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Non-affinity factors modulating vascular targeting of nano- and microcarriers☆

Jacob W. Myerson [a], Aaron C. Anselmo [b], Yaling Liu [c], Samir Mitragotri [b], David M. Eckmann [a], Vladimir R. Muzykantov [a,*]

[a] University of Pennsylvani, United States
[b] University of California, Santa Barbara, United States
[c] Lehigh University, United States

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ABSTRACT

Particles capable of homing and adhering to specific vascular biomarkers have potential as fundamental tools in drug delivery for mediation of a wide variety of pathologies, including inflammation, thrombosis, and pulmonary disorders. The presentation of affinity ligands on the surface of a particle provides a means of targeting the particle to sites of therapeutic interest, but a host of other factors come into play in determining the targeting capacity of the particle. This review presents a summary of several key considerations in nano- and microparticle design that modulate targeted delivery without directly altering epitope-specific affinity. Namely, we describe the effect of factors in definition of the base carrier (including shape, size, and flexibility) on the capacity of carriers to access, adhere to, and integrate in target biological milieus. Furthermore, we present a summary of fundamental dynamics of carrier behavior in circulation, taking into account interactions with cells in circulation and the role of hemodynamics in mediating the direction of carriers to target sites. Finally, we note non-affinity aspects to uptake and intracellular trafficking of carriers in target cells. In total, recent findings presented here may offer an opportunity to capitalize on mitigating factors in the behavior of ligand-targeted carriers in order to optimize targeting.

Contents

Abbreviations: RES, reticulo-endothelial system; PEG, poly(ethylene) glycol; RBC, red blood cell; ICAM, intercellular adhesion molecule; NIPAm, n-isopropylacrylamide; AFM, atomic force microscopy; GPIIb/IIIa, glycoprotein IIb/IIIa, integrin $\alpha_{IIb}\beta_3$; PLGA, poly(lactic-co-glycolic acid); vWF, von Willebrand Factor; GPIbα, glycoprotein Ib, alpha subunit; RGD, arginylglycylaspartic acid; IgG, Immunoglobulin G; PECAM, platelet endothelial cell adhesion molecule; VCAM-1, vascular cell adhesion molecule 1; PAAm, polyallylamine; PAH, poly(allylamine hydrochloride); BSA, bovine serum albumin.

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* Corresponding author at: Department of Pharmacology, University of Pennsylvania, 10-125 Translational Research Center, 3400 Civic Center Blvd, Philadelphia, PA 19104-5158.
E-mail address: muzykant@mail.med.upenn.edu (V.R. Muzykantov).

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1. Introduction

The vascular system is both the route to and the intended site for therapeutic intervention via drug delivery in many diseases. Blood components and endothelial cells lining the luminal surface of blood vessels represent preferred targets for pharmacotherapy of ischemia, inflammation, bleeding and thrombotic disorders, stroke, pulmonary diseases, and neurological diseases, among others. Devising carriers that optimize delivery of drugs in the vascular system may improve management of these prevalent conditions with high morbidity and mortality [1–6].

Carriers designed for this goal (including liposomes, polymeric and non-polymeric particles, protein conjugates and dendrimers, etc.) may accumulate at the desired site either relatively non-specifically (e.g., by mechanical or charge-mediated retention) or via specific interaction provided by ligands with affinity to molecules typical to or enriched in target tissues. Ligand presentation allows these carriers to specifically bind to endothelial surface determinants or, for instance, components of blood clots (e.g., platelets and fibrin) and blood cells. The latter – red blood cells, white blood cells, platelets – may serve as either target or a secondary carrier for drug delivery. "Active targeting" using ligands (e.g., antibodies and their derivatives, peptides, aptamers, etc.,) in theory offers more controlled delivery. It also enables guided sub-cellular addressing of drugs via anchoring to specific cellular determinants providing internalization via appropriate pathways [7–11].

However, many characteristics of a drug carrier and its microenvironment in the vascular system modulate its circulation and distribution and its interactions with target and non-target counterparts. As a result, these factors must be taken into account in the course of design and application of a targeted drug delivery system [12–15]. The goal of this review is to briefly analyze how factors pertaining to vascular physiology and parameters of carrier design other than affinity modulate vascular targeting and drug delivery with nanocarriers and microcarriers.

