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Vascular Nanomedicine: Current Status, Opportunities, and Challenges

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Abstract

The term “nanotechnology” was coined by Norio Taniguchi in the 1970s to describe the manipulation of materials at the nano (10^{-9}) scale, and the term “nanomedicine” was put forward by Eric Drexler and Robert Freitas Jr. in the 1990s to signify the application of nanotechnology in medicine. Nanomedicine encompasses a variety of systems including nanoparticles, nanofibers, surface nano-patterning, nanoporous matrices, and nanoscale coatings. Of these, nanoparticle-based applications in drug formulations and delivery have emerged as the most utilized nanomedicine system. This review aims to present a comprehensive assessment of nanomedicine approaches in vascular diseases, emphasizing particle designs, therapeutic effects, and current state-of-the-art. The expected advantages of utilizing nanoparticles for drug delivery stem from the particle’s ability to (1) protect the drug from plasma-induced deactivation; (2) optimize drug pharmacokinetics and biodistribution; (3) enhance drug delivery to the disease site via passive and active mechanisms; (4) modulate drug release mechanisms via diffusion, degradation, and other unique stimuli-triggered processes; and (5) biodegrade or get eliminated safely from the body. Several nanoparticle systems encapsulating a variety of payloads have shown these advantages in vascular drug delivery applications in preclinical evaluation. At the same time, new challenges have emerged regarding discrepancy between expected and actual fate of nanoparticles in vivo, manufacturing barriers of complex nanoparticle designs, and issues of toxicity and immune response, which have limited successful clinical translation of vascular nanomedicine systems. In this context, this review will discuss challenges and opportunities to advance the field of vascular nanomedicine.

Keywords

nanomedicine; vascular; targeting; drug delivery; animal models

Vascular pathologies, such as atherosclerosis, myocardial infarction, stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE), are leading causes of morbidities and mortalities in the world.[1–3] Therefore, significant preclinical and clinical research efforts are focused toward these diseases as well as their diagnosis, prevention, and treatment.

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Conflicts of interest

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Disease pathogenesis for these involves a variety of cellular and biomolecular entities within the vascular compartment, which often present reciprocal mechanisms of inflammation and thrombosis, precipitating in vessel occlusion and tissue injury. Therefore, current therapeutic approaches are directed toward one or more cellular or molecular component of these mechanisms. Most clinical approaches utilize systemic oral or intravenous (bolus or transcatheter infusion) delivery of therapeutics (e.g., anticoagulants, antiplatelet agents, fibrinolytics, and anti-inflammatory molecules) in a highly regulated regimen. Such direct systemic drug administration can lead to several unwanted effects[4–8]:

1. Suboptimal circulation time and bioavailability of drugs due to plasma-induced deactivation by circulating inhibitor molecules.
2. Drug clearance into nonspecific tissues leading to suboptimal concentration at target disease site in the vasculature.
3. Systemic and off-target drug actions that cause harmful side effects including coagulopathy, neurotoxicity, nephrotoxicity, and hemorrhage.

Such problems can be possibly resolved by spatiotemporally restricting drug delivery and action at therapeutically effective doses at the target vascular pathology site. An excellent example for such “targeted” drug action is represented by the design and applications of drug eluting stents (DESs), where polymer coatings applied on the stent metal frame act as a matrix for locally sustained release of anti-inflammatory drugs such as paclitaxel and sirolimus to prevent restenosis of stented blood vessel.[9–11] However, interventional procedures like angioplasty and stenting are expensive, necessitate specialized expertise in terms of personnel and facilities, and may not be applicable or accessible to many patients in various vascular disease scenarios or within required treatment windows.[12–15] Therefore, pharmacotherapeutic approaches that can be administered relatively easily, and can localize and enhance drug availability and activity at the vascular disease site, can provide significant advantages in treating many disease scenarios. This is where “nanomedicine”-based approaches present significant promise.[16] Although the concept of manipulating matter at very small scale was put forward by Richard Feynman in the 1950s,[17] the term “nanotechnology” was actually coined by NorioTaniguchi in the 1970s[18] to describe the manipulation of materialsat the nano(10^{-9}) scale, and buildingonthat theterm “nanomedicine” was put forward by Eric Drexler and Robert Freitas Jr. in the 1990s to signify the application of nanotechnology in medicine.[19,20] Within this field, the technologies and applications in treating vascular pathologies predominantly involve either direct bioconjugation or chemical modification of drug molecules to enhance their disease site-specific availability and activity,[21–25] or the utilization of particulate delivery platforms (i.e., nanoparticles and microparticles) to encapsulate the drugs for disease site-directed delivery via passive and active mechanisms.[26] To elucidate and review these approaches, it is first necessary to provide a summary description of the cellular and molecular components of vascular disease pathology. To this end, the next section will describe the major cellular and molecular players in the thromboinflammatory niche of major vascular diseases. Building on that, subsequent sections will describe various designs and experimental findings regarding nanomedicine systems directed at treating these pathological conditions, together with a discussion of opportunities and challenges. For convenience of the readers,

Table 1 provides acronyms, abbreviations, and corresponding full names of molecules, motifs, cells, materials, and terminologies used throughout the descriptions.

Major Cellular and Molecular Components in Vascular Disease

Blood is a fluid connective tissue composed of cellular components, namely, red blood cells (RBCs), white blood cells (WBCs), and platelets suspended in an aqueous plasma phase rich in various proteins (predominantly albumin, immunoglobulins, and fibrinogen), coagulation factors, salts, and ions. In the circulatory system, blood flows through blood vessels, namely, arteries, veins, and capillaries, whose luminal wall is lined by endothelial cells (ECs) sitting on a subendothelial matrix composed predominantly of collagen (types I, III, and IV).[27,28] Healthy ECs present a dense covering of carbohydrate-rich brush-like polymers on their luminal (i.e., blood exposed) surface, termed the “glycocalyx,” which renders important thromboresistant properties by virtue of sterically hindering protein adsorption and platelet adhesion.[29,30] Furthermore, the glycocalyx allows binding of several anticoagulant molecules such as antithrombin, heparin cofactor II, thrombomodulin (TM), and tissue factor pathway inhibitor (TFPI), all of which play unique roles in downregulating various outputs of the coagulation process. These important protective functions of the endothelial lining (with its glycocalyx), cumulatively, prevent clotting of blood at the vessel wall (i.e., thrombus formation) and thus prevent vessel occlusion. However, various vascular disease scenarios can injure and denude this endothelial lining, and this can lead to prothrombotic mechanisms.

One prime example is atherosclerosis, which is an inflammatory vascular disease of arteries where increased concentration of low-density lipoprotein (LDL) cholesterol in plasma and dysregulated cholesterol metabolism can injure and inflame the luminal endothelium and induces expression of several leukocyte adhesion molecules like P-selectin, E-selectin, intercellular cell adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and integrin $\alpha_L\beta_2$.[31–33] Leukocytes, predominantly monocytes and neutrophils, do not bind to healthy endothelium but can bind to diseased ECs via these adhesion proteins, which then primes ECs for further active inflammatory mechanisms like transcytosis into subendothelial intima, transformation of monocytes to macrophages, macrophage, neutrophil, and endothelial secretion of various inflammatory chemokines and cytokines. Leukocyte adhesion, rolling, and transmigration into intima are also mediated by mechanisms involving CC-chemokine receptor 1 (CCR1), CCR2, CCR5, and CXC-chemokine receptor 2 (CXCR2). Transcytosed lesional macrophages can ingest modified LDLs via scavenger receptors and transform over time into lipid-rich foam cells. Platelets, which are traditionally considered to be significant players in the advanced thrombotic events associated with later stages of atherosclerosis (e.g., hemorrhagic, eroded, or ruptured plaques), are now also implicated in several biomolecular events during the initial stages of atherosclerotic lesion development and progression.[34–38] For example, diseased and injured endothelium can secrete von Willebrand factor (VWF) from their Weibel-Palade bodies and platelets can bind to this locally secreted and deposited VWF via the glycoprotein Ibα (GPIbα) component of the platelet surface receptor complex GPIb–IX–V.[37,38] Thus, endothelial VWF as well as P-selectin can promote platelet tethering and rolling via interaction with platelet GPIbα and P-selectin glycoprotein ligand-1

