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Improving Nanoparticle Delivery in Cancer Nanomedicine: Insights Based on Biodistribution Research

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Abstract

Introduction: Cancer is one of the leading causes of death worldwide, and while chemotherapy and radiotherapy remain primary treatments, they are limited by poor tumour specificity, systemic toxicity and drug resistance. Nanoparticle (NP)-based drug delivery offers a promising alternative, with improved solubility, controlled release, and targeted delivery, to enhance efficacy and minimise adverse effects. However, delivery remains inefficient, often resulting in off-target accumulation, immune clearance, renal filtration, and poor tumour penetration. This review explores how biological and physiological barriers limit NP-based delivery and evaluates strategies such as biomimetic cloaking, synthetic surface modifications, and tumour-responsive targeting to improve therapeutic accumulation and efficacy.

Methods: This review looked at strategies to improve NP delivery in cancer by analysing their biodistribution and interaction with biological surfaces and barrier. Peer-reviewed studies were identified through PubMed and Google Scholar using keywords such as "nanoparticle clearance", "tumour penetration", "immune evasion", "biomimetic cloaking", and "PEGylation". Articles published between 1990 and 2025 were included if they investigated NP delivery barriers, biodistribution, or design strategies that are specific to cancer. Review articles that provided contextual backgrounds were also considered.

Results: Biomimetic cloaking of nanoparticles improves NP circulation and tumour accumulation. Red blood cell membrane-coated NPs evade immune recognition and reduce opsonisation by displaying self-marker proteins that prolong circulation. Platelet membrane cloaking can improve tumour targeting by taking advantage of platelet interactions with damaged vasculature and circulating tumour cells. PEGylation forms a hydrophilic barrier, preventing opsonisation and clearance by macrophages. Zwitterionic coatings neutralise surface charge to reduce renal filtration, while NP size optimisation (50-150 nm) helps balance circulation time and tumour permeability. However, tumour penetration remains a challenge, particularly in solid tumours with high interstitial pressure.

Implications: These findings show the importance of integrated NP systems that combine immune evasion, tumour targeting, and local release mechanisms. These innovations align with the shift towards personalised and biomimetic therapies, improving targeted cancer treatments. Continued research is needed to bridge the gap between preclinical findings and clinical applications, improving cancer treatment outcomes. Future work should focus on scalable, low-immunogenic solutions to the systemic and tumour-specific barriers to unlock the full potential of cancer nanomedicine.

Keywords: nanoparticle biodistribution; cancer nanomedicine; immune clearance; protein corona; tumour microenvironment; targeted drug delivery

Introduction

Cancer is a highly diverse and globally prevalent disease affecting more than 10 million people each year and responsible for 6 million deaths annually, making it the leading cause of mortality worldwide [1]. Despite advances in diagnostics and technology, cancer treatment still faces many challenges, particularly in drug delivery. Drugs often struggle to reach the tumour, are quickly cleared by the immune system or sequestered in organs, and in many cases, tumours develop resistance [2]. Most anticancer agents are administered systemically; however, only a small fraction reaches the tumour, often less than 1% with nanoparticle-based formulations [3]. This inefficiency not only limits therapeutic efficacy but also increases damage to healthy tissues due to high toxicity, emphasising the need for improved treatment methods.

Nanomedicine has been explored in cancer treatment as a promising strategy to overcome these limitations and improve therapeutic outcomes. The application of nanotechnology in medicine, using the ability to design and manipulate materials at the nanoscale, brings transformative benefits to diagnosis, treatment and prevention [4]. This has been seen in nanoparticles for drug delivery, nanosensors for diagnostics and smart

therapeutic devices. In cancer treatment specifically, nanoparticles have been extensively explored because they can be tailored in size, they have modifiable surface charge, and they can be engineered to enable targeted binding or controlled drug release to suit specific therapeutic needs. Nanoparticles allow for controlled drug release using the enhanced permeability and retention (EPR) effect, where leaky tumour vasculature and poor lymphatic drainage allow them to passively accumulate in tumour tissue. This enhances the local drug concentration at the tumour site while reducing systemic toxicity. Nanoparticles can also be manipulated using biomimetic coatings to evade immune detection.

