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NEXT-GENERATION NANO-DRUG DELIVERY SYSTEMS FOR CANCER IMMUNOTHERAPY: BRIDGING INNOVATION AND CLINICAL TRANSLATION

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ABSTRACT

Background: Cancer immunotherapy, including checkpoint inhibitors and CAR-T cell therapies, has transformed oncology. However, systemic toxicity, poor tumor penetration, immunosuppressive tumor microenvironment, and limited response rates of 20–40% in solid tumors continue to restrict therapeutic success. Nanotechnology-based drug delivery systems offer a promising avenue to overcome these limitations through targeted delivery, controlled release, and co-loading of multiple therapeutic agents. **Objectives:** This review aims to comprehensively examine recent advances in nano-drug delivery platforms for cancer immunotherapy, evaluate their mechanisms of tumor targeting and immune modulation, assess progress in clinical translation, and identify key challenges and future directions in the field. **Methods:** A systematic review of published literature was conducted covering lipid nanoparticles, biomimetic nanoparticles, stimuli-responsive carriers, polymeric and inorganic nanoplatforms, and their applications in checkpoint inhibitor delivery, cancer vaccines, tumor microenvironment modulation, and

immunogenic cell death induction. Clinical trial data, FDA-approved nanomedicines, and regulatory frameworks were also analyzed. **Key findings:** Lipid nanoparticles, particularly ionizable LNP-mRNA systems validated by COVID-19 vaccines, have demonstrated strong clinical potential for personalized neoantigen vaccines and cytokine delivery, with Moderna's mRNA-4157 showing promising Phase II results in melanoma. Biomimetic nanoparticles utilizing cancer cell, macrophage, and platelet membranes exploit homotypic targeting and immune evasion but face significant standardization and manufacturing challenges. Stimuli-responsive systems exploiting tumor pH, matrix metalloproteinases, redox gradients, and external triggers such as near-infrared light and magnetic fields enable selective intratumoral drug release with reduced systemic toxicity. Several nanomedicines including Doxil, Abraxane, Onivyde, and Vyxeos have achieved FDA approval, validating the clinical feasibility of the nanomedicine approach. Active and passive targeting strategies, when combined, demonstrate superior efficacy over either mechanism alone. Artificial intelligence and multi-omics integration are emerging as powerful tools for nanoparticle design optimization and patient stratification. **Challenges:** Critical barriers to clinical translation include heterogeneity of the enhanced permeability and retention effect across patients and tumor types, manufacturing scalability and batch-to-batch reproducibility, high production costs particularly for personalized nanovaccines, anti-PEG antibody development, complement activation-related pseudoallergy, and evolving regulatory pathways for biomimetic and hybrid nanoplatforms. **Conclusions:** Nanotechnology holds significant potential to enhance cancer immunotherapy outcomes, particularly for difficult-to-treat solid tumors. Realizing this potential requires interdisciplinary collaboration, rigorous clinical validation, standardized manufacturing processes, and biomarker-driven patient selection. The convergence of nanomedicine, immunotherapy, and personalized medicine may ultimately enable curative outcomes in metastatic cancers.

KEYWORDS: Nanomedicine, Cancer Immunotherapy, Lipid Nanoparticles, Biomimetic Nanoparticles, Tumor Microenvironment, Checkpoint Inhibitors, Personalized Nanovaccines, Stimuli-Responsive Delivery, Clinical Translation.

1. INTRODUCTION

1.1 The Promise and Limitations of Cancer Immunotherapy

The landscape of cancer treatment has undergone dramatic transformation with the advent of immunotherapy. Checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 have

demonstrated remarkable success in melanoma, lung cancer, and other malignancies.[1] Similarly, CAR-T cell therapies have achieved unprecedented response rates in hematologic cancers.[2] Despite these breakthroughs, most patients with solid tumors do not benefit from current immunotherapies, with response rates typically ranging from 20-40%.[3]

