

Review Article

Nano-Engineering Strategies to Minimize Immune Side Effects in Advanced Drug Delivery: Design Principles, Platforms, and Immunological Mechanisms

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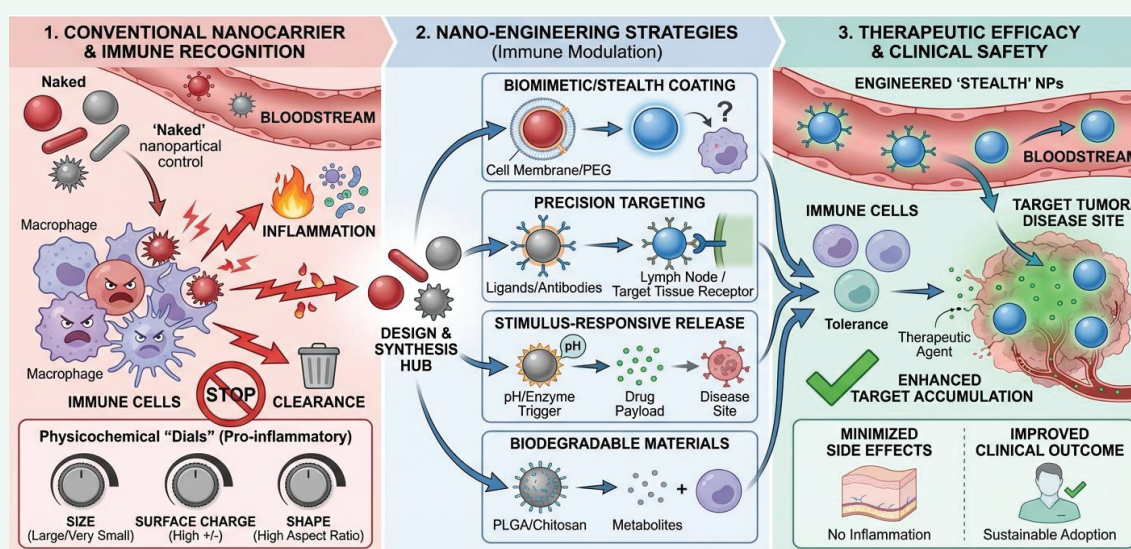
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- Nanoparticle drug delivery
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Abstract

Nano-engineered drug delivery systems promise targeted therapeutic action; however, their inherent immunogenicity presents a major roadblock to clinical safety and efficacy. Moving beyond simple biocompatibility, this review argues that immune stealth and precision targeting must be co-engineered from the first stage of nanoparticle design. We analyze how fundamental physicochemical parameters, size, surface charge, and chemical functionality, act as “immune system dials,” directing responses from benign tolerance to adverse inflammation. The article critically evaluates how advanced strategies, including biomimetic coatings, lymph node-focused delivery, and stimulus-responsive release, are being harnessed to reprogram nanoparticle-immune interactions from hostile to therapeutic. Finally, we confront the translational gap, highlighting that overcoming immunogenic side effects is not merely a technical challenge but a prerequisite for the sustainable clinical adoption of next-generation nanomedicines.



Graphical abstracts

INTRODUCTION

The types of advanced drug delivery systems include: mainly targeted drug delivery systems, controlled release systems, nanotechnology-based delivery, smart drug delivery systems, implantable delivery devices and transdermal and mucosal delivery systems [1]. Among them nanotechnology-based drug delivery systems play a crucial role in modern therapeutic strategies due to their ability to improve efficacy, precision, and safety in treating various diseases [2]. Hence, this review is specifically focused on nano-technology based drug delivery systems. While offering significant impact in the therapeutic applications, they may cause to provoke immunological side effects in the body at the same time. Hence, it's crucial to consider the minimization of those side effects, while reaching to the targets of nano-technology based drug delivery systems. Nanotechnology-based drug delivery systems interact directly with the immune system as their nanoparticles circulate throughout the body. These nanoparticles, such as FeriCipXT-coated PEGylated rutile TiO₂ NPs, are engineered for targeted and sustained drug release, but upon administration, they can be recognized as foreign by macrophages, dendritic cells, and lymphocytes of the reticuloendothelial system. This immune recognition may trigger activation of immune cells, resulting in cytokine release and antigen presentation, which can produce unwanted side effects such as inflammation, immune cell recruitment, and potential hypersensitivity or immunotoxicity. Although modifications like PEGylation aim to improve biocompatibility and reduce immunogenicity, interactions with immune cells remain a critical determinant of safety and efficacy, highlighting the need for comprehensive evaluation of nanoparticle-immune crosstalk to mitigate adverse immunological reactions [3] (Figure 1).