In oncology, many nanoparticle-based therapies have been approved for clinical use. Liposomal doxorubicin (Doxil) and albumin-bound paclitaxel (Abraxane) have shown improved pharmacokinetics and reduced toxicity compared to typical cancer therapeutics, highlighting the benefits of nanomedicine in cancer. However, Abraxane still suffers from poor colloidal stability in circulation, leading to early drug release and biodistribution patterns like free paclitaxel [5]. Some of the challenges remained, opening the idea to focusing more on biological processes, such as immune clearance, protein corona formation, and the complex tumour microenvironment, as opposed to nanoparticle formulation and drug mechanisms when examining nanoparticles and their use in cancer therapy. Focusing on this allows researchers to build a cohesive picture that connects nanoparticle design to the outcome of biodistribution in the clinic. It is essential to understand why nanoparticles fail to reach tumours to translate these ideas into clinical success. This review will explore how current knowledge of nanoparticle biodistribution, including barriers such as immune clearance, protein corona formation, and tumour microenvironment, can serve as the basis for improved design strategies for effective delivery.

Methods

This literature review examined strategies to improve nanoparticle (NP) delivery in cancer by analysing their biodistribution and interactions with biological barriers. Searches were conducted using PubMed, and Google Scholar with keyword combinations such as *"nanoparticle clearance," "tumour penetration," "immune evasion," "biomimetic cloaking,"* and *"PEGylation."* Studies were included if they were peer-reviewed, published between 1990 and 2025, and investigated NP delivery barriers, biodistribution and design strategies for cancer. Some review articles that are not specific to cancer were included for context. Boolean operators were used to refine search queries, and English-language filters were applied to include only peer-reviewed articles accessible for detailed analysis.

Results

Biomimetic Cloaking Enhances Circulation Time and Tumour Accumulation

Bare nanoparticles, especially those lacking 'self' markers or stealth coatings, are rapidly cleared by the mononuclear phagocyte system. This leads to off-target accumulation in the liver and spleen, where they can cause inflammation and systemic toxicity [6]. Red blood cell membranes and platelet membranes have both been explored as cloaking mechanisms that improve nanoparticle delivery to tumours, useful in cancer treatment. Red blood cell membrane coating strategies are useful as they have CD47 on their surface, which inhibits phagocytic activity via its "don't eat me signal" making the nanoparticle immunologically inert [7]. Platelet membrane-cloaked nanoparticle (PNP) surfaces retain CD47 as well as other proteins such as CD55, CD59 and functional surface markers from the platelet membrane. These receptors regulate the complement system and suppress phagocytosis, so nanoparticles can evade immune detection and avoid rapid clearance from the blood [8]. This prolonged circulation is particularly advantageous in cancer nanomedicine, where longer circulation time increases the probability of nanoparticles reaching tumour sites via the enhanced permeability and retention (EPR) effect. PNPs also have functional surface markers such as P-selectin, GPIbα, and GPVI, which are essential for binding to tumour-associated endothelium and exposed collagen in the tumour microenvironment [9]. These findings suggest that biomimetics can help nanoparticles evade immune recognition and exploit natural mechanisms to improve the delivery of drugs to tumours.

Biomimetic coatings have shown broad applicability in both a therapeutic and diagnostic context, emphasising how cancer nanomedicine can be elevated. Indocyanine green (ICG), a near-infrared fluorescent dye commonly used in medical imaging, can be loaded into nanoparticles and has been shown to circulate for long periods and avoid clearance by cloaking themselves in platelet membranes that express CD47, mimicking 'self' signals for stealth targeting [7]. This prolonged circulation allows greater tumour accumulation of near-infrared imaging agents like ICG, which improves contrast and can be used to improve detection sensitivity in cancer. In cancer therapy, platelet membrane-coated nanoparticles loaded with doxorubicin showed enhanced drug retention in vivo and improved antitumour efficacy in murine breast cancer models compared to free drug or bare nanoparticles [9].

However, it is important to note the challenges that come with translating biomimetic coating into the clinic on a large scale. In PNPs, not all membrane proteins contribute equally to tumour targeting. Integrin αIIβ3, despite being one of the most abundant platelet receptors, likely remains in its inactive conformation on PNPs due to the absence of inside-out activation signals, and therefore contributes minimally to adhesion [10]. In contrast, receptors such as

GPIb, GPVI, and P-selectin are sufficient to support efficient adhesion and retention in both in vitro and in vivo models [11]. However, as platelet membranes are biological materials, they introduce significant technical and regulatory challenges, including variability between donors, safety concerns, and limited scalability [12]. These inconsistencies present challenges for standardisation and scalability in translational applications of biomimetic coatings in nanomedicine.