Several factors limit immunotherapy efficacy. Systemic administration often causes immune-related adverse events affecting multiple organ systems.[4] Poor penetration into solid tumors prevents therapeutic concentrations from reaching cancer cells.[5] The immunosuppressive tumor microenvironment (TME) actively suppresses immune responses through regulatory cells and inhibitory cytokines.[6] Additionally, therapeutic resistance develops through multiple mechanisms including loss of antigen presentation and upregulation of alternative immune checkpoints.[7]

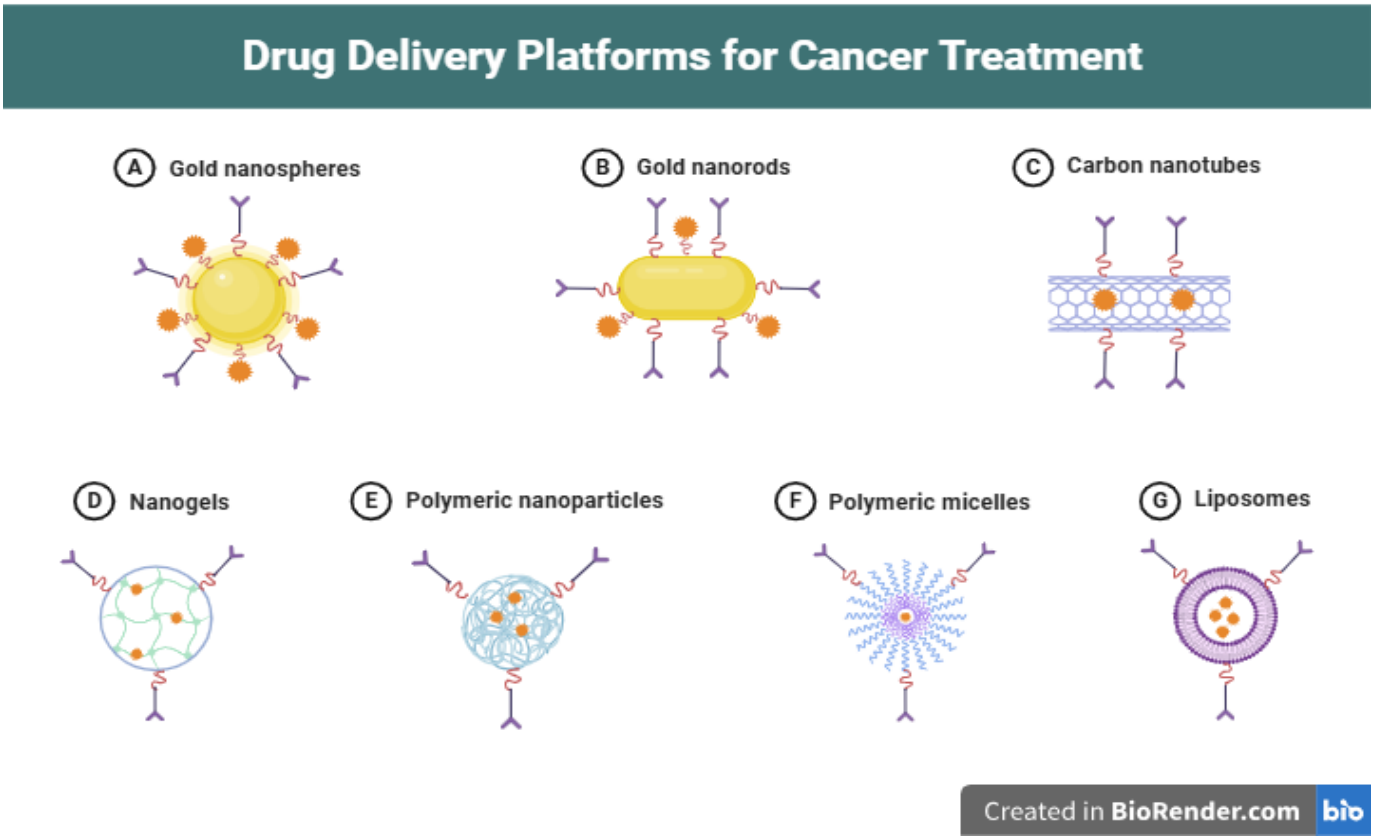
1.2 Nanotechnology as a Transformative Solution