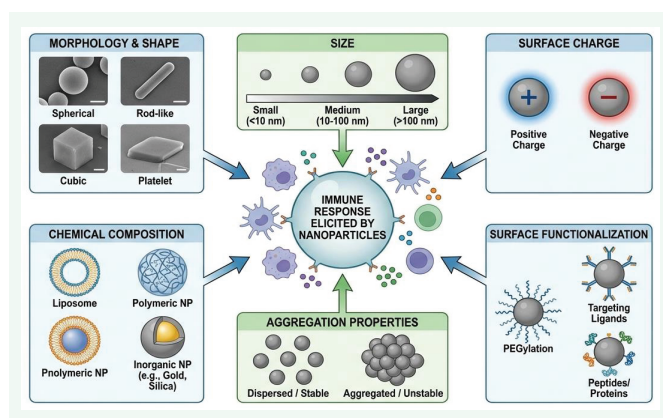


Figure 1 Schematic representation of several factors governing the immune response elicited by nanoparticles. These factors are morphology, size, shape and surface charge of nanoparticles and their chemical composition and aggregation properties [4].

However, the integration of nanotechnology in drug delivery presents new aspect to overcome challenges in immunotherapy by balancing potent activity with minimized immune side effects these strategies use for precisely control the delivery and release of drugs directly to target sites, thereby reducing the off-target immune activation that can cause adverse immune-related events. Nano drug delivery systems have shown promise in delivering immune checkpoint inhibitors (ICIs) and other anticancer agents more effectively by enhancing accumulation in tumors and preventing widespread immune activation in healthy tissues. This targeted approach helps to comfort immune system over activation, which is a key cause of side effects such as inflammation and tissue damage in organs throughout the body. Also, Nano-engineering Provide organelle-specific drug delivery within cells to further improve therapeutic outcomes and minimize toxicity [5]. So, the likelihood and severity of immune side effects depend on nanoparticle characteristics like size, material, charge, and surface functionalization [6,7]. This brings the scientist's attention towards careful designing of nano-based drug delivery systems which is crucial to minimize unwanted immune reactions and to balance therapeutic efficacy with safety. This review focuses on engineering principles and strategies aimed at minimizing immune side effects, with an emphasis on immunological mechanisms and translational challenges. Key advances in targeting antigen-presenting cells, inducing immune tolerance, and achieving tissue-specific delivery are discussed. The review also highlights emerging biomimetic and stimulus-responsive approaches to overcome current limitations [8].

DESIGN PRINCIPLES INFLUENCING IMMUNE RECOGNITION AND MECHANISM

Effective design of nanoparticle-based drug delivery systems hinges on carefully tuning several physicochemical properties such as particle size, shape, surface charge, chemical modifications, and biodegradability as mentioned before. They play a decisive role in nanomedicine performance. Adjusting these features influences performance of the nanoparticles to evade premature clearance by the immune system, and their capacity for specific cellular uptake by target immune cells [9]. Immunological mechanism involved for defense body against the foreign matters and pathogens. Mechanisms divided in to main two parts. Which are innate and adaptive. When considering nano drug delivery mainly focus on immunological mechanism. Immunological mechanisms deeply influence nano-drug delivery by controlling nanoparticle (NP) recognition, clearance, and efficacy via innate and adaptive responses. Innate

processes like opsonization and MPS uptake dominate initial clearance, while adaptive antibody formation involved limit repeat dosing. Engineering counters these for stealth and targeting [10]