(PSGL-1).[36–40] Platelets can also mediate the binding of leukocytes to diseased endothelium and thus the activated platelet–endothelium–leukocyte triad forms the major inflammatory phenotype in this disease. Activated integrin $\alpha_{IIb}\beta_3$, present on the platelet surface at high density (50,000–80,000 per cell), assumes the ligand-binding form upon platelet activation and binds its natural ligand fibrinogen (Fg), as mediated by molecular interactions with arginine–glycine–aspartic acid (RGD) and AGD-based peptide sequences.[41–45] Integrin $\alpha_V\beta_3$ is principally a fibronectin/vitronectin receptor that helps extracellular matrix (ECM) anchorage and focal adhesion of ECs. However, in activated proinflammatory environment, $\alpha_V\beta_3$ and $\alpha_{IIb}\beta_3$ can interact with each other via RGD-mediated bridging by Fg to secure the attachment-activated platelets on inflamed endothelium at the atherosclerotic lesion site.[46–48] These platelet–endothelium–leukocyte interactions as well as macrophagic ingestion of lipids result in a cascade of chronic inflammatory events. These involve recruitment, activation, and infiltration of more inflammatory cells, secretion of matrix degrading enzymes (e.g., matrix metalloproteinases or MMPs, and neutrophil elastase), degradation of collagenous matrix, and migration of smooth muscle cells (SMCs) and fibroblasts. Proinflammatory biomolecules like interleukin-1β (IL-1β), regulated upon activation normal T cell expressed and secreted (RANTES), monocyte chemoattractant protein-1 (MCP-1) and macrophage colony-stimulating factor (M-CSF) secreted by activated platelets, endothelium, and leukocytes facilitate inflammatory cell recruitment, lesion-associated cellular transformations, and plaque progression. Activated platelets also secrete PDGF (platelet-derived growth factor) and TGF-β (transforming growth factor-β) that stimulate endothelial and SMC migration, proliferation, new blood vessel formation, and matrix synthesis within the atherosclerotic lesion site. Matrix protein (e.g., collagen) secretion by SMCs and fibroblasts counterbalance matrix degradation, and subsequent development of a lipidic necrotic core in the subendothelial region covered by a fibrous collagenous cap. In vulnerable atherosclerotic lesions, matrix degradation is upregulated due to high MMP and elastase activity, while matrix production is downregulated (e.g., by signaling mechanisms of interferon gamma [IFN-γ] produced by T-cells). In the presence of stress and hemodynamic alterations, ruptures and fissures develop in such “high-risk” plaques causing intraplaque hemorrhage or exposure of the subendothelial collagen and necrotic lipidic core to flowing blood. This results in more platelet adhesion, activation, and aggregation via Fg-to-$\alpha_{IIb}\beta_3$ and P-selectin-to-PSGL-1 interactions, and the status transforms into a complex thrombotic (i.e., atherothrombosis) phase. The phosphatidyl serine (PS)-rich activated platelet surface allows colocalization and activation of coagulation factors (e.g., FIXa + FVIIIa in tenase complex, and FXa + FVa in prothrombinase complex) and cofactors (e.g., Ca^{2+} ion) from blood, promoting coagulation cascade stimulation and amplification, thereby leading to high levels of thrombin generation. The thrombin converts local Fg into fibrin which assembles and cross-links in presence of activated FXIIIa to form an occlusive clot that restricts blood flow.[37,38,49,50] Such thrombo-occlusive events occurring in the coronary artery leads to myocardial infarction (i.e., heart attack) and in the carotid artery leads to stroke, which remain the two highest mortality factors in the global population.

While atherosclerosis and atherothrombosis occur in the relatively high shear regions of the arteries, another distinct mechanism with some overlapping cellular and molecular

components occurs in the low shear regions of the veins. Especially near the valves in the vein, the low flow and eddies in circulation can lead to endothelial dysfunction, activation, and subsequent adhesion of platelets and leukocytes (predominantly neutrophils and monocytes). Here, the intercellular interactions can prime neutrophils to become activated and these active neutrophils (and also reportedly some macrophages) can decondense and secrete their DNA triggered by unique histone citrullination mechanisms involving intracellular myeloperoxidase, peptidyl arginine deaminase 4 (PAD-4), and elastase activities.[51–55] These extracellularly secreted decondensed DNA (e.g., neutrophil extracellular traps or NETs) can arrest and activate more platelets, and trigger coagulation mechanisms to enhance thrombin generation and fibrin deposition.[56–58] These thromboinflammatory mechanisms are characteristic in DVT and have also been recently implicated in the microvascular thrombosis in acute lung injury (ALI) as well as cancer-associated thrombosis. Venous thrombi can also dislodge, travel via circulation, and occlude distal vascular beds, for example, PE that occurs post-DVT or trauma and in cancer patients. Fig. 1 shows schematics of characteristic components of thrombotic and thromboinflammatory mechanisms typically seen in various vascular disease pathologies.

Based on the earlier-described cellular and molecular components of vascular diseases, it becomes intuitively evident that therapeutic approaches that can downregulate or inhibit the proinflammatory and prothrombotic molecules on ECs, leukocytes, and platelets disrupt the various intercellular interactions, mitigate inflammatory signals, inhibit coagula-tory pathways, and rapidly degrade occlusive blood clots, and can have significant benefit in treating the various conditions. Thus, the drug molecules for such treatment span the categories of receptor inhibiting molecules and antibodies, gene therapy for receptor downregulation and signaling pathway inhibition, anticoagulant molecules, and fibrinolytic agents. In addition, with the purpose of detection and diagnosis of the pathologic conditions, different contrast agents and imaging probes can be directed toward the cellular and molecular entities. Therefore, nanomedicine strategies for these disease scenarios have focused on direct chemical modification as well as particle-based formulation of these drugs and imaging agents in various ways to enhance pharmacokinetic profile, favorable biodistribution, disease site-selective delivery, and site-localized function. The following sections will provide salient examples of such approaches and technologies.

Direct Modification of Therapeutic Agents

A potential issue for many drug molecules directly administered in the vascular compartment (e.g., via intravenous administration) is their nonspecific interaction with plasma proteins as well as specific interactions with inhibitors in circulating plasma, and rapid clearance through liver and kidney, all of which reduce drug circulation lifetime and bioavailability. One of the earliest strategies to reduce these effects was put forward by Helmut Ringsdorf during the 1970s, which involved conjugation of the drug molecule to high-molecular-weight water-soluble macromolecules that may form a protective shield around the drug molecule while keeping it in circulation.[59–61] Furthermore, drug conjugation to the polymer can be mediated by chemical bonds (e.g., amide, orthoester, ester, anhydride, carbonate, and urethane) that can be cleaved by mechanisms such as enzymatic and/or pH-sensitive reactions to release active drugs for subsequent action.

The “Ringsdorf model” for polymer-conjugated prodrug system has been attempted on several drug molecules in treatment of vascular diseases, especially fibrinolytic drugs and anticoagulant molecules. For example, PEG (polyethylene glycol)-based modification (PEGylation) of fibrinolytic agents such as tissue plasminogen activator (tPA), streptokinase (SK), urokinase (UK), and staphylokinase (SAK) has been reported.[62–66] In some studies, it was found that the “protective” property of PEG-SK conjugates could be improved by increasing the molecular weight of PEG.[63] PEGylated systems of truncated SK variants with promising in vitro fibrinolytic activity and enhanced in vivo circulation residence time have also been reported recently, although the in vivo fibrinolytic capacity of these systems were not reported.[67] In preclinical ex vivo studies using beagles, PEG-conjugated urokinase was able to maintain fibrinolytic capacity for long periods of time (i.e., prolonged bioactivity in plasma), while free urokinase rapidly lost its activity in plasma due to inhibitor effects.[64] Recombinant tPA has also been conjugated to PEG and the PEG-tPA product was reported to show partial enhancement of circulation lifetime and bioactivity compared with free tPA in canine models.[62] The PEGylation strategy has also been reported for anticoagulant molecules. For example, PEG has been conjugated to the thrombin inhibitor hirudin and these PEG-hirudin systems have been evaluated in vitro, in vivo, and even in clinical studies in human patients. The studies showed that PEG-hirudin maintains its anticoagulant activity while providing a substantially longer circulation lifetime compared to unconjugated hirudin.[68,69] In another interesting design, the anticoagulant anionic macromolecule heparin was conjugated to a polyarginine-modified cationic form of the fibrinolytic tPA, such that the tPA can be released in the presence of the cationic heparin antagonist protamine.[70] The purpose of this design was to impart charge-induced drug release and the system was tested in vitro with promising result, but has not been reported in any in vivo evaluation. The antiproliferative drug paclitaxel (clinically used in DESs for mitigating restenosis and intimal hyperplasia) has been conjugated also to polymers such as polyglutamic acid (PGA) to result in products like Xyotax that have been studied for cancer treatment, but such designs also may find use in vascular antiproliferative therapies. Other direct chemical or structural modification of therapeutic molecules involve strategies to enhance targeting and selectivity of drug delivery (and action) at the disease site by recombinant modifications or conjugation of specific antibodies, antibody fragments, and peptide ligands. For example, the direct modification of tPA with anti-ICAM antibody to enable specific delivery of the drug to inflamed endothelium has been reported and this system demonstrated targeted fibrinolytic efficacy in vivo in lung embolism in mouse models.[71] In a parallel design, tPA has been conjugated to RBCs to render long circulation time as well as incorporation into nascent clots for clot-specific fibrinolytic activity.[72–74] Compared with free tPA, the RBC-tPA system has shown the ability to allow “prophylactic fibrinolysis” in vivo in mouse models of pulmonary thrombosis when administered before vascular injury, although it did not show efficient lytic ability when administered 10 minutes after vascular injury. In an approach to direct fibrinolytic drugs to platelet-rich thrombi, urokinase was modified with a monoclonal antibody 7E3 (abciximab) that binds to integrin $\alpha_{IIb}\beta_3$ on the surface of platelets.[75] The urokinase-7E3 system showed significantly enhanced binding to $\alpha_{IIb}\beta_3$-coated substrates in vitro and enhanced plasmin generation on such substrates, and in ex vivo studies this system showed enhanced targeted fibrinolytic and antiplatelet ability at lower concentrations compared with free urokinase. A similar design rationale and

experimental findings were reported where a SAK mutant was engineered to bear the tripeptide sequence of RGD that is known to have binding capability to many cell surface integrins, including platelet $\alpha_{IIb}\beta_3$.[76] The SK-RGD system showed enhanced platelet targeting and fibrinolytic ability in vitro and also demonstrated the ability to render efficient clot lysis as well as reduced reocclusion incidents in vivo in porcine coronary artery balloon injury model.