Nanoparticle-based drug delivery systems address many limitations of conventional immunotherapy. These nanoscale carriers, typically ranging from 10–200 nm, can improve pharmacokinetics and biodistribution profiles.[8] Targeted delivery reduces off-target toxicity while increasing therapeutic concentrations at tumor sites.[9] Nanoparticles enable co-delivery of multiple agents, allowing synergistic combinations of immunotherapy with chemotherapy or other modalities.[10] Stimuli-responsive systems can release drugs specifically within the TME in response to pH, enzymes, or other triggers.[11]

The success of lipid nanoparticle (LNP)-based mRNA vaccines for COVID-19 has validated the clinical potential of nanomedicine and accelerated development of similar platforms for cancer therapy.[12] This review focuses on recent advances in nano-delivery systems for cancer immunotherapy, emphasizing mechanisms, applications, and pathways toward clinical translation.

2. FUNDAMENTALS OF NANO-DRUG DELIVERY

2.1 Diversity of Nanoplatforms for Cancer Immunotherapy



The arsenal of nanoscale drug carriers available for cancer immunotherapy has expanded considerably over the past decade. Each platform brings distinct structural features and functional capabilities that can be matched to specific therapeutic requirements. Understanding these differences helps researchers select the most appropriate carrier for their intended application.

Gold nanospheres have garnered attention due to their unique plasmonic properties, which enable both diagnostic imaging and therapeutic heating when exposed to specific wavelengths of light.[13] These spherical particles can be synthesized with precise size control, and their surfaces readily accommodate various targeting molecules through gold-thiol chemistry.[14] Gold nanorods extend these capabilities by offering tunable optical absorption based on their aspect ratio, allowing customization for different tissue depth.[15]

Carbon nanotubes represent a fundamentally different structural paradigm. These cylindrical nanostructures possess exceptional mechanical strength and the ability to penetrate cellular membranes more readily than spherical particles.[16] Their high aspect ratio and large surface

area permit substantial drug loading, while functionalization of the sidewalls enables aqueous dispersion and targeted delivery.[17] However, concerns about long-term biodegradability have tempered enthusiasm for clinical applications.[18]

