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Review

Stealth Strategies for Cancer Nanomedicine: A Review of Immune Evasion and Tumor Targeting

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Abstract

Nanocarrier platforms can improve cancer therapy through enhanced selectivity and reduced systemic toxicity. Yet mononuclear phagocyte system (MPS) clearance sharply limits delivery; in preclinical models, often less than 1% of the injected dose reaches tumors. Surface-engineering strategies that let nanocarriers evade immune recognition have emerged to prolong circulation and improve therapeutic outcomes. These fall into two families: synthetic coatings, including PEG grafting and zwitterionic polymers, and biomimetic approaches, including cell-membrane cloaking (red blood cell, cancer cell, and immune cell membranes) and molecular immunomodulation. This review examines both. PEGylated liposomes remain the clinical gold standard with 55-h circulation in humans, though anti-PEG immunity and complement activation-related pseudoallergy (CARPA) represent ongoing challenges. Membrane-coated carriers borrow nature's own stealth mechanisms, such as CD47-mediated "don't eat me" signaling, to achieve prolonged circulation and, in specific preclinical comparisons, half-lives exceeding those of matched PEG-coated controls. They also avoid the anti-polymer antibody responses associated with PEG. Despite favorable preclinical data, clinical translation of second-generation biomimetic platforms remains stalled due to manufacturing complexity, regulatory uncertainty, and insufficient differentiation from existing FDA-approved therapies. This review critically evaluates pharmacokinetic and biodistribution outcomes, immunogenicity profiles, and translation barriers, while identifying scalable manufacturing protocols and regulatory engagement as prerequisites for realizing the clinical potential of biomimetic nanocarriers in oncology.

Keywords: nanocarriers; stealth nanoparticles; PEGylation; zwitterionic polymers; cell membrane coating; immune evasion; drug delivery; cancer therapy

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1. Introduction

Nanocarrier platforms promise precise cancer drug delivery with enhanced tumor selectivity, reduced systemic toxicity, and improved therapeutic indices. Despite decades of preclinical success, immune-mediated clearance remains a key barrier to clinical translation. Upon intravenous administration, the MPS rapidly recognizes nanoparticles as foreign, triggering opsonization and sequestration by hepatic Kupffer cells and splenic macrophages; elimination occurs within minutes to hours [1,2]. While protective against pathogens, this immune surveillance drastically limits tumor delivery to often less than 1% of the injected dose [3,4]. To circumvent this barrier, biomimetic "stealth" nanocarriers engineer surfaces

that masquerade as endogenous entities, evading immune recognition and prolonging circulation. Doxil (PEGylated liposomal doxorubicin), approved by the FDA in 1995, achieves 55-h circulation in humans and has been used clinically for three decades, validating the stealth nanocarrier concept [5]. Stealth strategies fall into two families. The first is synthetic: surface modifications such as polyethylene glycol (PEG) grafting create hydrophilic barriers that reduce protein adsorption and opsonization [6,7]. The second is biomimetic, and takes two forms. Cell-membrane cloaking wraps nanoparticles in membranes derived from red blood cells, cancer cells, or immune cells; native antigens such as CD47 engage inhibitory receptors on macrophages and prolong circulation [8,9]. Molecular immunomodulation instead displays defined immune-regulatory proteins on the nanoparticle surface: the 'don't eat me' signal CD47, which inhibits macrophage phagocytosis, and complement regulatory proteins (CD55, CD59, Factor H) [10,11]. Each approach offers distinct advantages and limitations in terms of pharmacokinetics, manufacturability, and immunogenicity. This review examines immune recognition and evasion, compares synthetic versus biomimetic stealth strategies in preclinical models, evaluates biodistribution and immunogenicity outcomes, and identifies outstanding challenges that must be addressed to realize the therapeutic potential of stealth nanocarriers. The scope is confined to stealth approaches for cancer therapy; non-cancer applications, non-nanoparticle biomimetic systems, and purely immunostimulatory platforms (cancer vaccines, adjuvants) are excluded.

Search Strategy

Primary evidence sources were identified through a PRISMA2020-informed search of PubMed/MEDLINE, Web of Science, Scopus, Google Scholar, and EMBASE (2008–2025) using combinations of the terms "stealth nanoparticle," "PEGylation," "zwitterionic," "cell membrane coating," "CD47," "complement activation," and "enhanced permeability and retention" [12]. Figure 1 summarizes the identification and screening process, which yielded 38 primary studies for inclusion. Studies were eligible if they reported primary data or mechanistic analysis on stealth or biomimetic nanocarriers relevant to cancer therapy; non-cancer applications, non-nanoparticle systems, and purely immunostimulatory platforms were excluded, consistent with the scope defined in Section 1. A small number of landmark pre-2008 studies of foundational mechanisms were retained through hand-searching. Because this article is a narrative rather than a fully systematic review, these primary studies were supplemented by additional background and mechanistic reviews identified through hand-searching of reference lists, cited throughout the text alongside the primary literature. The search and clinical-trial status were last updated in November 2025. Generative AI (Claude, Anthropic) assisted the revision of this manuscript: language editing, restructuring of text in response to reviewer comments, verification of cited references and reported values against their primary sources, and preparation of the comparison tables and the schematic overview figure (Figure 2). All AI-assisted output was checked and edited by the authors, who are responsible for the final content.