In another approach, a recombinant system was constructed by fusing urokinase-type plasminogen activator (uPA) with single-chain variable fragment (scFv), an antibody to platelet–endothelial cell adhesion molecule (PECAM).[77] Compared with unconjugated uPA, the anti-PECAM scFv-uPA showed enhanced ability to target cerebral arterial vasculature and lyse clots effectively in vivo in a mouse model, demonstrating its potential in treating cerebrovascular occlusions (e.g., in ischemic stroke). In a related study, the anti-PECAM scFv-uPA construct was further modified via recombinant techniques to include a thrombin-activatable domain, such that the anti-PECAM scFv could render targeted delivery to clot site endothelium while clot-localized high thrombin levels could cleave the uPA for clot site-specific action.[78] This modified system demonstrated minimal effect on circulating fibrinogen and an enhanced targeted fibrinolytic affect in pulmonary reperfusion injury in mice. A similar recombinant fusion construct was recently developed with an scFv directed at platelet α_{IIb} instead of PECAM, so as to target clot-associated platelets instead of endothelium.[79] This novel construct, termed “PLT/uPA-T,” showed binding ability to both quiescent and active platelets as well as fibrinolytic ability in microfluidic assays in vitro. The PLT/uPA-T construct also showed the ability to lyse nascent clots in a thrombin-responsive manner but not preexisting clots in transgenic (for human GP α_{IIb}) mouse models of ferric chloride ($FeCl_3$)-induced carotid artery thrombosis in vivo, thus showing promise for thromboprophylaxis. In another scFv-based approach, a direct FXa inhibitor namely tick anticoagulant peptide (TAP) was conjugated to an scFv directed at fibrin ($scFv_{59D8}$), and this construct showed targeted anticoagulant activity in human blood-based assays in vitro.[80] In yet another approach, single-chain urokinase plasminogen activator (scuPA) was conjugated to an scFv directed toward platelet glycoprotein $\alpha_{IIb}\beta_3$, such that the scFv-scuPA system was able to prophylactically prevent carotid thrombosis in vivo in mice, in a targeted fashion without affecting the systemic hemostasis status (measured by tail-bleeding assays).[81] In further refinement, platelet $\alpha_{IIb}\beta_3$-directed scFv was conjugated to a recombinant microplasminogen engineered to be activated by thrombin, such that thrombin-triggered release of platelet-targeted microplasminogen could enable local plasmin generation and clot lysis in mouse models of mesenteric thrombosis and PE.[82]

An alternate “clot-targeted triggerable release” design for fibrinolytic agent tPA was also recently reported, where tPA was camouflaged by albumin by two different strategies, one by conjugating anionically modified tPA (modified by low-molecular-weight heparin [LMWH]) with cationically modified albumin (modified by protamine) and the other by conjugating albumin to tPA via a thrombin-cleavable peptide linker sequence GFPRGFPAGGC.[83] An additional component of this design was potential decoration of the albumin-based camouflage shell with clot-homing ligands (e.g., the platelet $\alpha_{IIb}\beta_3$ targeting peptide CQQHHLGGAKQAGDV derived from fibrinogen) such that upon homing to the clot, the shedding of the albumin camouflage shell could be rendered by heparin dosing

(to reverse heparin–protamine association) or thrombin-triggered cleavage of the linker, leading to clot-localized release of tPA. In vitro, these systems have shown ability to bind to platelets and in vivo these systems have shown the ability to render fibrinolytic activity at levels equivalent to free tPA but with reduced systemic side-effects. In another recent approach, a prodrug nanoparticle comprising the antiplatelet and antithrombotic drug diosgenin conjugated directly to PEG was reported, where the prodrug nanoparticle was shown to be safe toward cell viability in vitro and to be capable of reducing thrombus burden in vivo in a cerebral artery thrombosis model in mice.[84] Fig. 2 shows schematic representations of the various design approaches involving direct modification of vascular therapeutic molecules, discussed earlier. While these systems allow for longer circulation lifetimes and potential targeting of clot-relevant cellular and molecular components, such direct modification can also potentially pose issues of affecting the bioactivity and stability of the actual drug molecules. Also, transforming drug molecules into larger high-molecular-weight systems by modification with other proteins and polymers may sterically limit their diffusion and permeation capabilities in larger compact clots. An alternative strategy to protect the drugs in circulation, increase residence time and potentially achieve targeted delivery (and release) at the clot site, is to package these in micro- and nanoparticulate vehicles, as reviewed in the subsequent sections.

Incorporation of Therapeutic Agents in Nanoparticles without Clot-Targeting Mechanisms

Due to the issues associated with direct systemic delivery of vascular therapeutic agents as well as potential challenges associated with direct drug modifications, significant research has been directed in the past two decades toward incorporation of the agents within microscale and nanoscale drug carrier systems. To this end, studies have extensively focused on using particulate drug carriers such as liposomes, polymeric particles, lipoprotein particles, micelles, quantum dots (QDs), gold particles, dendrimers, ultrasound-sensitive bubbles iron oxide particles, and nanogels (Fig. 3).

Liposomes are amphiphilic phospholipid-based vesicular structures originally reported by Sir Alec Bangham, where the phospholipids self-assemble to form particles with a lipidic (hydrophobic) shell and an aqueous core.[85,86] These systems can technically encapsulate both lipophilic and hydrophilic drugs in their lipid membrane and aqueous core volume fractions, respectively. For amphiphilic phospholipid molecules, liposome formation is thermodynamically for a molecular *packing fraction* (v/al) of approximately 1, where “v” is the hydrophobic volume, “a” is the hydrophilic surface area, and “l” is the hydrophobic length. In an aqueous environment, the amphiphilic molecules tend to form planar lamellar bilayer assemblies that ultimately fold into spherical vesicles containing a lipidic shell and aqueous core.[87] Such vesicle morphologies can have single lamellar shell (unilamellar) or multiple concentric shells (multilamellar). Liposome size ranges may vary from approximately 50 nm to a few microns in diameter. Large microscale multilamellar vesicles may be morphologically transformed into nanoscale (diameter of 50–200 nm) unilamellar vesicles by nano-extrusion or sonication. Moreover, modifications to the liposome outer surface using hydrophilic polymers such as PEG can impart steric

hindrance to coronal adsorption of blood proteins (i.e., opsonization) and macrophagic uptake, thus rendering “stealth” properties that avoid rapid macrophagic clearance from circulation.[88] This results in enhancing the circulatory lifetime of liposomes and their payload.[89] This liposome approach has been clinically utilized in the formulation of cancer drugs such as Doxil, Daunosome, and Myocet, thereby making liposomes popular choices in examining drug delivery to other diseases including vascular.[90] Accordingly, various vascular drugs, especially fibrinolytic agents, have been encapsulated in liposomes for in vivo delivery. The earliest studies with such formulations demonstrated enhanced circulation residence time and in vivo efficacy of the drugs, for example, of the fibrinolytic drugs SK and tPA, when encapsulated within liposomes compared with direct administration.[91–93] Subsequent studies showed the ability of liposome-encapsulated SK formulations to improve therapeutic efficacy in vivo in rabbit and canine models of vascular occlusion.[94–96] In related studies, Erdoğan et al demonstrated using radiolabeled SK in a rabbit jugular vein thrombosis model that lipid-based vesicular systems (liposomes, niosomes, and sphingosomes) are capable of encapsulating SK and making it bioavailable in thrombus at levels similar to free SK administration intravenously.[97] During the late 1980s and 1990s, recombinant tPA was approved as the fibrinolytic drug of choice replacing SK in the United States and United Kingdom, due to relatively higher affinity of tPA for “fibrin” (i.e., clot) compared with “fibrinogen.” However, a significant challenge with tPA is its rapid inhibition by plasminogen activator inhibitor type 1 (PAI-1) present in plasma, leading to its circulation half-life being approximately 5 minutes.[98] Consequently, liposomal encapsulation of tPA has been studied to enhance his circulation residence time.[99] Studies with liposome-encapsulated tPA has shown that the drug can be encapsulated in PEGylated liposomes at an entrapment efficiency of approximately 20 to 40%, its circulation lifetime can be increased by four- to fivefold compared with free tPA (tested in vivo), and tPA released from such liposomes can render effective fibrinolysis in vitro and in vivo. Liposomes have also been assessed for encapsulation and delivery for other vascular therapeutics (e.g., anticoagulants), DNA/RNA, and molecular imaging agents. For example, LMWH has been incorporated in cationically charged liposomes for delivery via oral, subcutaneous, and inhalation route to explore enhancement of bioavailability of the drug.[100] In another interesting approach, LMWH-loaded liposomes were immobilized on stents to reduce the risk of in-stent thrombosis.[101] Liposomes have also been used to deliver DNA and siRNA in preclinical treatment evaluation in vascular diseases,[102–107] although most of these approaches use liposome surface decorated with targeting fusigenic or cell penetrating peptides, as described in the next section. Besides fibrinolytic drugs, anticoagulants and gene therapy agents, liposomes have also utilized for imaging of vascular diseases by encapsulating imaging contrast agents such as the MRI probe gadolinium (Gd), by either direct loading of Gd salts or by lipid conjugation of Gd chelates.[108–110] Analogous to amphiphilic lipid-based liposomal systems, amphiphilic block copolymer-based vesicular systems (polymersomes)[111–113] can also be used to encapsulate and deliver vascular therapeutics, although the limited investigations in this field have utilized “active targeting” of polymersomes, as described later in this article.