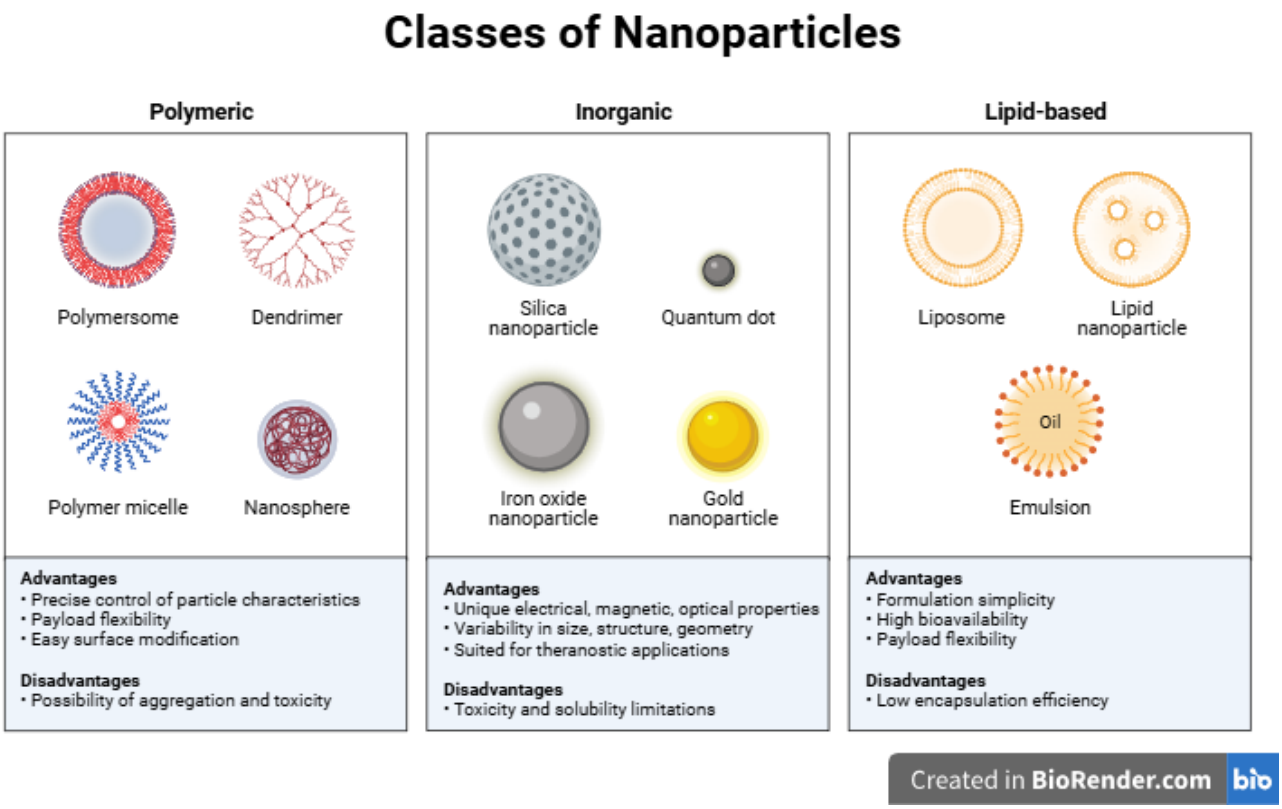
Nanogels occupy a middle ground between solid nanoparticles and molecular therapeutics. These crosslinked polymer networks swell in aqueous environments, creating a hydrogel matrix at the nanoscale.[19] The gel structure protects encapsulated biologics from degradation while allowing responsive swelling or shrinking based on environmental triggers like pH or temperature.[20] This responsiveness makes nanogels particularly suitable for site-specific drug release.[21]

Polymeric nanoparticles manufactured from biodegradable polymers offer predictable degradation kinetics that can be engineered by adjusting polymer composition and molecular weight.[22] As the polymer matrix gradually hydrolyzes, encapsulated drugs release in a controlled manner over hours to weeks.[23] This sustained release reduces dosing frequency and maintains therapeutic concentrations.[24]

Polymeric micelles form spontaneously when amphiphilic block copolymers encounter aqueous environments.[25] The hydrophobic blocks collapse inward, creating a core that solubilizes poorly water-soluble drugs, while hydrophilic blocks extend outward to interface with biological fluids.[26] This core-shell architecture has proven especially valuable for delivering chemotherapeutic agents with limited aqueous solubility.[27]

Liposomes remain the most clinically successful nanoplatform, with numerous FDA-approved formulations demonstrating safety across diverse patient populations.[28] These vesicular structures composed of phospholipid bilayers closely resemble cell membranes, contributing to their biocompatibility.[29] Both hydrophilic drugs in the aqueous core and hydrophobic drugs within the lipid bilayer can be accommodated.[30] Surface modification with polyethylene glycol extends circulation time by reducing recognition by the immune system.[31]

2.2 Classification of Nanoparticle Platforms



A systematic classification of nanoparticles reveals three major categories, each encompassing multiple specific platforms with shared characteristics but distinct applications.

Polymeric nanoparticles demonstrate remarkable versatility in both structure and function. Polymersomes consist of amphiphilic block copolymers that self-assemble into vesicles with thick membranes capable of embedding membrane proteins.[32] Dendrimers feature precisely branched architecture emanating from a central core, with each generation of branching creating new surface groups for drug attachment or targeting ligand conjugation.[33] Polymer micelles leverage amphiphilicity to create nanoscale micelles with drug-loaded cores.[34] Nanospheres represent dense polymer matrices where drugs distribute throughout the particle volume.[35]