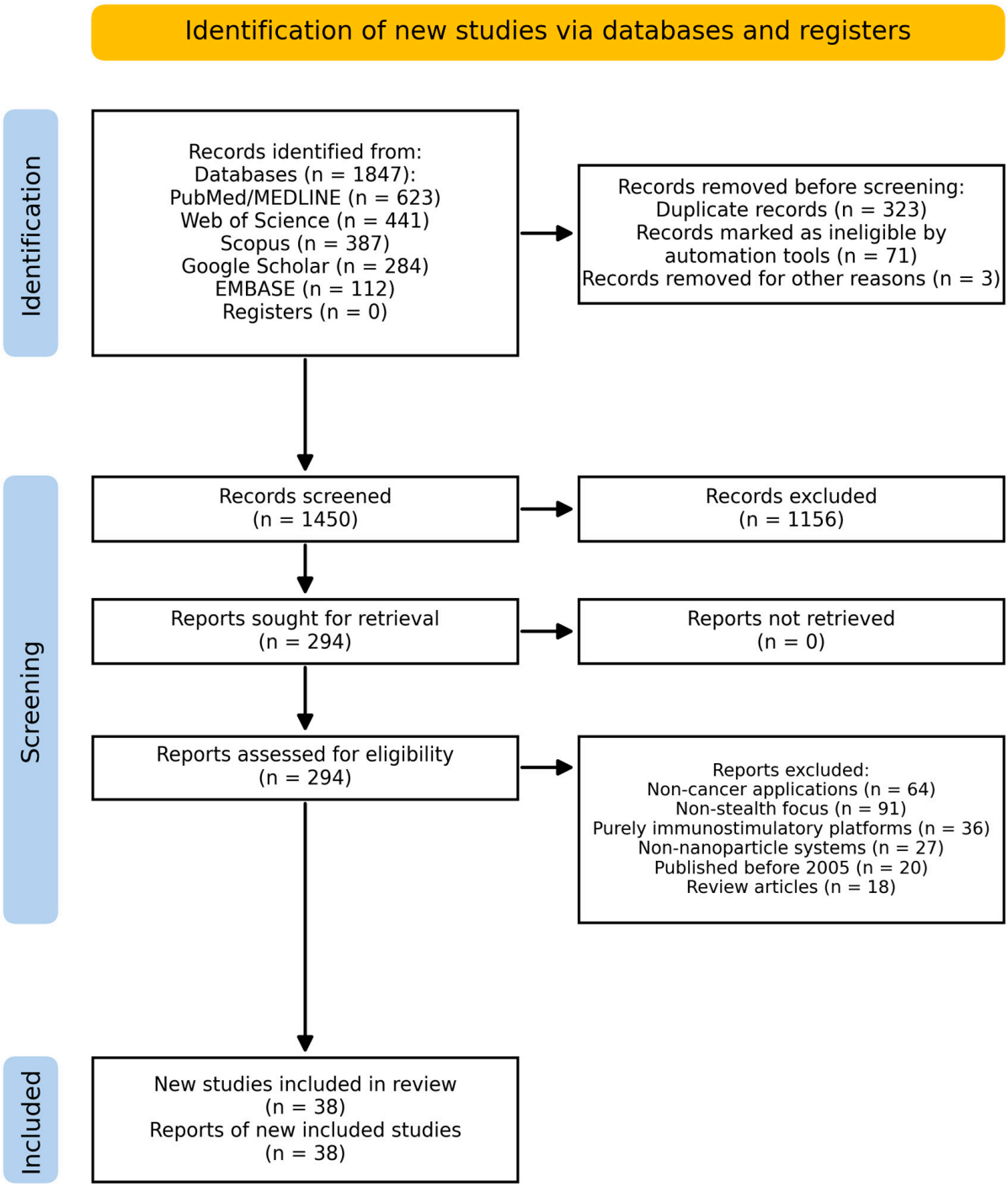


Figure 1. PRISMA flow diagram of study identification, screening, and inclusion, generated with the PRISMA2020 R package/Shiny app [12].

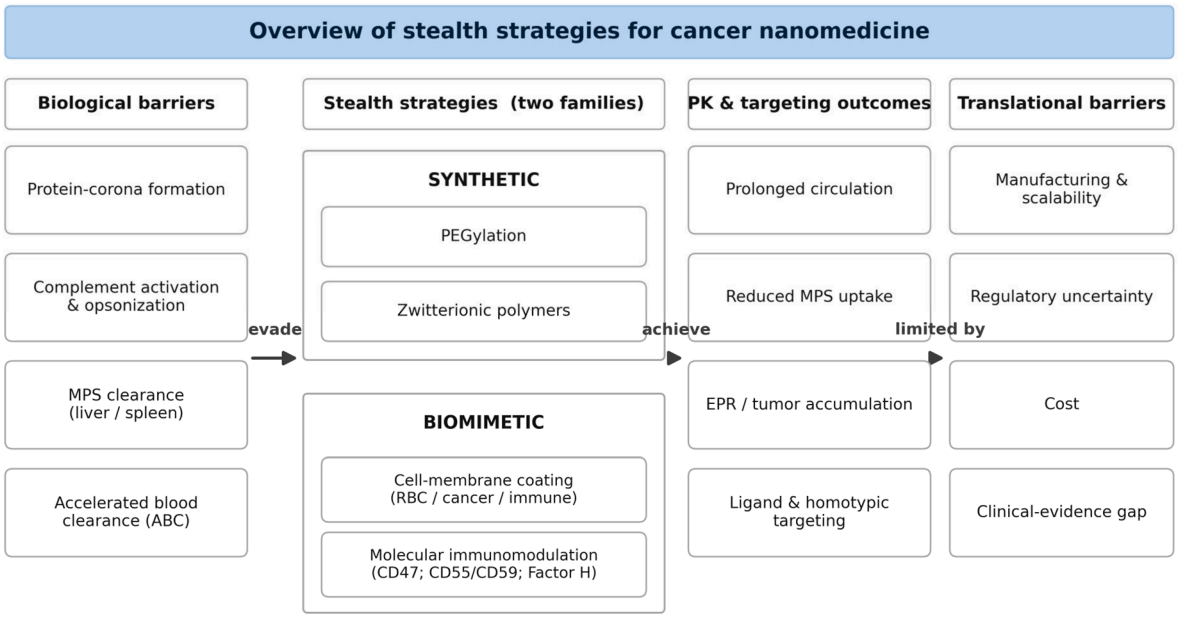


Figure 2. Overview of the review: the biological barriers to nanocarrier delivery, the synthetic and biomimetic stealth strategies that evade them, the resulting pharmacokinetic and targeting outcomes, and the barriers to clinical translation.

2. Overview of Immune Recognition of Nanoparticles

Figure 2 maps the biological barriers described in this section, the two families of stealth strategies that counter them, and the pharmacokinetic outcomes and translational barriers discussed later in this review.

2.1. Opsonization and Complement Activation

Nanoparticles encounter a complex plasma protein milieu within seconds of entering the bloodstream; adsorbed proteins form a "protein corona." Complement components (C1q, C3, C5) and immunoglobulins function as opsonins, marking particles for phagocytic clearance [10]. The complement system, comprising over thirty plasma and membrane-bound proteins, can be activated via three pathways, each converging on the cleavage of C3 into C3b, which covalently attaches to nanoparticle surfaces [13]. Phagocytosis is triggered when macrophage complement receptors (CR1, CR3) recognize C3b-opsonized nanoparticles [10]. Beyond opsonization, complement proteins can directly damage nanoparticle integrity. The membrane attack complex (MAC, C5b-9) inserts into lipid bilayers, creating pores that destabilize liposomes and cause premature drug release [1]. Complement evasion strategies can therefore be designed by conjugating complement regulatory proteins (e.g., Factor H, Factor I, CD55, and CD59) to nanoparticle surfaces [10,11]. Complement activation pathways also vary between species; the relative contribution of complement activation pathways can differ between humans and rodents. This interspecies variability further complicates clinical translation [13]. Complement activation also generates anaphylatoxins (C3a, C5a) that bind receptors on mast cells and basophils, triggering degranulation and histamine release [1]. This phenomenon, termed complement activation-related pseudoallergy (CARPA), can manifest as hypotension, tachycardia, dyspnea, and chest pain within minutes of nanoparticle infusion [1]. Clinically, 1–10% of patients receiving Doxil experience CARPA [1]. The non-oncology siRNA lipid nanoparticle Onpattro (patisiran) carries a higher infusion-reaction rate still (about 19% of patients versus 9% on placebo in the APOLLO trial) and is managed with mandatory premedication. Whether these reactions are mechanistically classical CARPA is taken up in Section 7.3 [1,14].

2.2. Clearance

Opsonized nanoparticles are efficiently captured by tissue-resident macrophages, particularly hepatic Kupffer cells [2]. A large majority (commonly reported as roughly 60–90%) of systemically administered conventional nanoparticles accumulate in the liver and spleen, with less than one percent reaching tumor sites. The most widely cited figure is a 0.7% median across the preclinical literature [4], although this delivery-efficiency metric has since been debated [15]. These cells express Fc receptors (FcγRI, FcγRII, FcγRIII) and complement receptors (CR1, CR3, CR4) that recognize opsonin-coated particles, initiating receptor-mediated endocytosis and phagolysosomal degradation [2]. Within the protein corona, "opsonins" (e.g., immunoglobulin G (IgG), complement C3b, and fibrinogen) promote MPS uptake, whereas "dysopsonins" (e.g., apolipoprotein E (ApoE), clusterin, and serotransferrin) prolong circulation by inhibiting macrophage recognition [2]. A sound stealth design therefore engineers nanoparticle surfaces to selectively recruit dysopsonins while repelling opsonins, although this is complicated by the dynamic nature of protein adsorption [2]. Pharmacological modulation of the MPS itself has also been explored as a complementary strategy. For example, transient saturation or blockade of Kupffer cell phagocytic capacity by pre-dosing with blank carriers can increase the circulation time and tumor delivery of a subsequently administered dose [16].