Effect of Size and Shape on Nanoparticles

By controlling the size and shape of NPs, researchers can influence how the particles are distributed in the body, how they are recognized and taken up by immune cells (such as dendritic cells), and how long they circulate in the bloodstream. Smaller sizes often enhance tissue penetration and favor uptake by target immune cells, while specific shapes can increase the efficiency of cellular interaction and uptake [11]. Size and shape mainly affect for their circulation in bloodstream, internalization, and biological distribution. According to Li, Yang, and Sun's article from 2022, macrophages are primarily responsible for internalizing particles larger than 1 μm , which causes them to be quickly removed from circulation. Furthermore, the systemic use of such large particles is limited due to the substantial risks of physical obstructions, such as pulmonary embolism and blockage of small blood vessels. However, the longer circulation times and higher cellular accumulation of nanoparticles smaller than 10 nm are offset by a higher risk of toxicity because of ineffective cellular clearance and excessive intracellular retention, with particles smaller than 5 nm being particularly vulnerable. Larger particles have a greater capacity to load drugs, but their systemic applicability is limited by their tendency to cause vascular blockages. Crucially, the study finds that the ideal range of nanoparticle sizes for efficient immune modulation and tolerance induction is typically between 100 and 200 nm. Within this size range, nanoparticles can effectively target antigen-presenting cells, reduce embolic risks, and avoid the mononuclear phagocyte system's rapid clearance. This research emphasizes the significance of careful nanoparticle diameter optimization in order to balance the optimization of therapeutic efficacy and ensuring safety in immune-targeted therapies. This knowledge provides a useful foundation for the development of next-generation nanomedicines intended to treat inflammatory and autoimmune diseases [12] (Table 1) (Figure 2).

Surface Charge and Chemistry and nanocarrier types

Surface charge and chemistry are important determinants when explaining interactions of nanoparticles with the immune system, dictating solubility, stability, and, crucially, cellular uptake and activation patterns of antigen-presenting cells (APCs), particularly in dendritic cells [12-16]. Experimental evidence has shown that particles with

Table 1: Nanoparticle Size Categories and Biological Effects

Size Range	Biological Characteristics	Immune Interaction & Risk	Reference
	Very small; high intracellular retention, poor clearance	High toxicity risk due to intracellular accumulation	13,14
5 - 10 nm	Small; longer circulation, enhanced tissue penetration	Risk of toxicity remains due to ineffective clearance	4,13
10 - 100 nm	Optimal for cellular uptake and tissue penetration	Targets immune cells like dendritic cells effectively	13,15
100 - 200 nm	Ideal size range for immune modulation	Efficient uptake by antigen-presenting cells; reduced embolic risks; avoids rapid MPS clearance	4,13,15
> 1 μm	Large; rapidly internalized by macrophages	Quick removal from circulation; high risk of vascular blockages (embolism)	4,15

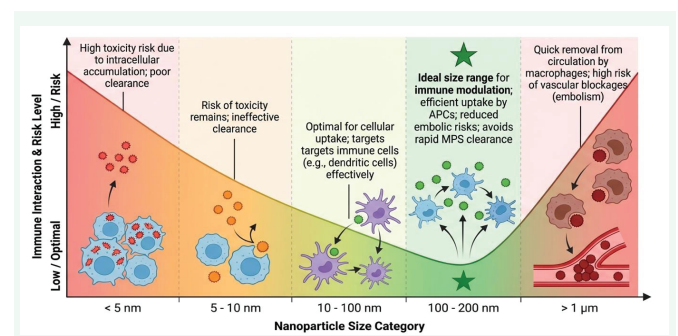


Figure 2 Nano Particle Size vs. Immune Interaction Risk

a high surface charge, whether positive or negative, tend to exhibit greater stability due to enhanced electrostatic repulsion. Positive surface charges, in particular, facilitate higher uptake by dendritic cells, which can provoke a robust Th1 immune response. For example, a study by Fromen et al., systematically compared cationic and anionic nanoparticles in pulmonary delivery and found that cationic nanoparticles were preferentially associated with both CD11b and CD103 dendritic cell subtypes, boosting chemokine production and enhancing local immune responses. This is an effective beneficial characteristic for vaccines but requiring careful modulation to avoid adverse reactions[17].

In further experimental optimizations in advanced surface modifications are focused on fine-tune those immunological responses [18]. PEGylation, for example, creates a hydrophilic steric barrier that reduces nonspecific protein adsorption and opsonization, substantially prolonging circulation and reducing rapid clearance by macrophages or the reticuloendothelial system. However, too-dense PEG coverage can reduce cellular uptake and, in some individuals, promote the formation of anti-PEG antibodies which can accentuate the need for optimized density and configuration of surface PEG

for each application [19]. Similarly, tailored hydrophobic modifications are leveraged to provide either adjuvant activity (in vaccine formulations) or, with hydrophobic peptides, to block TLR signaling for anti-inflammatory purposes. The selection and design of these moieties determine whether nanocarriers activate or evade innate immune signaling pathways, making advanced surface chemistry optimization foundational to controlling immune compatibility and pharmacokinetics [19].