The primary advantage of polymeric systems lies in precise control over particle characteristics through polymer selection and formulation parameters.[36] Payload flexibility accommodates diverse drug types, from small molecules to proteins and nucleic acids.[37] Surface modification proceeds readily through chemical conjugation or physical adsorption.[38] The main disadvantages include potential aggregation during storage and concerns about toxicity from polymer degradation products, particularly acidic byproducts

from PLGA.[39]

Inorganic nanoparticles bring unique physical properties unavailable from organic materials. Silica nanoparticles can be synthesized with ordered mesoporous structures that maximize drug loading capacity.[40] Quantum dots exhibit size-dependent fluorescence useful for tracking and imaging.[41] Iron oxide nanoparticles respond to magnetic fields, enabling both guided delivery and hyperthermic therapy.[42] Gold nanoparticles convert absorbed light into heat with exceptional efficiency.[43]

These inorganic platforms offer distinctive electrical, magnetic, and optical characteristics that enable theranostic applications combining therapy and diagnostics.[44] Variability in size, structure, and geometry can be precisely controlled during synthesis.[45] Suitability for theranostic applications represents a key advantage over purely therapeutic platforms.[46] However, the non-biodegradable nature of most inorganic materials raises questions about long-term safety.[47] Toxicity concerns and solubility limitations have slowed clinical translation.[48]

Lipid-based nanoparticles leverage naturally occurring or synthetic lipids to create biocompatible delivery systems. Liposomes feature one or more concentric phospholipid bilayers surrounding aqueous compartments.[49] Lipid nanoparticles for mRNA delivery use ionizable lipids that become cationic at acidic pH, facilitating endosomal escape.[50] Oil emulsions consist of lipid droplets stabilized by surfactants.[51] Solid lipid nanoparticles replace liquid oils with solid lipids, improving stability. [52]

Exceptional biocompatibility stems from the similarity between these carriers and natural membranes.[53] High bioavailability results from multiple uptake mechanisms including fusion with cell membranes.[54] Payload flexibility extends to hydrophobic drugs in lipid phases and hydrophilic drugs in aqueous compartments.[55] The primary limitation involves relatively low encapsulation efficiency for certain therapeutic molecules, requiring optimization of lipid composition and drug-to-lipid ratios.[56]

Table 1: Comparison of Nanoparticle Platforms for Cancer Immunotherapy.

Platform Type	Key Advantages	Major Limitations	Clinical Status	Representative Examples	Ref
Lipid Nanoparticles (LNPs)	High mRNA encapsulation efficiency; Efficient endosomal escape; Established manufacturing processes; Clinical validation from COVID-19 vaccines	Predominant liver accumulation; Cold storage requirements Anti-PEG antibody development; High manufacturing cost	Phase II/III trials ongoing	mRNA-4157 personalized neoantigen vaccine (Moderna); BNT142 bispecific antibody mRNA (BioNTech); IL-12 encoding mRNA LNPs	[28-30, 33, 38, 42]
Liposomes	Excellent biocompatibility; Multiple FDA-approved formulations; Versatile cargo loading capacity; Well-characterized pharmacokinetics	Rapid clearance by RES; Variable EPR effect in patients; Limited deep tumor penetration; Batch-to-batch variability	FDA approved (Doxil, Onivyde, Vyxeos)	Doxil (PEGylated liposomal doxorubicin); ThermoDox (thermosensitive); Onivyde (liposomal irinotecan)	[13, 123, 125, 126, 128]
Polymeric NPs (PLGA)	Controlled drug release kinetics; Biodegradable and biocompatible; Tunable physicochemical properties; Co-delivery of multiple agents	Acidic degradation byproducts; Limited hydrophobic drug loading; Complex manufacturing scale-up; Sterilization challenges	Preclinical to early Phase I/II	PLGA-PEG nanovaccine carriers; BIND-014 PSMA-targeted docetaxel; Combination chemotherapy NPs	[14, 136, 137]
Cancer Cell Membrane-Coated NPs	Homotypic tumor targeting; Immune system evasion; Preservation of natural biomarkers; Reduced immunogenicity	Source cell availability and standardization; Complex characterization requirements; Manufacturing scalability issues; Unclear regulatory pathway	Preclinical studies	CCM-NPs for photothermal therapy; Hybrid membrane coating systems; Cancer vaccine platforms	[47-53, 59-62]
Immune Cell Membrane-Coated NPs	Inflammation-targeting (macrophage membranes); Natural tumor homing (neutrophil membranes);	Complex membrane isolation procedures; Stringent quality control needs; Limited membrane	Preclinical studies	Macrophage membrane-NPs for TAM reprogramming; Platelet membrane-NPs for CTC capture;	[54-58, 59-62]