2.3. Accelerated Blood Clearance (ABC) Phenomenon

An unexpected consequence of repeated nanoparticle administration is the accelerated blood clearance (ABC) phenomenon, first observed in rodents receiving multiple doses of PEGylated liposomes [17]. Upon initial exposure, PEGylated nanoparticles elicit production of anti-PEG IgM antibodies by splenic B cells. Subsequent doses are then cleared rapidly by IgM-mediated complement activation and Kupffer cell hyperresponsiveness, which cuts the circulation half-life from tens of hours to under one hour in the liposomal systems originally studied (the magnitude of reduction is formulation-dependent; see Section 6.1 for lipid-nanoparticle values) [17,18]. The ABC effect is dose-dependent and reversible, and can be mitigated by strategies such as free PEG pre-infusion (which saturates circulating anti-PEG antibodies), branched PEG architectures (which reduce IgM epitope accessibility), or switching to alternative stealth polymers [18–20]. Paradoxically, the clinical relevance of ABC remains debated. While reproducible in mice and rats, ABC has not been consistently observed in humans treated with PEGylated liposomal doxorubicin; some studies report stable or even decreased clearance with repeat dosing [21]. Pre-existing anti-PEG antibodies are also detectable in an estimated 20–70% of healthy individuals, attributed to environmental PEG exposure via cosmetics, pharmaceuticals, and excipients such as poloxamers [22]. The implications for biomimetic nanocarrier design are twofold: first, screening patients for anti-PEG antibodies may be necessary to predict pharmacokinetic outcomes; second, alternative stealth coatings (zwitterionic polymers, cell membranes) that avoid anti-polymer immunity should be prioritized.

3. Synthetic Stealth Strategies

3.1. PEGylation: Mechanisms, Limitations, and Anti-PEG Immunity

Polyethylene glycol (PEG) conjugation to nanoparticle surfaces (PEGylation) remains the gold-standard stealth technology. PEG conjugation was responsible for the clinical success of many FDA-approved formulations, particularly PEGylated liposomal doxorubicin (Doxil); other stealth mechanisms, such as albumin binding in Abraxane, achieve similar goals through non-PEG routes [5,23]. PEG chains create a dense hydrophilic "brush" layer that sterically hinders protein adsorption; approaching proteins must compress PEG chains and displace water molecules, both energetically unfavorable processes [6]. This

steric barrier reduces complement binding, opsonization, and macrophage recognition, prolonging circulation half-life by orders of magnitude relative to bare nanoparticles [6]. Doxil, approved by the FDA in 1995, exemplifies the promise of PEGylation. Its circulation of half-life of 55 h in humans is an approximately 1000-fold increase in plasma area-under-the-curve (AUC) over free doxorubicin. This raises tumor drug AUC about 30-fold and lowers cardiotoxicity risk more than threefold [5]. The liposomal formulation consists of hydrogenated soy phosphatidylcholine, cholesterol, and mPEG2000-distearoylphosphatidylethanolamine (DSPE) in an approximately 56.3:38.4:5.3 molar ratio, producing approximately 100-nanometer vesicles with surface-grafted PEG chains [5]. Over 90% of encapsulated doxorubicin remains sequestered in the bloodstream, and tumor accumulation reaches 25% of the injected dose per gram in breast cancer xenografts [5]. Yet PEGylation is not without limitations. First, PEG provides incomplete shielding: some protein adsorption and complement activation persist, particularly on high-surface-area particles or those with suboptimal PEG chain length and density [22]. Second, anti-PEG antibodies can trigger the ABC phenomenon in rodents, though clinical relevance in humans remains uncertain [21,22]. Third, complement activation by PEGylated liposomes can cause CARPA in susceptible patients, necessitating premedication with antihistamines and corticosteroids [1]. Fourth, the membrane attack complex can destabilize PEGylated liposomes, causing premature drug release and off-target toxicity [1]. Fifth, PEGylation introduces an adverse effect termed palmar–plantar erythrodysesthesia (hand–foot syndrome), which is dose-limiting and reported far less frequently with non-PEGylated liposomal doxorubicin (Myocet) [24]. Countermeasures to mitigate anti-PEG immunity include pre-infusion with high-molecular-weight free PEG, which saturates circulating anti-PEG IgM and restores prolonged circulation for at least forty-eight hours in sensitized mice [20]. Multiple-dosing regimens can also attenuate ABC after the third or fourth dose, possibly via immune tolerance or antibody saturation [18]. Nonetheless, the specter of anti-PEG immunity and the high prevalence of pre-existing anti-PEG antibodies in human populations motivate exploration of alternative stealth polymers [22,25].

3.2. Zwitterionic Polymers and Other Synthetic Alternatives

Zwitterionic polymers have emerged as promising alternatives to PEGylation, demonstrating high hydrophilicity, non-fouling properties, and reduced immunogenic liability [26,27]. Zwitterionic polymers (e.g., polycarboxybetaine (PCB), polysulfobetaine (PSB), and phosphorylcholine (PC)) present both cationic and anionic groups on the same monomer, resulting in a net-neutral charge. These polymers generate a dense hydration layer via electrostatic interactions with water dipoles [28]. This hydration layer repels protein adsorption more effectively than PEG in some systems, and zwitterionic nanoparticles largely avoid the anti-polymer antibody responses observed with PEG [26,29]. A landmark study by Banskota et al. demonstrated that genetically encoded zwitterionic peptide (ZIP)–paclitaxel conjugate micelles increase paclitaxel circulation half-life seventeen-fold compared to free drug and 1.6-fold compared to non-stealth controls. Across several mouse tumor models, they improved efficacy and widened the therapeutic window relative to the clinical standard Abraxane [26]. In mice, zwitterionic lipid nanoparticles (LNPs) maintained circulation (10.3 h) even after repeated dosing, whereas PEGylated LNPs succumbed to ABC (a 2.8-h half-life after the second dose), indicating zwitterionic resistance to anti-polymer immunity [30]. ZIPs further refine this approach by enabling sequence-dependent tuning of the protein corona: specific ZIP sequences reduce serum protein adsorption by up to 60% and enrich dysopsonins (ApoE, transferrin) while depleting opsonins [31]. Recent designs have pushed these trade-offs further. Polysulfobetaine micelles whose N-alkyl chain length is tuned can stay protein-nonfouling in circulation yet switch to cell-

binding at the tumor, driving transcytosis and deeper penetration [32]. Zwitterionic peptide dendrimers give colloidally stable carriers that co-deliver drugs with reduced systemic toxicity in mouse tumors [33]. Additional synthetic alternatives include polyoxazolines, polyglycerols, and polysaccharides (dextran, hyaluronic acid), each offering distinct stealth properties. Despite these advantages, zwitterionic polymers have seen limited clinical adoption due to formulation complexity, higher cost relative to traditional options, and regulatory inexperience, as no FDA-approved zwitterionic nanocarrier yet exists [28].