Collectively, these experimental strategies highlight the complexity of surface chemistry engineering, while surface charge is an important factor, layered modifications and biomimetic designs are necessary for overcoming the full spectrum of immunological side effects associated with nanoparticle therapeutics (Table 2).

Nanocarrier is help to transport drugs or bioactive substance to target delivery while minimizing side effects. Both hydrophobic and hydrophilic drugs are acceptable. Some key advantages are highlighted according to with. Drug solubility, protect payloads from degradation, and enable controlled release, which is vital in chemotherapy and wound healing applications [20,21] (Table 3 and Figure 3).

Biocompatibility and Biodegradability

Biocompatibility and biodegradability are vital considerations in nanotechnology-based drug delivery because they directly influence the safety, efficacy, and long-term fate of administered nanomaterials. Nanoparticles should interact benignly with biological tissues, avoid provoking chronic immune activation, and degrade into harmless byproducts for clearance, thereby minimizing side effects such as persistent inflammation or toxicity. Lack of biocompatibility can result in unwanted immune

responses such as activation of complement pathways or macrophage infiltration. And also, non-biodegradable particles risk accumulation in organs, leading to chronic pathological outcomes. Regulators require stringent cytotoxicity, immunotoxicity, and biodegradation profiling before clinical translation to ensure these risks are mitigated.

Recent advances have addressed these barriers by developing nanocarriers from natural and synthetic polymers, such as poly (lactide-co-glycolide) (PLGA), chitosan, and gelatin, which exhibit excellent biocompatibility and controlled biodegradability. For example, in chitosan/PLGA hybrid nanoparticles, the

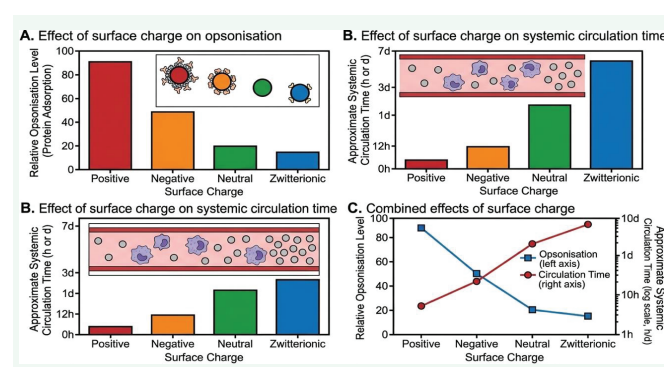


Figure 3 Influence of nanoparticle surface charge on opsonisation and systemic circulation. (A) Effect of surface charge on opsonisation. Positively charged nanoparticles exhibit high levels of opsonisation, whereas neutral and zwitterionic surfaces show reduced protein adsorption, indicating lower immune recognition. (B) Effect of surface charge on systemic circulation time. Neutral and zwitterionic nanoparticles display prolonged circulation, while positively charged nanoparticles are rapidly cleared from the bloodstream. (C) Combined effects of nanoparticle surface charge on opsonisation and circulation time. Relative opsonisation levels (left y-axis) and approximate systemic circulation times (right y-axis, logarithmic scale) are plotted as a function of surface charge. Neutral and zwitterionic nanoparticles demonstrate reduced opsonisation and extended circulation, consistent with enhanced immune evasion.

Table 2: Surface Charge-Dependent Nanoparticle Immune-Evasion Profiles

Charge Type	Opsonization	Circulation Time	Immune Activation	Key Mechanism	Reference
Positive	High	Short (~2-6h)	Th1 high (IFN- γ)	Electrostatic cell binding	11,15
Neutral	Low	Extended (~1-3d)	Tolerance favored	Minimal protein corona	17
Negative	Moderate	Moderate (~12h)	Complement (C3) risk	Minimal protein coronaV3	15
Zwitterionic	Minimal	Longest (~5-7d)	Stealth optimal	Hydration layer shielding	18