	Enhanced TME infiltration; Functional protein retention	yield per batch; Long-term storage stability concerns		T cell membrane-coated systems	
Inorganic NPs (Gold, Iron Oxide)	Multimodal imaging capabilities; Excellent photothermal conversion; Magnetic field guidance; High structural stability	Non-biodegradable materials; Long-term toxicity uncertainties; Reticuloendothelial system accumulation; Limited clinical translation success	Early Phase I/II trials	AuroShell gold nanoshells; Ferumoxytol iron oxide NPs; Gold-photosensitizer conjugates	[15, 75, 146, 147]
Stimuli-Responsive Systems	Tumor microenvironment-selective drug release; Significantly reduced systemic toxicity; Multiple triggering mechanisms available; Enhanced therapeutic specificity	Complex multi-step synthesis; Variability in trigger responsiveness; Incomplete cargo release; Manufacturing standardization challenges	Preclinical to Phase I	pH-responsive polymeric micelles; MMP-cleavable peptide linker NPs; NIR light-triggered systems	[11, 63-76]

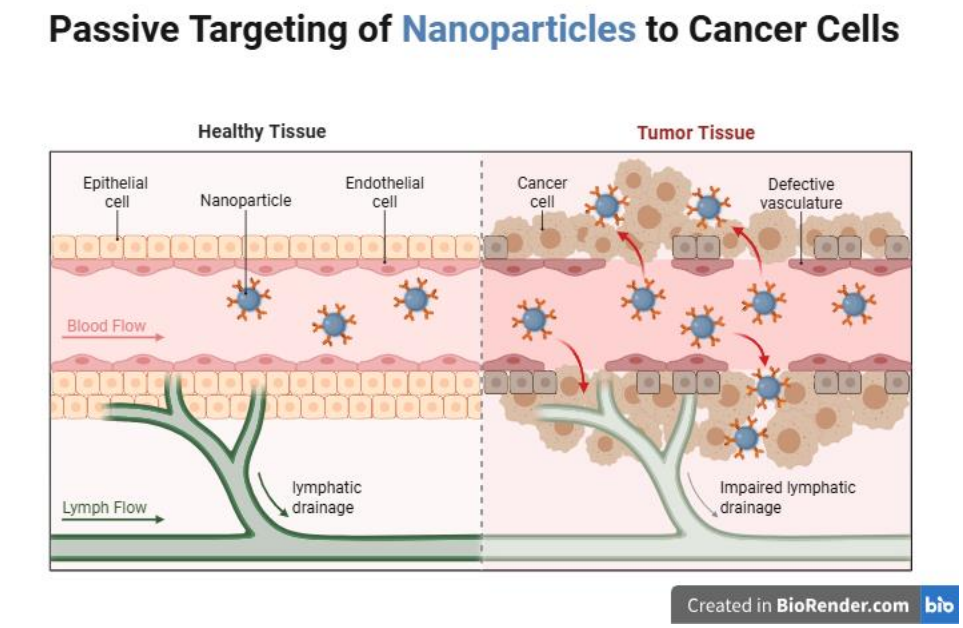
2.3 Key Physicochemical Properties

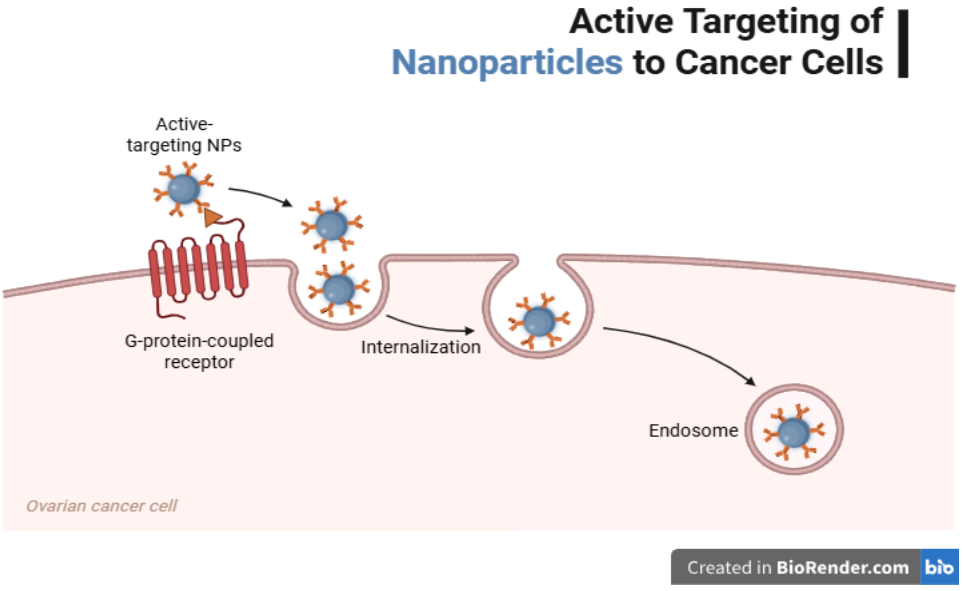
Successful nano-delivery requires careful optimization of physicochemical properties. Particle size influences biodistribution, with dimensions between 10–200 nm generally favoring tumor accumulation while avoiding rapid renal clearance.[57] Surface modification with polyethylene glycol (PEG) reduces protein adsorption and extends circulation time, though anti-PEG antibodies can develop with repeated dosing.[58] Drug loading capacity and stability during storage and circulation are critical for clinical translation.[59]

2.4 Biological Barriers

Nanoparticles must overcome multiple barriers to reach target cells. In circulation, protein corona formation alters surface properties and can trigger clearance by the mononuclear phagocyte system.[60] The dense extracellular matrix and abnormal vasculature in tumors impede nanoparticle penetration.[61] High interstitial fluid pressure within tumors opposes convective transport from blood vessels.[62] At the cellular level, endosomal entrapment and drug efflux pumps reduce therapeutic efficacy.[63]