While amphiphilic lipids and block copolymer molecules with packing parameter closer to 1 (i.e., cylindrical shape) form vesicles (i.e., liposomes and polymersomes), those

with packing parameter less than 0.5 tend to form compact micelles with a hydrophobic core and a hydrophilic shell. Micellar structures have been researched for encapsulation and delivery of hydrophobic cancer drugs, but their study in vascular drug delivery has been limited. For example, PEG-polycation micelles have been studied for gene delivery applications to atherosclerotic lesions using rabbit models.[114] Strategies based on micelles, directed at diseased or dysregulated endothelial components of sites of atherosclerosis and thrombosis, have recently been described.[115,116] Majority of such strategies require micelle surface modification involving ligand-based active targeting, which is discussed in the subsequent section. Among other encapsulating particle systems, polymer-based solid micro- and nanoparticles have remained important components in vascular drug delivery applications.[12,13,117,118] Using various phase segregation techniques, polymer-based solid nanoparticle carriers have been manufactured from biocompatible and biodegradable polymers such as poly-lactic-*co*-glycolic acid (PLGA), PEG, and polyvinyl alcohol (PVA) and these particle systems have been studied for encapsulation and delivery of fibrinolytic agents like SK and tPA, anticoagulant molecules like heparin, and antiproliferative agents like probucol, rapamycin, and paclitaxel that areknown to reduce restenosis, with promising outcomes in preclinical models and limited clinical studies.[94,95,119–129] Ultrasound-sensitive bubbles (e.g., those made of perfluorocarbon encapsulated within a lipidic or polymeric shell) are approved in the clinic for cardiac imaging.[130,131] Similar microbubbles have been studied for combined vascular therapeutic and diagnostic (i.e., theranostic) applications, where the drug-loaded bubble can be tracked by ultrasound image guidance and then destabilized by focused ultrasound for site-selective drug release. For example, PVA-based bubbles have been loaded with the gas nitric oxide (NO) that has vasodilatory and thrombo-resistant functions, for image-guided NO delivery to diseased vasculature.[131] Similar bubbles have also been described for delivery of DNA, double-stranded RNA and oligonucleotides, recombinant proteins, growth factors, and fibrinolytic agents.[132–136] Specifically, for fibrinolytic strategies, ultrasound-induced mechanical disruption of clots combined with ultrasound-triggered fibrinolytic delivery has led to strategies of “sonothrombolysis.” Another important class of nanostructures that have been extensively studied for drug delivery, including delivery of vascular therapeutics, is “dendrimers” which are highly branched polymeric nanostructures that may be synthesized by “convergent” or “divergent” chemical techniques.[137,138] A payload of genes, drugs, and imaging agents can be loaded in the dendrimer core, the branching zone as well as in the branch extremities.[139] In an early study, the fibrinolytic SK was bioconjugated to polyglycerol dendrimer (PGLD), and these PGLD-SK systems could be immobilized in the wells of ELISA plates via amide conjugation.[140] These immobilized PGLD-SK assays showed fibrinolytic activity in vitro with blood samples but were not reported in any in vivo evaluation. Recently, a poly(L-lysine)-based dendrimer system has been reported that can be loaded with the fibrinolytic drug nattokinase (NK) and these NK/PLL nanocomposite particles were shown to have safety toward hemolysis and cell viability, with conserved enzymatic activity in vitro.[141] In related studies, the same researchers have also reported on incorporating NK in dendrimers made from PEGylated polyglutamic acid, and this dendrimer system has shown low toxicity and excellent thrombolytic ability in vitro and in vivo.[142] Besides these, dendrimers also have been used for ligand-mediated active targeting in vascular drug delivery, as examined in the subsequent section.

Besides lipid- and polymer-based nanoparticle systems, inorganic nanoparticles, especially gold (Au) and iron oxide systems, have been studied in drug delivery and imaging in vascular diseases extensively.[143–148] Colloidal solid gold nanoparticles can be synthesized by reduction of chloroauric acid in the presence of a stabilizing agent, but also hollow gold nanostructures fabricated by galvanic replacement techniques have been extensively studied as carrier vehicles for drug delivery and imaging, and for near infrared (NIR) wavelength-triggered plasmonic properties that allow photothermally induced drug delivery.[149–153] Gold nanoparticles have been reported for cell-specific imaging, and for image-guided targeted drug delivery in cardiovascular diseases.[154,155] For example, particles having Au core coated with Apolipoprotein A-1 and phospholipids were shown to be internalized by atherosclerosis-relevant macrophages in ApoE −/− mice, thereby enabling enhanced molecular imaging of lesion-associated macrophage burden, extent of calcification, and stenosis.[156] Au nanoparticles were surface-modified by a peptide sequence that can be specifically degraded by MMPs and with an NIR fluorescence dye Cy5.5 in another study, to be used as a molecular imaging probe at sites of high MMP activity in atherosclerotic lesions.[157] Au nanoparticles can also enable photothermal ablation properties, and this has been utilized in recanalization of atherosclerotic plaques in coronary arteries in human postmortem ex vivo specimens.[158] Superparamagnetic iron oxide (SPIO) nanoparticles are categorized based on their hydrodynamic diameter, for example, oral-SPIO (300 nm–3.5 μm), standard-SPIO (SSPIO, 60–150 nm), ultrasmall-SPIO (USPIO, 5–40 nm), and monocrystalline iron oxide NPs (MION).[159] Moreover, MIONs containing a chemically cross-linked polysaccharide (e.g., dextran) shell are designated cross-linked iron oxide (CLIO) particles.[160,161] Various SPIO systems have been researched as contrast agents in MRI-based cellular and molecular imaging of vascular diseases.[162–171] Drug loading of SPIO systems can lead to efficient theranostic constructs, as demonstrated for the delivery of various antithrombotic and anticoagulant agents.[172,173] Iron oxide nanoparticles have also been incorporated along with paclitaxel within PLGA particles to form drug-loaded magnetic constructs, which could be guided by an induced magnetic field for carotid artery site-directed triggered release of the antiproliferative drug.[174] Other molecular imaging probes have also been combined with iron oxide nanoparticles to enable multimodal vascular imaging with enhanced resolution and sensitivity.[175–178] QDs are another class of inorganic nanoparticles that have undergone substantial research in vascular imaging. QDs are semiconductor nanocrystals (e.g., particles with a cadmium selenide core with a zinc sulfide shell) whose fluorescent properties vary with size and composition, and they are sufficiently electron dense to also allow electron microscopy.[179] The in vivo pharmacokinetics, biodistribution, and safety of QDs continueto be debated[180–183]; however, they have been studied in vascular drug delivery and imaging applications. As an example, QDs have been incorporated in high-density lipoprotein (HDL)-based plaque-targeting nanoparticles for imaging of atherosclerotic plaques.[184] Similar HDL particles have also incorporated MRI contrast agents, and these were assessed for targeted MR imaging of atherosclerotic plaques.[185–187] Ligand modification of QDs has also been assessed for active targeting to vascular disease sites, as discussed in the next section.