4. Biomimetic Stealth Strategies

Where synthetic coatings shield a particle with an inert polymer layer, biomimetic strategies instead give it the surface of a living cell: whole membranes, or the specific self-marker proteins those membranes carry. The emphasis shifts from passive concealment to active display of 'self.' The sections below move from whole-membrane coatings (red blood cell, cancer cell, immune cell) to the individual immunomodulatory proteins that can be grafted onto a carrier.

4.1. Red Blood Cell Membrane Coating

Red blood cell (RBC) membranes are a natural stealth coating, owing to their intrinsic "marker-of-self" properties and long circulatory lifespan (about 120 days in humans). The coated particles do not themselves reach that lifespan; Section 6.1 gives the circulation that is actually achieved. RBC membranes display CD47, a transmembrane glycoprotein that engages signal regulatory protein alpha (SIRPα) on macrophages and delivers a 'don't eat me' signal. This signal drives phosphorylation of immunoreceptor tyrosine-based inhibitory motifs (ITIMs), which block non-muscle myosin IIA accumulation and the cytoskeletal rearrangement needed for phagocytosis [34,35]. RBC membranes also bear glycophorin A and other sialic-acid-rich glycoproteins that resist opsonization by the complement system and macrophage recognition [36]. The seminal work by Hu et al. demonstrated that coating polymeric (PLGA) nanoparticles with RBC membranes confers a clear pharmacokinetic advantage. These RBC-membrane-coated nanoparticles (RBC-NPs) achieved a circulation half-life of 39.6 h in mice, versus 15.8 h for PEG-coated equivalents [37]. Luk et al. further showed that RBC-NPs reduced liver and spleen accumulation and enhanced tumor uptake in murine xenograft models without inducing anti-RBC autoantibodies after repeated dosing [9]. The coating is fabricated via lysis of donor RBCs to generate membrane vesicles, which are then fused onto nanoparticle cores via sonication or extrusion [8,9]. RBC membrane coating has been extended to diverse core materials beyond PLGA, including mesoporous silica, gold nanoparticles, iron oxide (Fe_3O_4), upconversion nanoparticles, and, more recently, metal–organic frameworks such as ZIF-8 for combined chemo- and phototherapy of liver cancer [38–40]. Applications span chemotherapy, photothermal therapy, and photodynamic therapy. Uniquely, Fe_3O_4–RBC-NPs have been extensively investigated as magnetic resonance imaging (MRI) contrast agents [38,41,42]. The modularity of this approach, in which stealth function (RBC membrane) is decoupled from therapeutic payload (core), enables rapid adaptation to emerging drug candidates [36].

4.2. Cancer Cell Membrane Coating (Homotypic Targeting)

Cancer cell membranes (CCM) retain tumor-associated surface antigens, adhesion molecules (selectins, cadherins, integrins), and chemokine receptors that mediate homotypic binding (preferential adhesion to cells of the same type) and enable tumor-specific targeting [8,38]. Pioneering work by Fang et al. showed that coating PLGA nanoparticles with B16-F10 melanoma cell membranes resulted in approximately twenty-fold higher uptake by homologous B16-F10 cells compared to RBC-NPs in vitro [8]. CCM-coated

nanoparticles (CCNPs) serve a dual function: (1) drug delivery via homotypic targeting, and (2) cancer vaccination via presentation of tumor antigens to dendritic cells, stimulating tumor-specific T-cell responses [8]. Cancer-cell-membrane coating has moved further still: source cells can be genetically engineered to enrich defined tumor antigens on the coat before harvest, and hybrid membranes pair homotypic targeting with red-blood-cell-derived stealth to lengthen circulation [43,44]. However, CCM coating alone may be inadequate for stealth, as tumor-associated antigens can elicit immune recognition. Hybrid membranes that combine RBC and CCM sources merge stealth (RBC-derived CD47) with targeting (CCM-derived adhesion molecules). In preclinical comparisons, they improved circulation and tumor selectivity relative to either membrane alone [43,44]. Additional approaches include post-coating functionalization, such as inserting targeting ligands (RGD peptides, folate, mannose) into the lipid bilayer, or genetically modifying source cancer cells to overexpress desired targeting receptors prior to membrane harvest [39,43].

4.3. Immune Cell Membrane Coating (Neutrophil, Macrophage, Platelet)

Immune cell membranes confer unique targeting and immunomodulatory functions. Neutrophil and leukocyte membranes express adhesion molecules (e.g., L-selectin, β2-integrins) that mediate rolling and firm adhesion on inflamed endothelium, enabling targeting of tumor vasculature [39,41]. Platelet membranes bind circulating tumor cells via P-selectin/PSGL-1 interactions and target inflamed endothelium, offering potential utility in mitigating metastasis [38,41]. Macrophage and tumor-associated macrophage (TAM) membranes enable targeting of the immunosuppressive tumor microenvironment; TAM-membrane-coated nanoparticles can reprogram TAMs toward anti-tumor M1 phenotypes [39,41]. T-cell and dendritic-cell membranes are being explored for immunotherapy applications: T-cell-membrane-coated nanoparticles present antigens and costimulatory signals, priming anti-tumor T-cell responses, while dendritic-cell-membrane-coated nanoparticles enhance antigen cross-presentation to $CD8^+$ T cells [41]. The diversity of immune cell membrane sources enables modular design of targeted immunotherapeutic nanocarriers tailored to specific therapeutic objectives [39,41].

4.4. Hybrid and Engineered Membrane Approaches

Hybrid membranes (fusions of two or more cell membrane types) combine complementary functionalities to overcome specific limitations of single-source coatings. For example, RBC–cancer cell hybrid membranes merge CD47-mediated stealth with homotypic tumor targeting, with improved circulation and tumor selectivity reported in preclinical models [43,44]. Platelet–mesenchymal stem cell (MSC) hybrid membranes enable dual targeting of inflamed vasculature and stromal compartments [43]. The stoichiometric ratio of components can be optimized for stealth or targeting; typically, the ratio of RBCs to targeting cells varies by formulation [44]. Source cells (RBCs, cancer cells, immune cells) may also be genetically engineered to overexpress targeting ligands, receptor agonists/antagonists, or imaging reporters [43]. A critical manufacturing challenge is achieving complete and uniform membrane coverage. Liu et al. demonstrated that incomplete coating is common due to limited membrane vesicle fluidity and electrostatic repulsion between membrane and core; partial coating reduces targeting efficiency and increases immune recognition [44]. Optimizing fusion conditions during membrane coating can improve coating completeness and reproducibility. Quality control assays (e.g., flow cytometry for membrane protein markers, immunofluorescence microscopy, Western blotting, and proteomics) are essential to verify coating integrity and batch-to-batch consistency [36,39].