Furthermore, immune recognition remains a concern. Repeated administration of cloaked nanoparticles may trigger the development of anti-membrane antibodies, increase the risk of accelerated clearance and reduce therapeutic efficacy over time [13]. Given these translational barriers, synthetic surface modifications such as PEGylation and zwitterionic coatings have emerged as more controllable and scalable alternatives for improving nanoparticle circulation and pharmacokinetics. These approaches may offer a practical route to overcome the limitations of biomimetic coatings while preserving their stealth functionality. This highlights the growing importance of biological and synthetic cloaking strategies in optimising nanoparticle delivery in cancer nanomedicine.

Surface Modifications Mitigate Immune Clearance but have Immunological Limits

To extend systemic circulation and improve the bioavailability of therapeutic nanoparticles, surface modifications such as PEGylation have been widely adopted in cancer nanomedicine. Polyethene glycol, also known as PEG, forms a hydrated, hydrophilic barrier that reduces serum protein adsorption and inhibits opsonisation, preventing clearance by the mononuclear phagocyte system [14]. This allows nanoparticles to remain in the circulation for longer and increases their likelihood of reaching tumour sites for improved treatment. PEGylation's ability to reduce premature clearance enhances the stability of drugs and promotes more consistent accumulation via the EPR effect. Therefore, it has been shown to improve the pharmacokinetics of a wide range of chemotherapeutic payloads, including doxorubicin and paclitaxel [15]. PEGylation has also been applied to imaging agents, such as blood pool contrast materials, where it improves imaging for cancer detection. In a breast cancer model, a PEGylated bifunctional polymer conjugate carrying both an MRI contrast agent (Gd-DO3A) and a photosensitiser showed prolonged blood circulation and improved tumour accumulation compared to non-PEGylated versions [16]. These pharmacokinetic improvements translated to clearer MRI contrast and better tumour visualisation for image-guided therapy, useful for improving the sensitivity in cancer detection.

Despite its widespread use, research has shown that PEG is not without limitations. Overexposure to PEG can induce the formation of PEG-specific antibodies in humans as the immune system recognises the repeated PEG structure as foreign. This T-cell-independent immune response can cause accelerated blood clearance (ABC). Subsequent doses of PEGylated drugs cause the production of anti-PEG antibodies, which rapidly remove the drugs from circulation, posing challenges for individuals who require repeated dosing or have prior PEG exposure through cosmetics, pharmaceuticals, or food [17]. This immunogenicity reduces circulation time and delivery efficiency, posing a significant barrier for nanoparticle formulations designed for multi-cycle cancer treatment. Alternative synthetic coatings, like zwitterionic coating, have PEG's stealth function while reducing immunogenic risk.

Zwitterionic polymers mimic the neutral charge of natural cell membranes to resist adsorption of proteins and complement activation. They create a hydrophilic surface that outperforms PEG in anti-fouling and maintains longer circulation. Zwitterionic-silica nanoparticles loaded with siRNA and daunorubicin demonstrated reduced serum protein adsorption, prolonged bloodstream retention, and 50% greater tumour cell killing in ovarian cancer models compared to non-zwitterionic controls [18, 19]. These properties make it a promising approach for improving tumour-targeted delivery and diagnostic accuracy in cancer nanomedicine.

Nanoparticle surface modifications can also be designed to respond to tumour-specific triggers like low pH or redox changes. PEG and zwitterionic coatings can be paired with pH- or redox-sensitive linkers that remain inert during circulation but release their payload upon encountering the acidic or oxidative conditions of the tumour microenvironment [14]. This responsiveness of the nanoparticle to the tumour increases delivery precision and reduces off-target toxicity, an essential consideration for cytotoxic cancer drugs.

The interaction between nanoparticle surfaces and blood proteins plays a critical role in shaping biodistribution, primarily through the formation of a protein corona. Surface chemistry determines which proteins adsorb to the nanoparticle, and this influences immune recognition and organ-specific accumulation. Understanding how different nanoparticle coatings influence protein corona composition is important to design nanoparticles that successfully reach and remain at their intended tumour site [20]. Synthetic surface modifications are central to protecting nanoparticles from premature clearance and guiding them toward tumours. PEGylation has been foundational in this space; its immunogenic limitations highlight the need for coatings that can better balance immune evasion, reproducibility, and precision in cancer drug delivery.