Incorporation of Therapeutic Agents in Nanoparticles with Active Clot-Targeting Mechanisms

Several nanoparticle systems described previously in the context of packaging of vascular therapeutics have also been studied to engineer “actively targeted” drug delivery systems where the nanoparticles can utilize specific molecular interactions to anchor at vascular disease sites. The molecular interactions can be mediated by antibodies and their fragments, proteins, peptides, etc., such that these can act as ligands to specific receptors that are exposed or expressed or upregulated at the site of vascular pathologies. Decoration of the nanoparticle surface with such ligands can be achieved by noncovalent or covalent bioconjugation techniques. The motivation for such molecular targeting is to enhance the specificity and selectivity of payload (drug) localization, and also in some cases utilize receptor-mediated internalization of drug-loaded nanoparticles within disease-specific cells.[188,189] Regarding noncovalent strategies to modify nanoparticle surface, ligands are adsorbed mostly via physical interactions (e.g., hydrophobic, affinity-based, and charge-based) with the particle surface. For example, in one study, polystyrene particles were coated with antibodies directed at P-selectin and E-selectin using adsorbed bacterial protein A molecules as spacers.[190] P- and E-selectins are upregulated on stimulated platelets, ECs, and monocytes in vascular inflammation and thrombosis, and therefore surface decoration of nanoparticles with antibodies directed at them can enable active targeting to such vascular disease sites. In another study, chitosan particles were coated with antiamyloid monoclonal antibodies to target amyloid β-protein deposits in cerebral vasculature of mice.[191] Other nanoparticles, such as liposomes, latex beads, and albumin particles, have been surface-decorated noncovalently with recombinant GPIbα (rGPIbα) and $rGP\alpha_2\beta_1$ to bind VWF and collagen, respectively, to allow potential targeting to vascular injury sites.[192–194] Affinity-based interaction between avidin and biotin is another strategy that has been extensively studied for decorating nanoparticle surface in vascular targeting. Avidin (and Streptavidin), a glycosylated positively charged protein with high affinity toward biotin (dissociation constant K_d of 10^{-15} M),[195,196] has been utilized to engineer ligand-decorated nanoparticles for drug delivery by incubating avidin-modified particles with biotinylated ligands, or vice versa. Using this approach, RBCs have been decorated with fibrinolytic molecules (e.g., tPA), and various nanoparticle systems have been decorated with antibodies targeted to various cell adhesion molecules (CAMs) in vascular disease.[197] Contrary to such noncovalent techniques, covalent techniques for bioconjugation involve specific chemical reactions between ligands to appropriate reactive groups on the nanoparticles. Common bioconjugation reactions in this aspect are amide linkages (reaction between amine and carboxyl motifs), hydrazine linkages (reaction between hydrazide and aldehyde motifs), sulfhydryl-mediated linkages (reaction between sulfhydryl group and maleimide, sulfone, acetamide, or pyridyl groups), and alkyne-azide–based cycloaddition (“click”) reactions.[198] Other unique bioconjugation techniques involve enzyme-catalyzed reactions, for example, Sortase A-catalyzed reaction with motifs bearing the peptide sequence LPETG[199] and transglutaminase-catalyzed cross-linking of peptide motifs bearing lysine and glutamine residues.[200] The noncovalent or covalent strategies can be used to conjugate ligands on preformed particles, or by pre-reacting to constituent macromolecules first followed by assembly of such molecules into nano- and microparticles.

Utilizing the various surface-modification techniques described earlier, several nanoparticle constructs have been described for vascular disease-specific delivery of therapeutics and imaging agents. For example, in one approach echogenic liposomes were surface-decorated with antibodies specific to fibrinogen, fibrin, and intercellular adhesion molecule-1 (ICAM-1), to permit ultrasound-induced cavitation for thrombolytic agent delivery (sonothrombolysis).[201–203] In a similar approach, lipid-shell based gas-filled microbubbles were surface-decorated with scFv directed at platelet αIIbβ3 to enable clot-specific targeting and ultrasound-based imaging, and image-guided assessment of thrombolysis after urokinase administration.[204] Liposomes have also been surface-modified with antibodies directed to LDL receptors LOX-1 for atherosclerotic lesion-targeted delivery of contrast agents in molecular imaging.[205] In another liposomal technology, named LipoCardium, targeted delivery of anti-inflammatory prostaglandins to atherosclerotic sites was achieved using liposomes surface decorated with antibodies specific for VCAM-1.[206] Besides decoration with antibodies, scFv fragments have also been utilized for active targeting of other nanoparticles to vascular disease sites. For example, elastin-like protein (ELP)-based micelles were surface decorated with platelet αIIbβ3-specific scFv and anticoagulant effector molecule TM using Sortase A-catalyzed bioconjugation, and the resultant scFv/TM-ELP micelles were capable of targeting platelet-rich thrombi in vivo to reduce thrombus growth via TM-mediated activation of protein C pathway of anticoagulation (FVa and FVIIIa inhibition).[207] The Sortase A-catalyzed conjugation of platelet αIIbβ3-specific scFv was also reported for surface-decoration of ultra-small iron oxide nanoparticles for contrast-enhanced MRI of carotid artery thrombosis in mice.[208] Similar scFv was also used to conjugate copper (^{64}Cu) chelating cage amine systems for effective PET imaging of platelet-rich thrombi in vivo.[209]

Besides antibodies and antibody fragments, peptide ligands have also been used for surface-modification of drug delivery particles. For example, small peptides that can bind to VWF, collagen, integrin αIIbβ3, and P-selectin on stimulated platelets have been used to surface-modify liposomes, to allow targeting to sites of endothelial injury, endothelial denudation, platelet activation, and thrombosis in vascular pathologies.[210–220] Therefore, these liposomal systems can be potentially utilized for spatio-temporally targeted drug delivery to sites of vascular disease and dysregulation. Besides liposomes, other lipidic and polymeric micelles have also been ligand-modified for vascularly targeted drug delivery. For example, micelles were surface-decorated with antibodies toward macrophage scavenger receptors (MSR) and loaded with Gd chelates or fluorescent probes to selectively target atherosclerotic lesions in ApoE −/− mice, for molecular imaging of the disease.[221,222] In another approach, Gd-loaded PEG-lipid micelles were surface-decorated with antibodies directed at oxidized LDL lipoproteins in atherosclerotic plaques, for targeted molecular imaging of the plaque.[223] Similar Gd-loaded micelles surface-decorated with anti-CD36 antibodies were able to target lesion-associated macrophages in plaques.[224] In another report, lipid-polymer hybrid particles were decorated with a peptide sequence KZWXLPX (Z: hydrophobic amino acid, X: any amino acid) and these constructs termed “nanoburrs” were able to actively bind exposed collagen IV at arterial injury sites for delivery of antiproliferative drugs to modulate SMC activity.[225,226] In yet another approach, a 9-amino acid sequence CGNKRTRGC (Lyp-1) was used to modify the surface of micelles to bind

p32 receptors in atherosclerotic plaques, and CREKA peptide was similarly used to bind fibrin–fibronectin clots for enhanced targeting of atherosclerotic plaques in vivo.[227,228]

Antibody and peptide ligand decorations on solid polymeric particles as well on polymer capsules have also been studied for targeted therapeutic delivery to vascular pathologies. For example, anti-ICAM-1 antibodies were conjugated to PLGA nanoparticles for specific targeting of inflamed ECs in vascular disease.[229,230] Anti-VCAM-1 antibodies were similarly used to modify the surface of microparticles and nanoparticles made of poly(sebacic acid)-co-PEG (PSAPEG) to enable atherosclerotic lesion-targeted delivery in ApoE −/− mice.[231] Instead of antibodies, peptide ligands have also used for vascular targeting of nanoparticles. For example, surface decoration with a fibrinogen-derived peptide sequence NNQKIVNLKEKVAQLEA was utilized to target polystyrene particles to ICAM-1 in mouse models.[232] Another ICAM-1-specific peptide sequence ITDGEATDSG (also known as LABL) has been reported for surface decoration of DNA complex nanoparticles and PLGA nanoparticles to demonstrate in vitro gene delivery to ICAM-1 expressing cells.[233,234] MRI contrast-enhancing nanoparticles, such as iron oxide particles, monocrystalline magnetic particles, and Gd-containing systems, have been described that are surface-decorated with VCAM-binding peptide sequences like cyclic VHSPNKK, VHPKQHR, and cyclic NNSKSHT for molecular imaging of atherosclerotic lesions.[235–237] In another approach, poly-L-lysine-co-poly-lactic acid copolymer (PLL-PLA) nanoparticles were surface-modified with RGD peptides to achieve co-localization with active platelets (via binding of platelet αIIbβ3) at the site of traumatic vascular injury and deliver anti-inflammatory drugs.[238,239] Surface decoration with RGD or AGD peptides for vascular targeting has been reported also using RBCs, latex beads, or albumin particles as the drug carrier vehicle.[240–245] HDL nanoparticles that are already amenable to natural uptake into atherosclerotic lesions due to lipoprotein transports have been further decorated with RGD ligands for active targeting to inflamed vascular sites.[246] In the area of polymer capsules, recent work has described calcium carbonate ($CaCO_3$)-templated submicron diameter polymer capsule structures made of poly(2-diisopropylaminoethyl methacrylate) (PDPA) and PEG, and stabilized with poly L-histidine (HIS), and these PDPA-HIS capsules were further surface-decorated with collagen IV targeting peptide TLTYTWS using “click” chemistry to enable targeting to exposed atherosclerotic plaque.[247] Vascular targeting ligands have also been used for decorating ultrasound-sensitive micro- and nanobubbles to direct them toward cell-surface receptor moieties like CAMs (e.g., ICAM and VCAM) and integrins (e.g., αVβ3), to achieve targeted therapy and molecular imaging of vascular inflammation and atherosclerosis.[248–250] In related work, similar bubbles with shells bearing maleimido-4(p-phenylbutyrate)-phospholipid were surface-conjugated using therapeutic antibody Abciximab (ReoPro by Eli Lilly) to target platelet integrin αIIbβ3 for enhanced molecular imaging of platelet-rich thrombi.[251] Other nanoparticles like dendrimers have also been investigated for active targeting to vascular disease, for example, by decorating them with cyclic RGD peptides for targeting endothelial integrin αVβ3 and also loading with radioactive Bromine (^{76}Br) for positron emission tomography (PET)-based targeted molecular imaging of ischemic tissue in mice.[252] Several other ligands relevant to disease-specific biomarkers and cellular phenotypes have been utilized for active targeting of dendrimers to vascular pathologies.[253–255]