4.5. Molecular Immunomodulatory Surface Display

4.5.1. CD47 ("Don't Eat Me" Signal) Functionalization

CD47 is a transmembrane glycoprotein (35 kDa core polypeptide, migrating at 45–55 kDa when glycosylated) ubiquitously expressed on healthy cells, serving as a "marker of self" to prevent autophagocytosis [34]. CD47 binds SIRPα on macrophages with micromolar monovalent affinity, but multivalent display on a cell or particle surface generates high avidity that amplifies the signal. The extracellular immunoglobulin variable (IgV) domain of CD47 engages the FG-loop of SIRPα through charge-complementary contacts. This triggers ITIM phosphorylation and recruits SHP-1/SHP-2 phosphatases, which block non-muscle myosin IIA accumulation at the phagocytic synapse and the cytoskeletal rearrangement needed for phagocytosis [45,46]. Cancer cells frequently overexpress CD47 to evade immune surveillance, and CD47 expression correlates inversely with patient survival across multiple tumor types [34]. Therapeutic strategies targeting the CD47-SIRPα axis include anti-CD47 blocking antibodies, several of which have advanced to later-stage clinical trials [45,47]. For nanocarrier applications, synthetic CD47-derived peptides or recombinant CD47 extracellular domains can be conjugated to nanoparticle carriers to mimic the "don't eat me" signal [48]. CD47-engineered adeno-associated viruses (AAVs) exhibit reduced macrophage uptake, demonstrating proof-of-concept for gene therapy vectors [45,49]. Application to nanoparticle drug carriers remains largely preclinical, but combination with PEGylation or membrane coating may provide synergistic stealth effects by engaging both steric (PEG) and active immunomodulatory (CD47) mechanisms.

4.5.2. Complement Regulatory Proteins (CD55, CD59, Factor H)

Complement regulatory proteins independently provide a stealth mechanism by directly inhibiting complement cascade progression. CD55 (decay-accelerating factor, DAF) disrupts C3 convertases (C3bBb, C4b2a), preventing C3b amplification on cell surfaces [10]. CD59 (protectin) inhibits formation of the membrane attack complex (C5b-9), preventing pore formation in lipid bilayers [9,10,36]. Soluble forms of complement regulatory proteins can be conjugated to synthetic nanoparticles to confer complement resistance. Wang et al. demonstrated that conjugating soluble CD55 domains or Factor H to PEG-coated nanoparticles reduces C3b deposition and leukocyte uptake in human blood in vitro, and prolongs circulation in murine sepsis models [11]. Similarly, Factor I, a serine protease that cleaves C3b into inactive iC3b, can be conjugated to nanoparticles to actively degrade opsonins in situ [11]. These approaches represent "active" complement evasion strategies that go beyond passive steric shielding, potentially offering superior stealth in complement-rich inflammatory environments such as tumors [10,11].

5. Biomimetic Tumor Targeting

5.1. Ligand-Based Targeting Combined with Stealth

Active targeting ligands (e.g., folate, RGD peptides, epidermal growth factor (EGF), transferrin, and monoclonal antibodies) recognize overexpressed tumor cell receptors (folate receptor-α, integrins $\alpha_V\beta_3/\alpha_V\beta_5$, EGFR, transferrin receptor) and enhance receptor-mediated endocytosis. However, conjugating ligands to bare nanoparticles often accelerates MPS clearance by increasing opsonization for macrophage scavenger receptors [2]. The solution is to combine ligands with stealth coatings. PEGylated or membrane-coated nanocarriers provide the prolonged circulation needed for passive accumulation in tumors via the enhanced permeability and retention (EPR) effect, and the surface ligands then improve tumor-cell binding and internalization after extravasation. Well-designed stealth-targeting platforms require several technical considerations. First, ligand density must be carefully tuned to balance targeting and stealth [43]. Second, ligand presentation can

be controlled via PEG spacers or membrane insertion [43]. Third, cleavable linkers (pH-sensitive, protease-cleavable) allow for ligand shedding in circulation to maintain stealth. In pre-targeting, tumor-targeting ligands (antibodies, peptides) are administered first and allowed to bind tumor cells and clear from circulation. Ligand-binding nanoparticles (e.g., biotin-avidin, antibody-Fc-binding) are then administered, achieving tumor selectivity without prolonged systemic exposure of the targeted nanoparticle and minimizing MPS clearance [43].

5.2. EPR Effect and Its Variability

The EPR effect holds that nanoparticles preferentially accumulate in tumors due to leaky vasculature (fenestrations ranging from approximately 100 nm to over 1 μm depending on tumor type, with a commonly cited cutoff near 400–600 nm [50]) and impaired lymphatic drainage. EPR is a passive targeting mechanism that underlies the clinical success of Doxil, which relies on prolonged circulation to maximize tumor extravasation; Abraxane instead relies on active albumin-receptor transcytosis rather than EPR [5,51]. However, EPR varies widely: tumor accumulation ranges from less than 1% to over 10% of injected dose across preclinical models, and human solid tumors display even greater heterogeneity [51,52]. Factors contributing to EPR variability include tumor vascular density, pericyte coverage, extracellular matrix composition, interstitial fluid pressure, and tumor stage [53–55]. Within individual tumors, EPR is spatially heterogeneous, with nanoparticles confined to perivascular regions (50–200 μm from perfused vessels) and excluded from hypoxic, poorly vascularized zones [53]. Strategies to enhance EPR include vascular normalization, stromal depletion, interstitial fluid pressure reduction, and hyperthermia [53,54]. Patient stratification based on EPR status, using imaging agents (fluorescent nanoparticles, radiolabeled liposomes) to visualize vascular permeability, may enable personalized nanomedicine that reserves EPR-dependent therapies for viable cases [51].

5.3. Stromal and Vascular Targeting Strategies

Targeting the tumor stroma offers an alternative to direct cancer cell targeting. Fibroblast activation protein (FAP) is overexpressed on cancer-associated fibroblasts (CAFs) in desmoplastic tumors (pancreatic, breast, colorectal cancers) and can be targeted with FAP-binding peptides or antibodies to deplete stromal barriers. Integrin $\alpha_V\beta_3$ and VEGFR2, overexpressed on tumor endothelium, enable vascular targeting; RGD-peptide nanoparticles selectively bind angiogenic vessels, delivering anti-angiogenic agents to collapse tumor vasculature. Platelet-membrane-coated nanoparticles inherently target inflamed endothelium and circulating tumor cells, providing passive targeting without ligand conjugation [41]. Extracellular matrix components also serve as targets: hyaluronan-binding peptides enable penetration of hyaluronan-rich stroma, while collagenase co-delivery degrades collagen barriers to enhance nanoparticle diffusion. Stromal targeting can synergize with cancer cell targeting; sequential administration of stromal-depleting and tumor-targeting nanoparticles may improve penetration and efficacy.

6. Pharmacokinetics

6.1. Comparative Pharmacokinetics and Biodistribution

Circulation half-life is the primary pharmacokinetic determinant of tumor delivery for passively targeted nanocarriers. Direct head-to-head comparisons of PEGylated, cell-membrane-coated, and zwitterionic nanocarriers reveal trade-offs rather than a single best option (Table 1). Bare nanoparticles (unmodified PLGA, liposomes, gold nanoparticles) exhibit half-lives of minutes to hours in rodents due to rapid opsonization and MPS clearance [9]. PEGylated nanoparticles achieve 10–20 h in mice and 55 h in humans (Doxil),

