Reactive oxygen species; rtPA, recombinant tissue plasminogen activator; SAKI, Sepsis-induced acute kidney injury; SIRP- α , signal regulatory protein- α ; SOD, superoxide dismutase; SPIO, Small particle of iron oxide; TDDS, targeted drug delivery system; TEA, triethyl amine; TEOS, tetraethyl orthosilicate; TNBC, Triple-negative breast cancer; tPA, tissue plasminogen activator; TPCA-1, thiophene-3-carboxamide; TPHL, T7-PEG-PHis-PLys; uPA, urokinase; VEC, vascular endothelial cell; VSMC, vascular smooth muscle cell.

Data Sharing Statement

No datasets were generated or analyzed during the current study.

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Author Contributions

All authors contributed to the study conception and design, reviewed the manuscript, and approved the final version. 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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Disclosure

The authors declare that they have no conflicts of interest in this work.

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