Table 3: Nanocarrier types and applications

Type	Description	Size Range	Examples	Reference
Lipid-based	Vesicular structures from phospholipids; versatile for aqueous or lipid-soluble drugs	80-300 nm	Liposomes, micelles	20
Polymeric	Synthetic or natural polymers; biodegradable options available for sustained release	10-100 nm	Nanoparticles, conjugates	20
Dendrimers	Highly branched, monodisperse structures with a core, branches, and surface groups	1-10 nm	PAMAM dendrimers	20
Carbon-based	Highly branched, monodisperse structures with a core, branches, and surface groups	1-100 nm	Nanotubes, fullerenes	20,21
Metallic/inorganic	Highly branched, monodisperse structures with a core, branches, and surface groups	1-100 nm	Gold nanoparticles, silica (e.g., MCM-41)	20,21

chitosan component can confer mucoadhesion and enhanced cellular uptake, while the PLGA core provides controlled release and structural stability, all within a biocompatible, biodegradable framework [22]. In one study, PEGylated L-arginine modified iron oxide nanoparticles (PEG-Arg@IONPs) were administered in mice and monitored by MRI, and were found to exhibit low long-term accumulation, good clearance (especially via kidney routes), and negligible histopathological damage in major organs over the study period [23]. Similarly, other biodegradable iron oxide nanoparticle constructs have been demonstrated in vivo to act as safe imaging agents, showing both biodegradation and acceptable biocompatibility profiles [24]. Therefore, adding biocompatibility and biodegradability to drug carrier systems reduces the likelihood of long-term immune system disruption, reduces off-target effects, and aids in the creation of next-generation therapies that improve patient outcomes (Table 4).

Passive and Active Engineering Approaches

Nanoparticle targeting improves delivery efficiency primarily by enhancing the concentration of therapeutic agents at specific sites while reducing systemic exposure also minimize side effects. This is achieved through two main mechanisms, which is active and passive.

Passive Targeting of Nanoparticles: This method involved to passively diffuse in the body to reach the target organ tissues by integrating the therapeutic agent [25]. Passive targeting mainly exploits the increased permeability and retention (EPR) effect present in pathological tissues ex: tumors or sites of inflammation. Providing nanoparticles to accumulate selectively and minimize off-target immune reactions and toxicity. This approach offers advantages such as extended nanocarrier half-life, improved bioavailability, selective accumulation, and simplified manufacturing but depends heavily on individual physiological factors and tends to have non-specific distribution [26]. When considering nanoparticle characteristics is influence for passive targeting. Passive targeting mostly achieved by diffusion transport. Particle size is highly involved for this method. Optimal size is 20nm to 200nm. additionally smaller lipid nanoparticles benefit from prolonged circulation and its enhanced accumulation in target tissues.

Tuning the lipid composition of nanoparticles is contribute in controlling parameters essential for passive targeting Which are size, surface characteristics, and stability. This enables selective accumulation in diseased tissue via the EPR effect while minimizing immune clearance and systemic side effects, making lipid composition a fundamental aspect of effective passive nano-engineered drug delivery systems [27]. Other fact is Surface characteristics, which is critically involved in passive targeting of nanoparticles (NPs) by influencing their circulation time, bio distribution, and interaction with biological barriers. The main aspects includes are Surface charge, Surface Hydrophilicity and Surface Coatings and Polymers. Together, these surface characteristics modulate the nanoparticle's ability to evade immune clearance, extend circulation time, and passively accumulate in target tissues with pathological features such as leaky vasculature and impaired lymphatic drainage. Modulating these properties is fundamental for achieving efficient passive targeting with minimal immune side effects.

Active Targeting: By using this method nanoparticle targeting involves incorporating targeting elements. Mainly divided into antibody-based targeting, peptide-based targeting, aptamer-based targeting, and small-molecule-based targeting. By using this strategy aim is nanoparticles specifically to cells, tissues, or organs by exploiting unique physiological or pathological features of the target area. Once the nanoparticles reach their target region and, they can interact specifically with target cells, provide the targeted delivery of drugs, genes, or other therapeutic agents encapsulated in the Nano particles.