representing the current clinical gold standard [5,9]. However, 40–60% of the injected dose accumulates in the liver and spleen, and only 2–8% (as whole-tumor %ID) reaches tumors at 24 h [5,9]. This whole-tumor metric should not be confused with the per-gram value (up to 25% ID/g) cited for Doxil in Section 3.1. RBC-membrane-coated nanoparticles achieved 39.6 h in mice, a 2.5-fold improvement over the PEG-coated PLGA comparator (15.8 h) and an approximately forty-fold improvement over bare cores (on the order of an hour or less in most reports) [9,37]. This comparison should be read cautiously. The PEG-coated PLGA comparator in Hu et al. (15.8 h) circulates far more briefly than optimized PEGylated liposomes such as Doxil (55 h in humans); the advantage of membrane coating over PEGylation is therefore specific to the formulations compared, not a general rule. Other cell-membrane-coated nanoparticles (cancer cell, platelet, leukocyte membranes) typically achieve 20–40 h in rodent models, depending on core material and membrane source [38,39]. Zwitterionic nanoparticles exhibit pharmacokinetics similar or slightly superior to PEGylation in limited head-to-head studies, with the added benefit of avoiding the diminishing returns caused by ABC upon repeated dosing [30]. This addresses a clinically important problem. In sensitized individuals, anti-PEG antibodies can sharply reduce the circulation half-life: ABC-affected PEGylated liposomes in rodents clear in under one hour, approaching the kinetics of bare particles [18]. This advantage positions zwitterionic coatings as favorable for multi-dose regimens, though human pharmacokinetic data remains lacking. Tumor accumulation variability is a further critical translational challenge. The EPR effect is highly heterogeneous across tumor types, stages, anatomical sites, and patients [51,56]. Rodent xenografts often exhibit consistent, uniform EPR, whereas human solid tumors display patchy and heterogeneous accumulation [53,54]. Extracellular matrix density, interstitial fluid pressure elevation, high pericyte coverage, and hypoxia can all impede penetration, primarily confining accumulation to peritumoral regions [55]. Even long-circulating stealth nanoparticles may fail to reach viable tumor cells deep within poorly vascularized cores, limiting therapeutic efficacy [52].

Table 1. Comparison of major stealth nanocarrier strategies.

Strategy	Circulation Half-Life	Tumor Uptake	Main Advantages	Main Limitations	Clinical Status
PEGylation (synthetic; e.g., Doxil, Onivyde)	10–20 h (mice); 55 h (Doxil, human) [5,9]	2–8% ID at 24 h; up to 25% ID/g for Doxil in xenografts [5]	Simple, low-cost, well-characterized; established GMP; decades of clinical use	Anti-PEG IgM/IgG in 20–70% of people; ABC on repeat dosing; CARPA risk [22,25]	FDA-approved (Doxil, Onivyde, others)
Zwitterionic polymers (synthetic; PCB, PSB; ZIP–paclitaxel)	10.3 h (siRNA LNP [30]); largely maintained after repeat dosing	Similar or slightly higher than PEG in limited studies	Strong hydration/antifouling; no anti-polymer antibody response; resists ABC [26,30]	Formulation complexity; higher cost; limited GMP precedent	Preclinical/early translational; no approved product
Membrane coating (biomimetic; RBC/CCM/ immune cell)	39.6 h (RBC-NP, mice) vs. 15.8 h for PEG-NP [37]	Enhanced vs. PEG; reduced liver/spleen accumulation (mice) [9]	Native self-markers (CD47); homotypic targeting (CCM); modular payload [8,9,36]	Highest manufacturing complexity; batch variability; allo-/xeno-immunogenicity (CCM)	No oncology trials; non-oncology RBC nanosponge (CTI-005) in early-phase testing [57]

Note: %ID = percent of injected dose in whole tumor; %ID/g = percent of injected dose per gram of tumor tissue. The two metrics are not directly comparable. The zwitterionic circulation half-life reported here (10.3 h) reflects the siRNA lipid nanoparticle system of Zhao et al. [30] specifically; it is distinct from the zwitterionic peptide–paclitaxel micelle system of Banskota et al. [26] discussed in Section 3.2 and should not be read as a general zwitterionic-polymer value.

6.2. Organ-Specific Clearance Patterns

The liver (primarily Kupffer cells) and spleen (marginal zone macrophages) dominate nanoparticle clearance, collectively accounting for roughly 60–90% of injected dose for conventional nanoparticles [2,9]. Hepatic sequestration is size-dependent: particles larger than two hundred nanometers are preferentially trapped in liver sinusoids, while smaller particles (10–100 nm) circulate longer but may still undergo Kupffer cell uptake [2]. Splenic clearance involves both marginal zone macrophage phagocytosis and mechanical filtration through inter-endothelial slits (approximately 200–500 nanometers, variably reported up to ~1 μm), removing rigid particles and opsonized aggregates [2]. Renal clearance matters only for ultrasmall nanoparticles (under 8 nm hydrodynamic diameter) that can cross the glomerular filtration barrier. Most therapeutic nanocarriers (50–200 nm) are too large for renal elimination and instead rely on MPS-mediated hepatobiliary excretion [2]. Lung accumulation occurs with cationic or aggregated nanoparticles, while anionic stealth nanoparticles largely avoid pulmonary sequestration unless particle size exceeds five micrometers. Biodistribution to other organs (heart, kidney, brain, bone) is typically minimal (under approximately 5% of injected dose each) for stealth nanocarriers. This reflects effective MPS evasion and limited extravasation across intact endothelial barriers in healthy tissue [9]. Brain accumulation requires additional strategies (e.g., receptor-mediated transcytosis, or focused-ultrasound-mediated transient blood–brain barrier disruption) due to the impermeability of cerebral capillaries.

6.3. Intratumoral Penetration and Retention

Tumor accumulation for stealth nanoparticles ranges from 2–8% of injected dose at twenty-four hours in rodent xenograft models [9]. Penetration depth from vessels is limited to 50–200 μm due to elevated interstitial fluid pressure, dense extracellular matrix (collagen, hyaluronan), and high cellular density, all of which impede diffusion [53]. Nanoparticles accumulate primarily in perivascular and peripheral tumor regions, with minimal penetration into avascular hypoxic cores [55]. Retention time in tumors depends on nanoparticle degradation kinetics, drug release rate, and lymphatic clearance. Non-degradable inorganic cores (gold, quantum dots) can persist for weeks to months, which raises chronic-toxicity concerns. Biodegradable polymeric cores (PLGA, PLA) degrade over days to weeks, releasing the encapsulated drug locally and clearing byproducts through renal or hepatobiliary routes [38]. Long-circulating nanoparticles enable multiple extravasation events over extended periods, increasing cumulative tumor exposure compared to short-circulating particles that deliver a single bolus.

7. Safety and Immunogenicity

7.1. Acute and Chronic Toxicity Profiles

PEGylated nanocarriers exhibit favorable safety profiles in clinical nanomedicine, with toxicities generally attributable to drug payloads (doxorubicin cardiotoxicity, paclitaxel neuropathy) rather than the carrier itself [5,24]. Doxil's dose-limiting toxicity is palmar–plantar erythrodysesthesia (hand–foot syndrome), an adverse effect reported far less frequently with non-PEGylated liposomal doxorubicin (Myocet), suggesting that PEG's prolonged circulation alters cutaneous capillary exposure [24]. Hematologic toxicities (neutropenia, thrombocytopenia) occur with PEGylated liposomal doxorubicin but at lower frequencies than with free doxorubicin, consistent with reduced free-drug exposure [5]. Cardiotoxicity, the primary concern with anthracyclines, is reported to be reduced more than threefold with Doxil compared to conventional doxorubicin, attributed to reduced peak plasma concentrations and cardiac tissue exposure [5]. Cell-membrane-coated nanoparticles have shown no acute toxicity in the short-term rodent studies published to date at therapeutic

doses; Luk et al. reported no behavioral changes, weight loss, or histopathological abnormalities in tumor-bearing mice treated with repeated doses of RBC-membrane-coated doxorubicin nanoparticles [9]. No anti-RBC autoantibodies were detected, though assay sensitivity varies across studies, suggesting immunological tolerance to autologous or allogeneic RBC membranes [9]. However, long-term chronic toxicity data (beyond three months) are lacking, and potential risks include autoimmunity (if neo-antigens form during manufacturing), thrombogenicity (if platelet-membrane-coated particles activate coagulation cascades), and non-degradable core accumulation. Inorganic nanoparticle cores (gold, iron oxide, mesoporous silica, quantum dots) raise distinct safety concerns relative to organic carriers due to non-biodegradability and potential for chronic accumulation in liver, spleen, and other organs. Iron oxide nanoparticles are partially biodegradable, but high doses may cause iron overload and oxidative stress [38]. Gold nanoparticles resist biodegradation and can persist indefinitely; while acutely non-toxic, their long intravascular half-life raises concern for long-term hepatic accumulation, and potential genotoxicity remains unresolved. Quantum dots containing cadmium or lead pose heavy-metal toxicity risks if core degradation releases free ions. Regulatory agencies require extensive absorption, distribution, metabolism, and excretion (ADME) studies for inorganic nanomedicines, representing a major translational barrier [36].