Among inorganic nanostructures for vascularly targeted delivery, cross-linked dextran-coated iron oxide (CLIO) nanoparticles have been surface-modified with peptides and ligands that can target CAMs and clot-associated fibrin to enable targeting to inflammatory, angiogenic, and thrombotic regions in atherosclerosis for contrast-enhanced MR imaging.[161] Such particles have also been surface-decorated using ligands specific for VCAM-1, P-selectin, and platelet integrin αIIbβ3, for contrast-enhanced targeted MRI of atherosclerosis and thrombosis.[256] Using another approach, SPIOs were surface-modified by Annexin V to enable specific interaction with anionic lipids (e.g., phosphatidylserine) on outer membrane leaflets of apoptotic cells and thus achieve selective targeting of such particles to "foam cells" in atheromatous plaque in rabbits for T2-weighted MRI.[257] QDs have also been decorated with anti-CAM antibodies directed to VCAM, ICAM, PECAM, etc. for in vivo optical imaging of atherosclerotic lesions.[258,259] Additional approaches for surface engineering of QDs for targeted optical imaging of vascular disease-specific markers comprise targeting to oxidized LDL receptor CD36, phosphatidylserine-exposing cells, and plaque-relevant MMPs.[260,261] As an alternative to direct targeting of QDs to the vascular disease site markers, they have also been used as "payloads" within other nanoparticle systems to achieve multimodal imaging of vascular disease sites. For example, QDs were loaded within paramagnetic micelles targeted to macrophagic scavenger receptors and also within HDL nanoparticles, for combined optical and MR imaging of atherosclerosis.[184,262] In another approach, gold nanoparticles were conjugated to QDs via a proteolytically degradable peptide sequence so that in the "conjugated" state the QD luminescence was quenched, whereas the luminescence was significantly enhanced once the conjugate was enzymatically cleaved.[263] Such unique strategies can potentially allow probing of proteolytic enzyme activities that are typical of atherosclerotic lesions.

Current State-of-the-Art in Vascular Nanomedicine Systems and Future Opportunities

As evident from the technologies and applications described in the previous sections, the field of "nanotechnology and nanomedicine" has opened up unique ways to achieve disease site-directed delivery of various therapeutic and imaging agents as singular or combination payloads in vascular pathologies (Fig. 4). Such localized delivery may possibly overcome issues of bioavailability and narrow therapeutic window for many therapeutic molecules by enhancing disease-localized concentrations with lower dose overall, thereby maximizing treatment effects in target tissue while avoiding systemic off-target side-effects. Concepts around local delivery in the cardiovascular domain arose decades ago through successful utilization of perivascular delivery systems in animal models.[264,265] For such applications, polymeric matrix systems loaded with heparin were placed around rat carotid arteries during balloon angioplasty, achieving sustained local release of drug for specific time periods and thereby reduce postprocedural arterial restenosis and occlusion. Similar polymeric matrices that incorporated ECs to provide a source of endogenous vasoregulatory molecules were reportedly capable of reducing neointimal hyperplasia in rat and pig models of vascular injury.[266,267] During the last three decades, other "site-localized delivery" systems have been engineered for vascular therapies, including intraluminal, intramural, and stent-based devices, that have demonstrated high efficiency in rendering target site-localized therapeutic

effect while reducing nonspecific distribution and off-target side-effects associated with systemic delivery.[268] Nanotechnology has enabled further refinement of such devices. As an example, silver nanoparticles have been incorporated in implantable and intravascular devices to prevent bacterial adhesion, growth, and biofilm development.[269] Catheters as well as stents have been modified with carbon nanotubes for mechanical enhancement and drug delivery functions.[270,271] Furthermore, stent designs have been refined with nanoscale fabrication and texturing techniques to allow enhanced drug loading, favorable biointeractions with tissues, and programmed drug release. Stents have also been modified with coatings containing drug-loaded nanoparticles for sustained drug delivery following endovascular procedures.[272–274] Nanomaterials are also being explored in fabrication of artificial vascular grafts and conduits to impart thromboresistant and infection-resistant properties.[275,276]

In the context of nanoparticle and microparticle systems for vascular drug delivery, recent studies have emphasized the emerging role of “biophysical” parameters such as shape, size, and elasticity in refining the design and enhancing the intravascular performance of the particles. For example, several recent computational and experimental studies have established that particle geometry plays a significant role in their distribution in the vascular compartment under the hemodynamic flow environment. These evaluations have identified that size of particles play important roles in their margination capabilities through the RBC volume as well as in their interaction with the target surface at the vascular wall. Computational and experimental studies have indicated that micro-scale particles have a higher margination probability through the flowing RBC volume compared with nanoscale particles.[277–281] Related studies have also indicated that particles of nonspherical geometry (e.g., ellipsoids, rods, and discs) have a higher probability of margination from flowing blood RBC volume toward the vascular wall and higher surface area of interaction at the wall that can benefit stable binding and retention for achieving enhanced wall-localized drug delivery under hemodynamic flow environment.[282–291] Additionally, particle stiffness (i.e., elasticity) has been shown to affect their margination and adhesion behavior in flow.[281,292–294] In fact, an optimal example of this is seen in naturewherebi-concavelargesize (~8 μm diameter) highly flexible RBCs tend to congregate toward the center of the flow volume while biconvex smaller (~2 μm diameter) stiffer platelets tend to marginate more toward the blood vessel wall.[295–299] Building on these findings, in recent years, unique designs and manufacturing approaches have focused on development of nano- and microparticles with tailored geometries and stiffness to customize their transport, interaction, circulation residence time, and targeting properties within the vascular compartment.[300–310] Such biophysical parameters can potentially be combined with ligand-based active targeting strategies on particle platforms to construct drug delivery systems possessing enhanced capabilities of targeting, anchorage, and site-specific delivery. Furthermore, in the context of active targeting of drug delivery particles to vascular disease sites, several studies have demonstrated the benefits of “heteromultivalent ligand modification” of the particles where ligand motifs directed at multiple types of targets are codecorated on the particle surface to enhance selectivity and anchorage strength under hemodynamic flow environment.[213,219,306,311] Such findings continue to present exciting opportunities to further explore the interplay between particle biophysical and biochemical factors, blood

flow environment, and vascular topology to fine tune drug delivery particle design toward specific vascular nanomedicine applications.[312,313]

While the majority of particulate delivery systems achieve release of encapsulated payload via diffusion and degradation/dissolution-mediated mechanisms,[314,315] robust research has also been focused on incorporating unique "triggered release" mechanisms in various drug delivery systems. In such designs, drug release is achieved by chemical and/or physical triggers of particle destabilization in the disease-specific environment. Such triggering can be from internal stimuli such as pH, enzyme action, temperature, and shear forces or external stimuli such as focused ultrasound, NIR irradiation, and magnetic impulses.[135,136,201,202,219,316–328] These unique "triggered release" approaches continue to add exciting refinements and attributes in the area of vascular nanomedicine, which can be leveraged to enhance delivery efficiency and release kinetics and therapeutic effects site selectively in various vascular pathologies.

Conclusion

Nanotechnology provides an efficient way to achieve improved delivery of drug molecules and imaging agents at sites of vascular disease, via packaging within micro- and nanoparticle vehicles that can be administered in circulation and can traverse through various transport and interaction barriers in blood flow to passively accumulate or actively anchor at target vascular sites. The success of these approaches depends on optimization of a variety of factors, including effective encapsulation of the payload within the particles, minimization of pre-target release of the payload, maintenance of sufficient circulation time periods to allow interaction with target cells and tissues, efficient margination (if needed) through flowing blood volume toward vascular wall, passive accumulation or active binding at the target site under hemodynamic conditions, efficient payload release via diffusion or site-specific triggers, and safe elimination of the vehicle (or its components) via metabolism, biodegradation, and excretion. As evident from the comprehensive descriptions in previous sections, meeting all these criteria optimally is quite challenging. At the same time, the ability to refine biophysical and biochemical design parameters as well as appropriate animal models and new and improved analysis techniques have allowed significant advancement toward optimization of vascular nanomedicine systems. Such advancements may allow design of vascular nanomedicine to customize toward specific disease treatment requirements, instead of using universal design criteria. For efficient clinical translation, vascular nanomedicine research should also focus on robust analysis of cost–benefit ratios, quality control, and regulatory hurdles for these technologies.