This approach aims to improve treatment efficacy and specificity while minimizing adverse effects on surrounding healthy tissue [27]. Targeted lipid nanoparticles can be generated through a one-pot assembly process or by post-insertion process. In practice, active targeting assemblies are tailored to balance ligand stability, targeting efficiency, and manufacturability. By optimizing these assembly strategies, nanoparticles are achieve precise receptor binding and that increased drug delivery with reducing off-target effects and immune reactions. Thus, active targeting assembly methods revolve around the timing

Table 4: Comparison of Biodegradable Polymers for Immunocompatible Nano medicines

Material	Degradation Time	Immune Profile	Applications	Clearance Route	Reference
PLGA	4-12 weeks	Minimal	Sustained chemo	Renal/hepatic	19
Chitosan	2-8 weeks	Anti-inflammatory	Oral/mucosal	GI/renal	19
Gelatin	1-4 weeks	Cell-mimetic	Vaccines	Proteolytic	20,21
PCL	6-24 months	Inert	Implants	Slower hydrolysis	20,21

and chemistry of ligand attachment direct conjugation during synthesis, post-insertion after synthesis, or one-pot co-assembly all designed to maximize targeting specificity and also functional surface properties of nanoparticles

TARGETING LYMPH NODES AND DEEP TISSUES

Lymph Nodes one of most important organ which help to presentation and adaptive immune activation by using various immune related Cells such as B cells and T cells. When design Nanoparticles for lymph node targeting generally Consider controlled size, surface charge, and functionalization those key strategies are optimize lymphatic uptake and cell-specific delivery. Targeting lymph nodes and deep tissues are using nano-engineered drug delivery systems that help for tailoring nanoparticles to efficiently migrate and accumulate in lymphatic vessels and lymph nodes, where immune responses are coordinated [28]. A drug release system by controlled release allows targeted drug release, sustained or triggered drug release, and combined release of drug combinations. This helps to develop safer and more effective treatments by reducing side effects and improving pharmacokinetics and drug circulation half-life. Also, these systems can also prevent the degradation and excretion of therapeutic molecules, thereby, External stimulation from the outside of the cell can also be used to trigger the release of bioactive molecules reducing the dose. Nanostructures can be use customized to respond to different stimuli that lead to drug release. The different characteristics of tumor cell microenvironment make it an ideal trigger for controlled drug release [29] (Figure 4).

CARPA AND INFLAMMASOME ACTIVATION IN PEGYLATED NANO CARRIERS

Nano-engineering approaches focus on CARPA and inflammasome activation within PEGylated nanocarriers to reduce immune-related side effects, which complements on drug delivery biocompatibility. CARPA associated with PEG leads to the binding of anti-PEG IgM to C1q, resulting

in the release of anaphylatoxin [30]. Strategies to mitigate this include using branched or shorter PEG (like PEG600 compared to PEG2000), maintaining a low density (under 5 mol%), and utilizing flexible anchors such as CHOL-PEG instead of DSPE-PEG to lower complement opsonization. Administering empty liposomes beforehand can promote tolerance, while the ABC phenomenon can be avoided through proper spacing of doses. The NLRP3 activation caused by PEG nanoparticles is a result of reactive oxygen species (ROS), lysosomal damage, and potassium (K⁺) efflux; nano-engineering methods incorporate ROS-scavenging antioxidants (for example, COL-loaded VHPK-PLGA), metal nanocrystals (such as NiCo that inhibits Neat1 transcription), or PEG substitutes like polysarcosine to hinder priming and assembly. PEG liposomes targeted with folate can effectively deliver anti-inflammatory drugs directly to FR- β + macrophages. Combining stealth features (such as zwitterionic coatings) with targeting ligands results in hybrid designs [31]

Nano-engineering strategies target anti-PEG antibodies to reduce immune side effects like accelerated blood clearance (ABC) and hypersensitivity in PEGylated drug delivery systems. That approaches modify nanoparticle surfaces or structures to evade pre-existing or induced APAs while preserving stealth properties and targeting [31] (Table 5).

Clinical Translation Challenges and comparing nanocarriers by immune compatibility

Clinically important nano-engineered platforms which are mRNA-loaded lipid nanoparticles (LNPs), antibody-drug conjugate (ADC) hybrids, and exosome-based systems.

mRNA-loaded lipid nanoparticles (LNPs)

LNPs is consisted by main four lipids. Which are ionizable cationic lipids, helper phospholipids, cholesterol, and PEGylated lipids. LNPs protect mRNA from RNases and immune clearance via encapsulation and PEG shielding during circulation. In this mechanism enter cells via endocytosis and endosomal acidification protonates ionizable lipids, promoting membrane disruption for cytosolic mRNA release and ribosomal translation. According to nano engineering strategies include iterative ionizable lipid design for muscle-selective delivery (pKa 6.6-6.9 optimal) and surface ligands for T-cell transfection [32].