2. Modulation of pharmacokinetics and targeting by carrier geometry

Two parameters defining carrier geometry, size and shape, profoundly modulate every aspect of behavior in the body, including access to delivery routes, clearance route and rate, specific and non-specific accumulation in target and non-target sites, binding, uptake and intracellular trafficking, and ultimately effects of the drug cargo.

2.1. Carrier geometry and blood clearance

One of the most important and extensively studied parameters modulating carrier behavior in the bloodstream is size. The sizes of typical carrier particles can range from below 10 nm to a few microns. Dendrimers, micelles, gold nanoparticles, and iron oxide nanoparticles often manifest diameters below 50 nm [16,17], while polymeric spheres, liposomes, and nano-shells are hundreds of nanometers in diameter [18,19]. Polymeric, lipid, and silica-based microspheres and microemulsions have diameters up to a few microns [20,21]. Moreover, carrier shape can also vary from spherical (e.g., lipid-based beads) to spheroidal, cylindrical, or discoidal particles [22–24], virus-templated particles [25], and nanopolypods [26] (Fig. 1a).

Generally, intravascular injection is needed for carriers in the size range of 50–300 nm. Smaller particles may access other administration routes (e.g., pulmonary), though the effectiveness of the vascular route is generally unrivaled. After administration, size is a key parameter modulating the pharmacokinetics of carriers in the vasculature. Particles smaller than 10 nm undergo renal filtration [27,28] and extravasation in tissues [29]. Drug carriers bigger than approximately 20 nm are eliminated from circulation predominantly by the reticulo-endothelial system (RES, including liver, spleen and lymph nodes) [30,31].

Ultra-short carbon nanotubes, quantum dots, gold nanoparticles, dendrimers and other smaller particles spread into various organs by passing through tight endothelial junctions (10–20 nm diameter) and can be easily excreted through the glomeruli of the kidneys [29,32]. Larger particles have the advantage of carrying higher payloads when used as targeted vascular carriers.

Overall, for longer circulation after intravascular injection, carriers should escape recognition and sequestration by the RES (including accumulation in bone marrow, red pulp, lymph nodes, and phagocytic cells in the sinusoids of the liver). In order to increase circulating half-life, sub-micron carriers can be coated with excipient polymers (e.g., poly(ethylene) glycol, PEG) [33–35], but size and shape also have an impact on rate and mechanism of clearance.

Deposition of spherical silica beads in non-RES organs was shown to reduce monotonically with diameter between 700 nm and 3 μm [36], while 3–4 μm plastic microspheres tend to accumulate permanently in the spleen [37]. Moreover, while engulfment by RES phagocytic cells happens for particles as big as 4–5 μm [38,39], generally, particles larger than ~500 nm are prone to mechanical entrapment in capillaries [40]. For instance, polystyrene particles larger than 5–7 μm mainly trap in the alveolar capillaries of the lungs [40], while particles bigger than 10 μm are retained in the liver, RES and lungs [41].

Generally, rigid spherical particles between 100 nm and 200 nm in diameter manifest longer circulation times because they are large enough to avoid sequestration in the liver and small enough to escape splenic filtration. For non-spherical particles, at least one dimension should be kept >100 nm to avoid accumulation in the liver. To avoid entrapment in the sinusoids of the spleen, at least two dimensions must be maintained <200 nm [42]. For long-circulating non-spherical particles, the effects of particle shape and size are thus closely related, where the geometry of non-spherical or flexible particles can significantly prolong the circulation time. In rodents, long worm-shaped PEG-polyethylethylene filomicelles manifest prolonged circulation time, avoid macrophage internalization, and favor accumulation in tumors [43,44] (Fig. 1b,c), and disk-shaped polystyrene particles have lengthened circulation half-lives relative to analogous spherical particles [45], with work comparing silica spheres and disks finding lesser accumulation in the liver for discoidal particles [36]. Similarly for hydrogel disks, Merkel et al. demonstrated prolonged circulation for particles with diameter comparable to RBCs, as compared to smaller particles of identical composition [46]. As discussed later in this review, carrier mechanical flexibility can generally confound trends relating clearance time to particle size, where softer particles generally exhibit longer circulation times related to altered hemodynamic behavior [43,47] and interactions with phagocytic cells [48,49].