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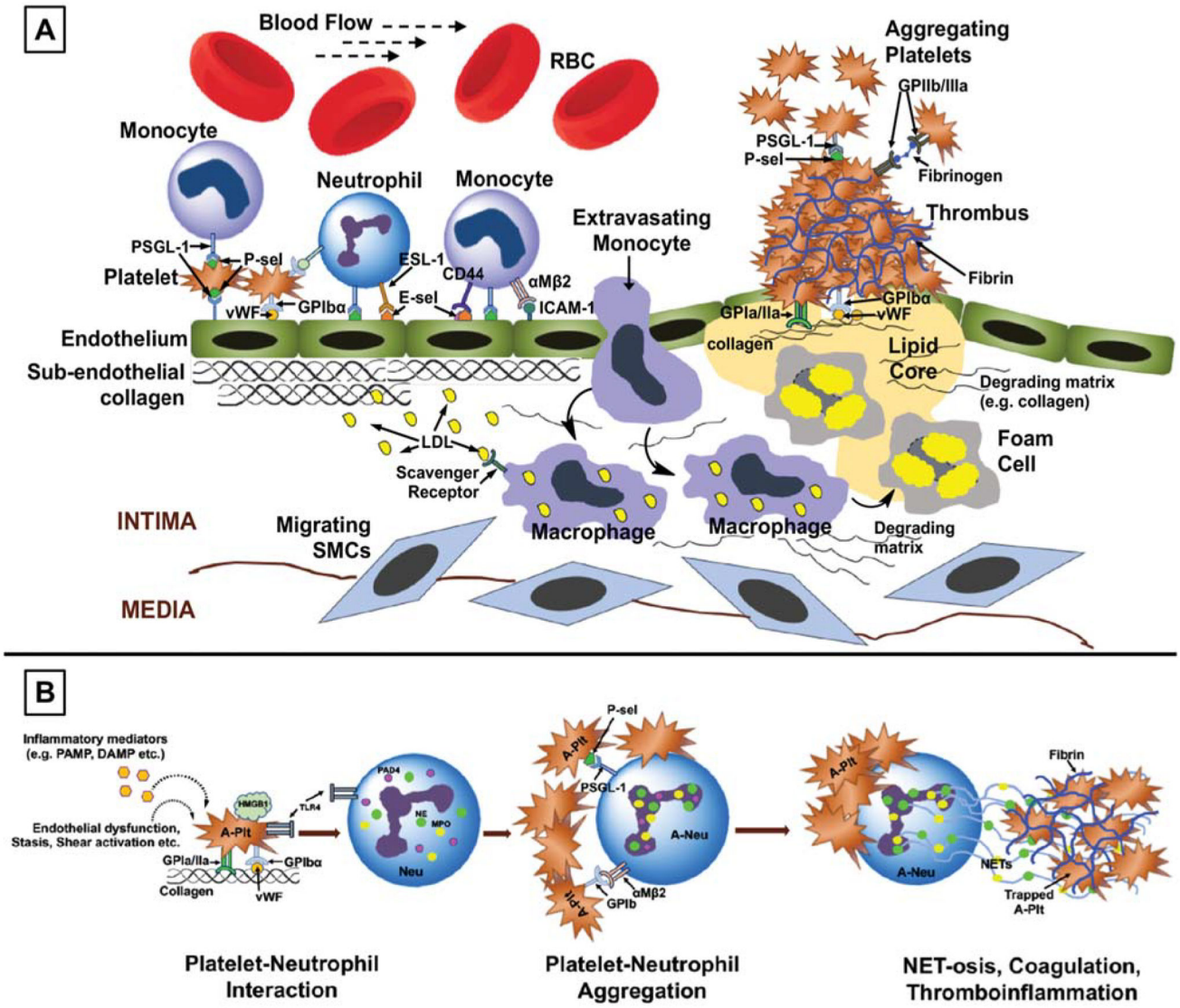

Fig. 1.

Schematic diagrams for cellular and molecular components in (**A**) atherosclerosis and atherothrombosis and (**B**) thromboinflammation (e.g., deep vein thrombosis, sepsis, and lung injury) pathologies in vascular diseases. RBC, red blood cell; P-sel, P-selectin; PSGL-1, P-selectin glycoprotein ligand 1; E-sel, E-selectin; vWF, von Willebrand factor; ICAM, intercellular adhesion molecule; LDL, low-density lipoprotein; SMC, smooth muscle cell; PAMP, pathogen-associated molecular patterns; DAMP, damage-associated molecular patterns; HMGB-1, high mobility group box 1 protein; A-plt, activated platelet; TLR 4, toll-like receptor 4; PAD 4, peptidylarginine deiminase 4; NE, neutrophil elastase; MPO, myeloperoxidase; Neu, neutrophil; NET, neutrophil extracellular trap.

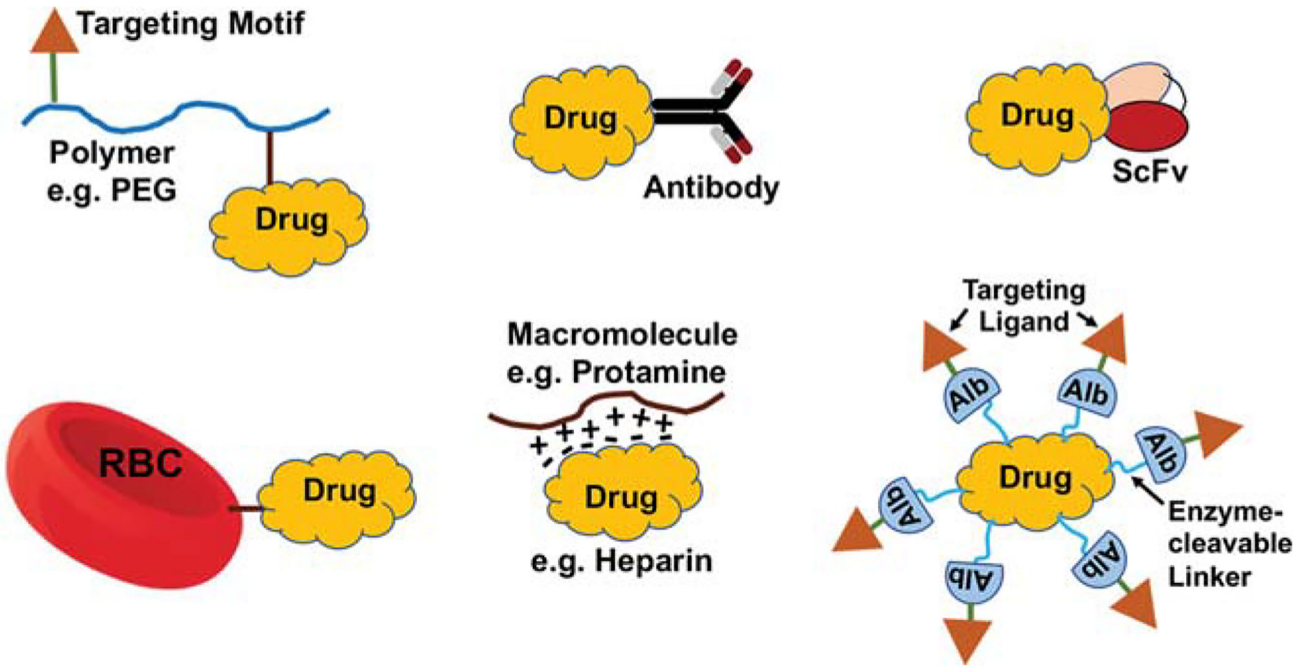

Fig. 2.

Schematic representations of various design approaches involving direct modification of therapeutic molecules in the development of vascular nanomedicine. PEG, polyethylene glycol; Alb, albumin.