Antibody-drug conjugate hybrids

Antibody-drug conjugate (ADC) consist in integrate monoclonal antibodies with nanoparticles which involved enhance payload capacity, targeting precision, and

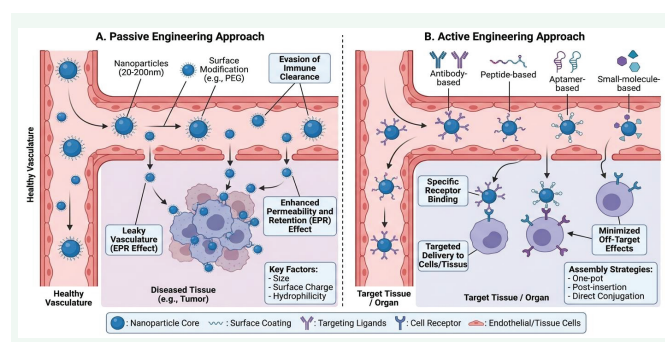


Figure 4 Passive and active engineering approaches for nanoparticle targeting.

Table 5: Key strategies table of PEG antibody

Strategy	Mechanism	Immune Benefit	Example	Reference
Branched/Y-PEG	Alters antigenicity, evades IgM binding	Reduces ABC/CARPA by 70-90%	DSPE-PEG2k branches	30,31
Brush Polymers	High-density short chains block recognition	Lowers repeated-dose clearance	BPL-LNPs vs. DMG-PEG	30
Mixed PEG Lengths	Dense "mushroom" to brush transition	Minimizes immunogenicity	PEG2000 + PEG550	30,31
Cleavable PEG	Enzyme/acid shedding post-circulation	Avoids chronic exposure	pH-responsive	31
Alternative Polymers	Replaces PEG entirely	No anti-PEG response	Polysarcosine, polyoxazoline	31
Immunomodulation	Depletes B cells or tolerizes	Suppresses new Ab formation	CD22-ligands	30,31

controlled release beyond traditional ADCs. By Antibodies bind tumor antigens and triggering receptor-mediated endocytosis of the nanoparticle. Intracellular, stimuli-responsive linkers and release payloads. LNPs fuse with endosomes to cytosolic delivery. ANCs boost efficacy via higher DAR (>100) and EPR-enhanced penetration, and reduced off-target toxicity while compared to ADCs. Antibody–drug conjugate (ADC) hybrids, or antibody-nanoparticle conjugates (ANCs), leverage nano-engineering to fuse antibody specificity with nanoparticle versatility for superior drug delivery strategies. These platforms had overcome traditional ADC constraints as limited drug-antibody ratios (DAR <10) by achieving DARs of 10^2 – 10^6 via high-capacity nanocarriers [33].

Exosome-based drug delivery systems

Exosome-based drug delivery systems involved to harness natural extracellular vesicles (30-150 nm) as biocompatible nano-engineered carriers for therapeutics like siRNA, miRNA, proteins, and chemotherapeutics. That's endogenous origin confers low immunogenicity, BBB penetration, and efficient cellular uptake, surpassing synthetic nanoparticles. Engineered exosomes bind target receptors via surface ligands, triggering clathrin-independent endocytosis or macropinocytosis; lipid raft interactions facilitate membrane fusion to direct cytosolic release. Post-uptake endosomal release occurs via pH-responsive fusion (exosomal phosphatidylserine flips), bypassing lysosomes; multivalent ligands amplify avidity by 5-10x. Hybrid exosomes with LNPs increase escape through ionizable lipid protonation at pH 5-6 [34] (Table 6).

Table 6: Comparing Nanocarriers by immune compatibility

Nanocarrier Type	Immune Compatibility	Clearance Mechanism	Key Strategies/Reference
Lipid (LNPs, Liposomes)	Moderate	Liver/spleen MPS (Kupffer cells); fast for cationic, slower neutral/PEGylated	Ionizable lipids, short/branched PEG, <100 nm soft particles ³⁵ .
Polymeric (PLGA, Chitosan)	High biocompatibility, biodegradable; low cytokine induction	Renal if <10 nm, else MPS; intermediate for anionic	Zwitterionic/PEG alternatives, ligand spacing control pubs ³⁶ .
Inorganic (Gold, Silica)	Lower activation. Size-tuned improves	Rapid phagocytosis if cationic/stiff; evaded by soft/small	Antioxidant coatings, negative zeta ³⁷ .
Exosomes	Excellent	Slow MPS evasion via membrane proteins; homotypic targeting	Surface ligands, hybrid with LNPs ³⁷ .
ADCs/Hybrids	High specificity, minimal systemic inflammation	Protease-mediated release; low off-target	Site-specific conjugation, cleavable linkers ³⁶ .