7.2. Immunogenicity of Biomimetic Components

Allogeneic or xenogeneic cell membranes may contain clinically relevant minor histocompatibility antigens, ABO blood group antigens, or species-specific proteins that could trigger alloimmune or xenoimmune responses. Autologous RBC membrane coating, using the patient's own erythrocytes, theoretically eliminates immunogenicity but is impractical at clinical scale due to the need for individualized manufacturing, batch testing, and rapid turnaround. Universal donor (O-negative) RBC membranes may reduce alloimmunity risk relative to fully mismatched donors by lacking A and B antigens, but Rh factor and other minor antigens remain immunogenic in sensitized individuals. Cancer-cell-membrane antigens cut both ways. Tumor-associated antigens (TAAs) and neoantigens can elicit anti-tumor immunity, a desired vaccine effect, but may also trigger autoimmunity if cross-reactive epitopes exist on normal tissues [8]. This duality complicates safety evaluation because immunogenic potency is desirable against tumors but undesirable systemically. The safety window for CCM-coated nanoparticles in humans remains undefined due to the absence of human dosing data and will require careful Phase I dose-escalation studies with immune monitoring [8]. Platelet membranes carry a theoretical thrombogenicity risk if P-selectin, tissue-factor remnants, or other procoagulant factors remain functional. No thrombotic events have been reported in preclinical studies, however, perhaps because of low platelet-membrane dosing or the absence of cofactors needed to activate the coagulation cascade [41]. For any PEG-containing biomimetic construct, the pre-existing anti-PEG antibodies discussed in Sections 2.3 and 3.1 remain a concern: they can mediate complement activation, anaphylaxis, or accelerated clearance on first exposure, and patient screening for anti-PEG IgM/IgG with premedication may mitigate these risks [22].

7.3. Infusion Reactions and CARPA

CARPA manifests within minutes of nanoparticle infusion as hypotension, tachycardia, dyspnea, chest pain, flushing, and urticaria, mimicking IgE-mediated anaphylaxis but mechanistically distinct [1]. CARPA is triggered by complement activation (C3a, C5a anaphylatoxin release), not IgE, and occurs independently of prior sensitization [1]. Clinical incidence ranges from 1–10% for Doxil [1]. Infusion reactions are also common with the siRNA lipid nanoparticle Onpattro, at a higher reported rate (about 19% of patients) than

the Doxil CARPA figure, and are managed with mandatory premedication [1,14]. Pigs are considered the gold-standard preclinical model for predicting CARPA risk, as they exhibit human-like complement sensitivity; rodents are relatively resistant and underpredict human responses [1]. Risk factors for CARPA include rapid infusion rate, high nanoparticle dose, pre-existing complement dysregulation (autoimmune disease, hemodialysis), and formulation characteristics (cationic charge, large size, aggregation) [1]. Mitigation strategies include slow infusion (over thirty to sixty minutes), premedication with antihistamines and corticosteroids, test dosing with low initial doses, and co-administration of complement inhibitors (soluble complement receptor 1, anti-C5 antibodies such as eculizumab) [1,11]. Biomimetic nanocarriers employing complement regulatory proteins (CD55, CD59, Factor H) or RBC membranes, which natively express these proteins, may inherently resist CARPA, though clinical validation is lacking [9,11]. Zwitterionic coatings reduce complement activation compared to PEGylation in some in vitro systems, potentially lowering CARPA risk, but human data are absent [30].

8. Emerging Solutions

8.1. Current Clinical Trials Using Biomimetic Nanocarriers

PEGylated liposomes and nanoparticles represent the predominant FDA-approved stealth platforms as of 2025. Doxil, approved in 1995 for AIDS-related Kaposi's sarcoma and subsequently for ovarian cancer and multiple myeloma, remains the flagship nanomedicine with over thirty years of clinical use [5,58]. Onivyde (PEGylated liposomal irinotecan), approved in 2015 for metastatic pancreatic cancer following gemcitabine failure, demonstrates the continued clinical utility of PEG stealth technology. Other approved nanomedicines include DaunoXome (non-PEGylated liposomal daunorubicin for HIV-associated Kaposi's sarcoma), Myocet (non-PEGylated liposomal doxorubicin citrate, approved in Europe for metastatic breast cancer), and Marqibo (sphingomyelin/cholesterol-based, non-PEGylated liposomal vincristine for relapsed acute lymphoblastic leukemia) [59]; Marqibo was subsequently discontinued from the U.S. market in 2022. Beyond liposomes, Abraxane (albumin-bound paclitaxel nanoparticles) uses albumin's natural circulatory properties for passive stealth, achieving FDA approval for metastatic breast cancer, non-small cell lung cancer, and pancreatic adenocarcinoma [23,51]. Within oncology, no cell-membrane-coated nanoparticle stealth drug carrier had entered clinical testing as of the search date (November 2025) [57]. The one clinical-stage example lies outside oncology. Cellics Therapeutics' CTI-005, a human red-blood-cell-membrane nanosponge, received FDA investigational-new-drug clearance and entered early-phase testing for bacterial pneumonia; it is a detoxification platform that carries no drug payload and does not target tumors [57]. The oncology gap reflects manufacturing challenges, regulatory uncertainty, and limited differentiation from PEGylated liposomes to justify the investment required for first-in-human trials [36]. Zwitterionic polymer-coated nanocarriers similarly lack clinical precedent, remaining confined to preclinical and early translational research [26,28]. Antibodies against the CD47-SIRPα axis (Hu5F9-G4/magrolimab, CC-90002, TTI-621, ALX-148) have been evaluated in oncology trials, with notable setbacks. Magrolimab's Phase 3 program in myeloid malignancies was discontinued in 2023–2024 after an FDA clinical hold for futility and increased mortality, while other SIRPα-directed agents remain under investigation [45,47,57]. In all cases, these are therapeutic antibodies rather than nanocarrier stealth modifications. No CD47-functionalized nanoparticle stealth carrier has entered clinical testing as of the search date.