Active Targeting and Tumour Penetration Strategies Address Microenvironmental Barriers

After nanoparticles successfully evade immune clearance, many still fail to accumulate efficiently or penetrate deeply into solid tumours. This is largely due to

physiological barriers, including irregular and leaky tumour vasculature and elevated interstitial fluid pressure. Solid tumours also have a dense extracellular matrix (ECM), and this limits nanoparticle extravasation and restricts drug delivery into the poorly perfused tumour cells [21]. Structural barriers in the tumour microenvironment therefore pose significant challenges to passive targeting strategies, which rely on the EPR effect to localise nanoparticles at tumour sites. In contrast, active targeting involves the addition of ligands such as antibodies, peptides or small molecules that bind to receptors overexpressed on tumour or endothelial cells, enabling more precise recognition and uptake by intended targets. This highlights the need for delivery systems that do not just circulate, but actively penetrate and adapt to the tumour microenvironment.

Several strategies can improve transport into tumours. Smaller nanoparticles have been used so that they can pass through the collagen-rich ECM to reach deeper tumour regions [22]. Another example is with pH-sensitive collagenase nanocapsules, which have been shown to degrade ECM collagen and penetrate deeply into 3D tumour-like collagen matrices, demonstrating their potential to enhance nanoparticle diffusion and improve therapeutic coverage in solid tumours [23]. Other approaches aim to modulate tumour vasculature. Anti-VEGF therapy can temporarily normalise blood vessel structure, which improves delivery. However, prolonged VEGF inhibition may stiffen the extracellular matrix, limiting nanoparticle penetration and highlighting the need for combination with ECM-modulating approaches [21, 24].

To overcome both immune and transport barriers, researchers have increasingly turned to biomimetic strategies such as platelet membrane cloaking. Platelet-coated nanoparticles use native adhesion proteins such as GPIbα, GPVI, and P-selectin to selectively bind tumour vasculature while evading immune detection [25]. These interactions help the nanoparticles stick more effectively to tumour blood vessels, cross into the tumour tissue, and stay there for longer. In animal models, platelet-coated nanoparticles built up more in tumours and reached deeper into the tissue compared to non-targeted ones, showing real promise for improving drug delivery in complex tumour environments [9].

The evidence across biomimetic, synthetic, and active targeting strategies highlights that effective nanoparticle delivery in cancer relies on overcoming both systemic and tumour-specific barriers. Cloaking techniques such as PEGylation and platelet membrane coatings have been shown to prolong circulation and reduce immune clearance, improving tumour accumulation [13, 20]. However, accumulation at the tumour site alone is insufficient.

Discussion

Improved tumour accumulation does not necessarily translate to better treatment outcomes, as many nanoparticles still struggle with effective drug release and uptake within tumour cells. These strategies are significantly limited by the tumour microenvironment, where elevated interstitial fluid pressure and dense ECM restrict nanoparticle diffusion into the tumour core [21]. Addressing this requires designs that not only evade immune detection but also penetrate deeply into tumour tissue. Strategies under investigation include engineering smaller nanoparticles [24], enzymatic ECM degradation via pH-sensitive collagenase nanocapsules [23], and temporary vascular normalisation using anti-VEGF therapies [24]. These approaches aim to disrupt the physical barriers that prevent nanoparticle entry, enhancing therapeutic access to poorly perfused tumour cores. PNPs show this by combining immune evasion with active vascular targeting through adhesion proteins such as GPIbα and P-selectin [21, 24]. These nanoparticles demonstrate superior tumour accumulation and deeper tissue penetration in vivo compared to non-targeted systems, supporting them as a preferred method for intratumoural delivery.

Surface chemistry of drug carriers determines their biodistribution in the body. PEGylation forms a hydration shell that reduces opsonisation and prolongs circulation, but its repeated use has revealed limitations, as it can become immunogenic in humans, leading to ABC upon repeated exposure [22]. In contrast, zwitterionic coatings offer similar stealth functionality while resisting complement activation and protein adsorption. Zwitterionic nanocarriers demonstrate prolonged circulation and reduced immunogenicity, supporting their potential as scalable, low-immunogenicity alternatives [18]. Their recombinant polypeptide design supports consistent manufacturing and batch reproducibility, important for translation into the clinic.