Ligand-induced Immune Activation and Receptor Down Regulation

Ligand induced immune activation and receptor downregulation in nano engineered drug delivery systems refer to two complementary mechanisms which are surface ligands on nanoparticles to either trigger immune responses or to repeatedly engage cell surface receptors so that they are internalized and downregulated, thereby modulating signaling and cell behavior [38]. While considering ligand induced immune activation Nano carriers can be decorated with ligands that bind to receptors on dendritic cells or macrophages, leading to receptor clustering, downstream signaling, cytokine production, and enhanced antigen presentation or T cell activation. Additionally, In cancer immunotherapy, TLR activating nanoparticles are designed to co deliver immune stimulants so that dendritic cells become more immunogenic while the particle accumulates in the tumor, synergizing with checkpoint targeting payloads [39].

Frequent or intense ligand-receptor interactions on nano-engineered carriers can promote receptor internalization and degradation, thereby decreasing the quantity of receptors on the cell membrane—an approach commonly utilized for immune monitoring modulation. For instance, nanoparticles with anti CD47 or anti PD L1 ligands can aggregate these checkpoints on tumor cells or T cells, facilitating their uptake and reduction, which suppresses signals and boosts antitumor immunity.

Incorporation within nanoscale engineered delivery systems. Conversely, the same carrier can concurrently provide a ligand that triggers an immune receptor and a small molecule or oligonucleotide payload that

inhibits inhibitory receptors like CD47 or PD-L1, thus accomplishing both dual immune activation and receptor downregulation. Thoughtful design of ligand concentration, linker chemistry, and material properties guarantees that the particle remains in circulation for an adequate duration, targets the appropriate tissue, and interacts with its targets in a regulated manner to prevent undue inflammation or cytokine storms while effectively providing therapeutic immune modulation [40].

CONCLUSION

This review underscores that minimizing side effects is not achieved through inertness alone, but through the intelligent design of nanoparticles that actively manage their immunological footprint. The optimal size, charge, and surface chemistry function as a coordinated “passport” that can evade immune surveillance, gain entry to specific tissues, and deliver their cargo with minimal collateral activation. Emerging bio-inspired and smart systems represent a paradigm shift, moving from passive carriers to active participants in immune communication. Nevertheless, the path from sophisticated design to patient bedside remains fraught with challenges. The very properties that ensure functionality, such as novel coatings or complex targeting ligands, can introduce new immunogenic risks. Therefore, future innovation must be guided by a predictive immunology framework, where long-term immune compatibility is a primary design criterion, not an afterthought. Ultimately, the success of nano-delivery platforms will be measured not just by their drug-loading capacity, but by their ability to operate within the complex immune landscape unnoticed, unharmed, and unharmed.

FUTURE DIRECTIONS

Advancing the field requires focused innovation in several key areas to enhance precision, safety, and multifunctionality. Future work must prioritize Precision and Personalized Nanomedicine, tailoring nanoparticle designs to individual patient profiles and disease biomarkers. Concurrently, the development of Stimuli-Responsive and Smart Systems, carriers that release drugs in response to specific pathological triggers like pH, enzymes, or redox state, is essential. Furthermore, innovation is needed in Combination and Co-Delivery Platforms to engineer multifunctional systems capable of delivering synergistic drug combinations or theranostic agents. A major frontier remains Crossing Biological Barriers, requiring new strategies to overcome obstacles such as the blood-brain barrier, mucosal layers, and dense tumor stroma. Finally, achieving Sustainable and Scalable Manufacturing is imperative to establish robust,

reproducible, and cost-effective production processes for clinical translation and commercial viability. Addressing these priorities through interdisciplinary collaboration will be crucial for realizing the full therapeutic potential of nanotechnology while ensuring patient safety.

CRedit Authorship Contribution Statement

Prabudda wijerathna: Writing – original draft, Investigation, Formal analysis, Visualization, Data curation, Conceptualization. Sarvananda L: Visualization, Writing – review & editing, Conceptualization. Amal D. Premarathna: Validation, Supervision, Writing – review & editing, Conceptualization.

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