8.2. Manufacturing and Scalability Barriers

Cell-membrane-coated nanoparticle manufacturing presents major challenges that impede clinical translation. Table 2 sets these against PEGylated and zwitterionic systems

across complexity, reproducibility, cost, quality control, and regulatory precedent. The process requires: (1) large-scale cell culture or blood collection for RBCs, (2) membrane isolation via hypotonic lysis, ultracentrifugation, or tangential flow filtration, (3) sterile processing to remove intracellular components (cytosol, organelles, nucleic acids), (4) membrane vesicle extrusion or sonication to generate uniform size distributions, (5) nanoparticle core synthesis and drug loading, and (6) membrane-core fusion via sonication, extrusion, or electrostatic assembly [36,39]. Each step must be performed under Good Manufacturing Practice (GMP) conditions with rigorous quality control [36]. Membrane protein composition, lipid profiles, and coating completeness present major reproducibility challenges due to batch-to-batch variability [36,44]. Protein degradation (oxidation, denaturation, proteolysis) is a further challenge, because it can render key stealth proteins such as CD47 nonfunctional. Lipid oxidation during storage likewise compromises membrane integrity and can generate immunogenic lipid-peroxidation products [36]. Manufacturing is further complicated by the choice of cell source. Autologous membranes from the patient eliminate immunogenicity but require individualized production with lead times of weeks, making them currently impractical for acute cancers. Allogeneic membranes (e.g., from universal-donor RBCs or immortalized cell lines) enable off-the-shelf production but raise immunogenicity concerns and require extensive donor screening [36]. Cancer cell membranes necessitate culturing patient-derived tumor cells or established cancer cell lines, each with distinct regulatory hurdles [36]. No established GMP protocols exist for membrane-coated nanoparticles as of 2025 [36]. Regulatory agencies including the FDA and EMA have not published guidance documents specific to cell-membrane-derived nanomedicines, leaving characterization requirements undefined. Anticipated requirements include proteomics, lipidomics, sterility and endotoxin testing, stability studies, immunogenicity testing in vitro and in vivo, and comparability studies after manufacturing changes [36]. The regulatory pathway, whether a 505(b)(2) new drug application, a biologics license application (BLA), or a hybrid pathway, remains ambiguous for platforms that combine synthetic cores with biological coatings [36]. Cost represents an additional barrier: cell culture, membrane purification, and multi-step manufacturing drive costs well above those of conventional liposomal formulations, which can be produced via thin-film hydration and extrusion [36]. Reimbursement decisions by payers will require demonstrating clear clinical superiority over existing therapies to justify premium pricing [36].

Table 2. Manufacturing and translational comparison of the three stealth strategies (PEGylation and zwitterionic coatings are synthetic; membrane coating is biomimetic). Sources: [5,36,39,57].

Attribute	PEGylation (Synthetic)	Zwitterionic (Synthetic)	Membrane Coating (Biomimetic)
Process complexity	Low (thin-film hydration, extrusion)	Moderate–high (polymer synthesis, conjugation)	Highest (cell sourcing, membrane isolation, fusion)
Reproducibility	High; well-characterized	Moderate; polymer-dependent	Low; biological batch-to-batch variability
Cost	Low	Higher than PEG	Highest (cell culture/blood, multi-step)
Quality control	Established (PEG MW, density, conformation)	Emerging (charge, corona)	Extensive, largely undefined (proteomics, lipidomics, coating completeness, protein function)
Regulatory precedent	FDA-approved class; clear pathway	None; no approved product	None; pathway ambiguous (505(b)(2)/BLA/hybrid); no FDA/EMA guidance

Table 2. *Cont.*

Attribute	PEGylation (Synthetic)	Zwitterionic (Synthetic)	Membrane Coating (Biomimetic)
Representative status	Doxil, Onivyde (approved)	Preclinical/early translational	Preclinical (oncology); CTI-005 (non-oncology) in trials
Key references	[5,24]	[26,30,32,33]	[9,36,37]

8.3. Regulatory Pathways and Characterization Requirements

The FDA's guidance documents on nanotechnology products emphasize physicochemical characterization (size distribution, zeta potential, morphology via TEM, surface chemistry, drug loading and release kinetics, endotoxin levels, sterility), in vitro biocompatibility (hemolysis, complement activation, cytotoxicity), and in vivo pharmacokinetics/biodistribution in relevant animal models. For PEGylated liposomes, additional characterization includes PEG molecular weight, PEG density (molar ratio), PEG conformation (mushroom vs. brush), and stability of PEG-lipid conjugates [5]. Cell-membrane-coated nanoparticles will likely require all standard nanoparticle characterization plus membrane-specific assays: proteomics to identify protein components, with particular attention to immunogenic proteins, alloantigens, and species-specific proteins; confirmation of key functional proteins (CD47, glycophorin A) via Western blot or flow cytometry; lipidomics to verify phospholipid composition; membrane orientation assays (protease digestion, lectin binding, antibody accessibility); coating completeness assays (flow cytometry, immunofluorescence); membrane thickness via cryo-TEM; and functional assays demonstrating macrophage phagocytosis inhibition in vitro [36]. Comparability protocols must be established to ensure batch-to-batch consistency; given the biological variability of cell membranes, acceptable ranges for protein and lipid variation must be defined [36]. Immunogenicity assessment will require in vitro assays (complement activation, cytokine release, T-cell proliferation) and in vivo studies in relevant species (immune cell profiling, anti-membrane antibody ELISA, histopathology) [36]. Humanized mouse models or non-human primates may be necessary to evaluate species-specific immune responses, particularly for CD47-SIRPα interactions. Clinical trials will demand extensive immune monitoring, including anti-drug antibody development, complement activation markers, and cytokine panels [36]. The absence of regulatory precedent means that first-in-class developers will bear the burden of defining acceptable characterization and manufacturing standards [36], discouraging investment despite promising preclinical data.

9. Conclusions

Stealth strategies have advanced the pharmacokinetic profiles and tumor-targeting capabilities of nanocarrier drug delivery systems in preclinical cancer models. To date, PEGylated liposomes have been the clinical gold standard and, with few exceptions, the only clinically deployed option [5]. Yet issues such as anti-PEG immunity, CARPA, and incomplete complement evasion motivate continued innovation in this field [1,18]. Cell-membrane-coated nanoparticles emerge as a promising "second-generation" biomimetic platform, borrowing nature's own stealth mechanisms to achieve pharmacokinetic outcomes that, in matched preclinical comparisons, exceed those of corresponding PEGylated counterparts [8,9,36]. Zwitterionic polymers offer an immunologically inert alternative to PEG with notable resistance to anti-polymer antibody formation, positioning them favorably for repeat-dose regimens [26,30]. CD47 peptides, immune checkpoint ligands, and complement regulatory proteins represent distinct stealth strategies that could synergize with these physical approaches [10,11]. Despite favorable preclinical data, clinical translation of cell-membrane-coated and zwitterionic nanocarriers remains stalled by manufacturing

complexity, regulatory uncertainty, cost, and insufficient differentiation from approved PEGylated products [36,39]. As of the search date, no cell-membrane-coated nanoparticle has entered clinical testing for an oncology indication as a stealth drug carrier (the sole clinical-stage example, an RBC-membrane nanosponge, is a non-oncology detoxification platform). Addressing this translational gap requires: (1) development of scalable manufacturing protocols with rigorous quality control, (2) proactive regulatory engagement, (3) human-relevant safety assessment models, (4) head-to-head clinical trials against approved comparators, and (5) personalized design approaches that account for patient-specific immune status and tumor biology [1,18,36]. Biomimetic nanocarriers hold genuine but still-unproven potential for cancer therapy. Whether this potential is realized depends on overcoming the manufacturing, regulatory, and evidentiary barriers described above. Without progress on those fronts, these platforms risk remaining confined to preclinical literature despite favorable pharmacokinetics. The next five years are likely to be decisive.

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