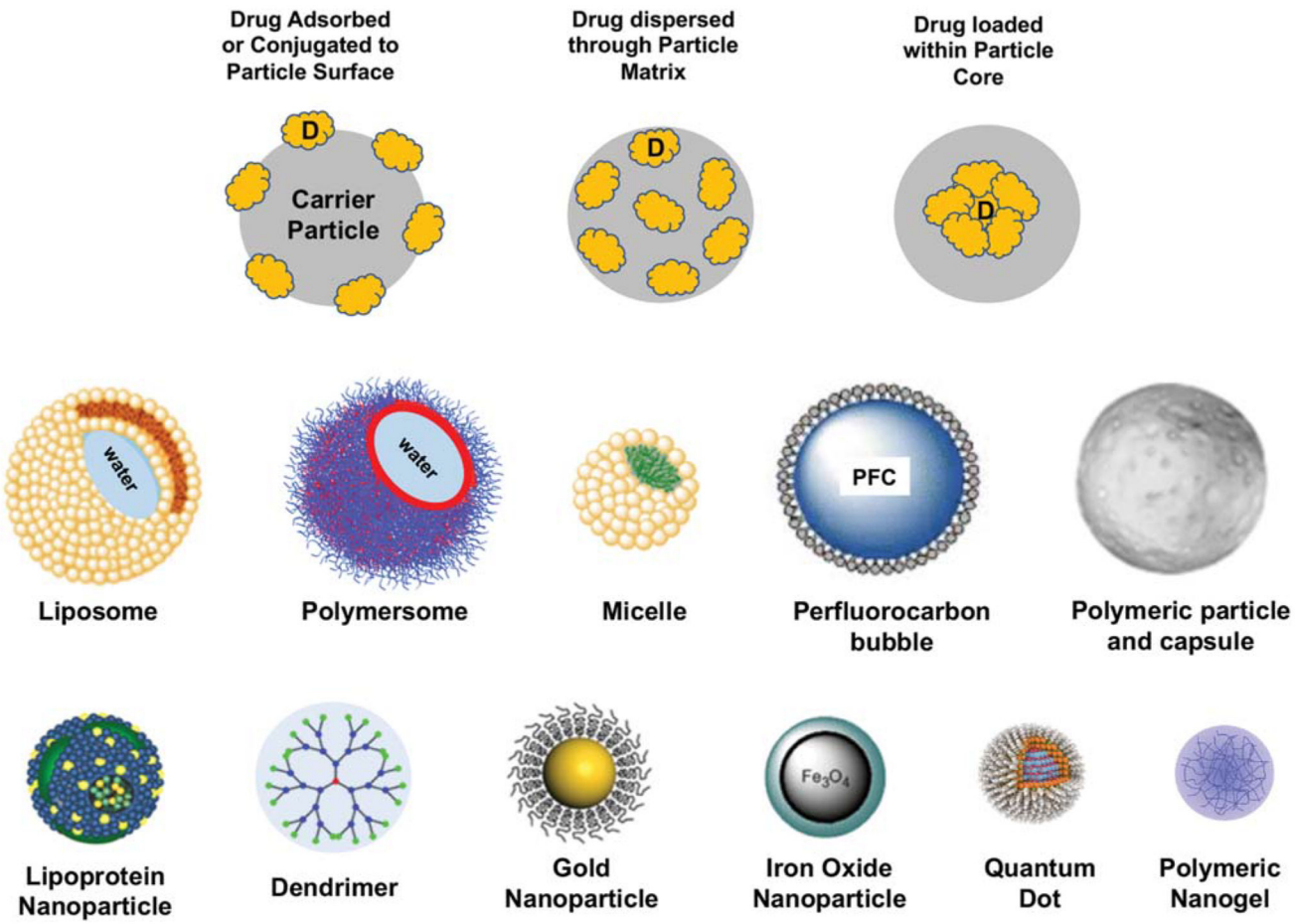

Fig. 3.

Schematic representations of various design approaches involving particle-based loading of drug (or imaging probes) in the development of vascular nanomedicine along with representative designs of characteristic nanoparticle systems used as particulate vehicles.

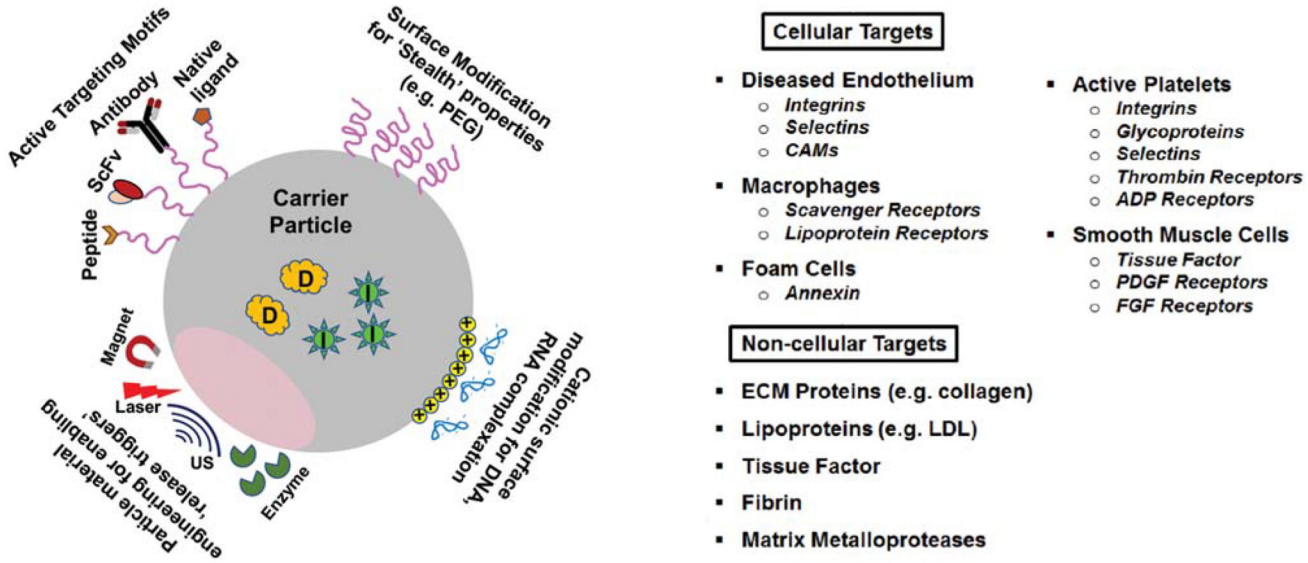

Fig. 4.

Schematic representations of various design approaches in engineering of nanoparticles for enabling surface “stealth” properties, active targeting to vascular disease-relevant proteins and cells, loading of charged payload (e.g., DNA, RNA) and stimuli-triggered release mechanisms, along with list of cellular and noncellular targets that such engineered nanoparticles have been directed to. US, ultrasound; ADP, adenosine diphosphate; CAM, cell adhesion molecule; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor.

Table 1

Alphabetical list of acronyms/abbreviations and corresponding full name of molecules, entities, and terminologies used throughout the article

Abbreviation/Acronym	Corresponding full name
AGD	Alanine-glycine-aspartic acid
ALI	Acute lung injury
CAM	Cell adhesion molecule
CCR	CC-chemokine receptor
CGNKRTRGC	Cysteine-cysteine-asparagine-lysine-arginine-threonine-arginine-glycine-cysteine (Lyp-1)
CLIO	Cross-linked iron oxide
CQQHHLGGAKQAGDV	Cysteine-glutamine-glutamine histidi ne-histidine-leucine-glycine-glycine-alanine-lysine-glutamine-alanine-glycine-aspartic acid-valine
CREKA	Cysteine-arginine-glutamic acid-lysine-alanine
DES	Drug-eluting stent
DNA	Deoxyribonucleic acid
DVT	Deep vein thrombosis
EC	Endothelial cell
ECM	Extracellular matrix
ELISA	Enzyme-linked immunosorbent assay
$FeCl_3$	Ferric chloride
Fg	Fibrinogen
Gd	Gadolinium
GP	Glycoprotein
GFPRGFPAGGC	Glycine-phenylalanine-proline-argi-nine-glycine-phenylalanine-proline-alanine-glycine-glycine-cysteine
HDL	High-density lipoprotein
HIS	Poly L-histidine
ICAM	Intracellular cell adhesion molecule
IFN	Interferon
IL	Interleukin
ITDGEATDSG	Isoleucine-threonine-aspartic acid-glycine-glutamic acid-alanine-threonine-aspartic acid-serine-glycine
K_d	Dissociation constant
KZWXLPX	Lysine-hydrophobic amino-acid-tryptophan-any amino acid-leucine-proline-any amino acid
LDL	Low-density lipoprotein
LMWH	Low-molecular-weight heparin
MCP	Monocyte chemoattractant protein
MION	Monocrystalline iron oxide nanoparticles
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
MSR	Macrophage scavenger receptor
NET	Neutrophil extracellular traps

Abbreviation/Acronym	Corresponding full name
NIR	Near infrared
NK	Nattokinase
NNQKIVNLKEKVAQLEA	Asparagine-asparagine-glutamine-lysine-isoleucine-valine-asparagine-leucine-lysine-glutamic acid-lysine-valine-alanine-glutamine-leucine-glutamic acid-alanine
NNSKSHT	Arginine-arginine-serine-lysine-serine-histidine-threonine
NO	Nitric oxide
NP	Nanoparticle
PAD	Peptidyl arginine deaminase
PDGF	Platelet-derived growth factor
PDPA	Poly(2-diisopropylaminoethyl methacrylate
PE	Pulmonary embolism
PECAM	Platelet-endothelial cell adhesion molecule
PEG	Polyethylene glycol
PET	Positron emission tomography
PFC	Perfluorocarbon
PGA	Polyglutamic acid
PLGA	Poly-lactic-*co*-glycolic acid
PLGD	Polyglycerol dendrimer
PLL	Poly(L-lysine)
PLL-PLA	Poly-L-lysine-co-poly-lactic acid
PS	Phosphatidyl serine
PSAPEG	Poly(sebacic acid)-co-PEG
PSGL	P-selectin glycoprotein ligand
PVA	Polyvinyl alcohol
QD	Quantum dot
RANTES	Regulated upon activation normal T cell expressed and secreted
RBC	Red blood cell
RGD	Arginine-glycine-aspartic acid
RNA	Ribonucleic acid
SAK	Staphylokinase
scFv	Single-chain variable fragment
scuPA	Single-chain urokinase-type plasminogen activator
SK	Streptokinase
SMC	Smooth muscle cells
SPIO	Superparamagnetic iron oxide
TGF	Transforming growth factor
TLTYTWS	Threonine-leucine-threonine-tyrosine-threonine-tryptophan-serine
TM	Thrombomodulin
tPA	Tissue plasminogen activator
TFPI	Tissue factor pathway inhibitor

Abbreviation/Acronym	Corresponding full name
UK	Urokinase
uPA	Urokinase-type plasminogen activator
VCAM	Vascular cell adhesion molecule
VHPKQHR	Valine-histidine-proline-lysine-glutamine-histidine-arginine
VHSPNKK	Valine-histidine-serine-proline-arginine-arginine-lysine-lysine
vWF	von Willebrand factor
WBC	White blood cell