Despite these advances, ligand-targeted nanoparticles still face significant hurdles due to inconsistent receptor expression in tumours. There is no single receptor that works across all tumours or even throughout a single tumour. This variability, shaped in part by the complexity of the tumour microenvironment, makes it difficult to rely solely on ligand–receptor interactions for effective targeting. In response, researchers are developing modular nanoparticle systems that can be tailored or adapted to the specific biological features of individual patients and tumours.

Looking ahead, future nanoparticle designers will need to combine immune evasion, tumour targeting and controlled release into a single platform that has all these functions. Coatings that remain inert in the blood but can respond to tumour-specific cues such as acidity, oxidative stress, or protease activity can enable more precise drug release at the tumour site. These stimulus-responsive systems hold promise for minimising side effects while increasing therapeutic precision. While preclinical studies have shown promise, moving these systems into the clinic remains difficult. Platelet membrane coatings raise concerns around donor variability and how to scale production safely, and, PEG-based nanoparticles, although

widely used, can trigger immune reactions in people previously exposed to PEG. Differences between patients and challenges in producing consistent batches also make regulatory approval more complicated.

Despite advances in combining these advantageous features to create an ideal nanoparticle, most evidence supporting nanoparticle drug delivery comes from in vitro and small-animal studies, which do not fully replicate the complexity of human tumours and systemic circulation. Only a few nanoparticle designs have advanced to clinical trials, and many fail to produce preclinical efficacy due to the biological and physiological differences between the experimental model and the patients. This highlights the need for more comprehensive in vivo models and large-scale clinical studies to validate reproducibility and therapeutic benefit.

Ultimately, strategies that blend active targeting with biomimetic and responsive features are crucial for overcoming the layered barriers in solid tumours and their environment. Combining immune evasion, vascular adhesion, and deep tissue penetration into one delivery system offers a powerful direction for cancer nanomedicine. However, successful translation will still require solutions to challenges such as large-scale manufacturing and consistent formulation. Bridging the gap between nanoparticle design and in vivo biodistribution, while accounting for the biological complexity of the tumour microenvironment, is a requisite for unlocking the full clinical potential of nanoparticle-based cancer therapies.

Conclusions

This review explored how a deeper understanding of nanoparticle biodistribution can inform the design of more effective cancer nanomedicine for clinical use. While nanoparticles offer targeted delivery and reduced toxicity, their journey through the body is complex and governed by biological barriers. Immune clearance, off-target organ accumulation, and poor tumour penetration remain key limitations in nanomedicine.

Biomimetic cloaking strategies, such as platelet membrane coatings, have shown promise by helping nanoparticles evade immune detection and interact more effectively with tumour environments. However, these biologically derived systems raise challenges in scalability and long-term safety. Synthetic approaches like PEGylation and zwitterionic coatings offer greater control and reduced immunogenicity, though PEG itself may trigger immune responses with repeated use. Zwitterionic surfaces show potential for long circulation and low recognition by the immune system.

However, reaching the tumour is only part of the challenge. Many nanoparticles struggle to move beyond the periphery due to high interstitial pressure and dense extracellular matrix. Approaches such as ECM degradation and vascular modulation may help improve delivery to poorly perfused tumour cores by reducing interstitial pressure and improving perfusion.

Ultimately, future nanoparticle systems will need to balance immune evasion, tumour targeting, and responsive drug release. As our understanding of tumour biology and systemic transport deepens, designing smarter, adaptive nanoparticles may finally bridge the gap between innovation in the lab and impact in the clinic.

List of Abbreviations

ABC: accelerated blood clearance
CD47: cluster of differentiation 47
DC: dendritic cell
ECM: extracellular matrix
EPR: enhanced permeability and retention
GPIb: glycoprotein Ib
GPVI: glycoprotein VI
NP: nanoparticle
PEG: polyethylene glycol
PNP: platelet membrane-coated nanoparticle
ROS: reactive oxygen species

Conflicts of Interest

The author declares that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

As this paper is a literature review, no ethics approval or participant consent was required.

Authors' Contributions

VO: conceived and designed the study, conducted the literature review, analysed and interpreted the data, drafted and revised the manuscript, and approved the final version to be published. VO agrees to be accountable for all aspects of the work.

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