2.5 Targeting Mechanisms for Tumor Delivery





Effective delivery of therapeutic nanoparticles to tumor sites requires exploiting the unique biology of cancer while navigating the defensive barriers erected by healthy tissues. Two complementary approaches have emerged, each capitalizing on different aspects of tumor pathophysiology.

Passive targeting relies fundamentally on the structural and functional abnormalities that characterize tumor vasculature and lymphatic drainage. In healthy tissues, endothelial cells form continuous, tightly joined barriers that restrict passage of particles larger than a few

nanometers.[64] Well-organized lymphatic vessels efficiently drain any materials that escape into interstitial spaces, returning them to circulation.[65] This tight regulation prevents accumulation of foreign materials in normal organs.

Tumors present a starkly contrasting microanatomy. Rapid proliferation of cancer cells outpaces blood supply, triggering secretion of vascular endothelial growth factor and other pro-angiogenic signals.[66] The resulting neovascularization produces structurally defective blood vessels with irregular diameters, dead ends, and gaps between endothelial cells ranging from hundreds to thousands of nanometers.[67] Simultaneously, compression of lymphatic vessels by expanding tumor mass, combined with abnormal lymphatic development, severely impairs drainage function.[68]

This combination creates what has been termed the enhanced permeability and retention effect (EPR). Nanoparticles sized between approximately ten and two hundred nanometers extravasate through the fenestrated tumor vasculature at much higher rates than through normal vessels.[69] Once in the tumor interstitium, impaired lymphatic function prevents efficient clearance, causing progressive accumulation over hours to days.[70] Larger particles face exclusion from tumors despite vascular gaps, while very small particles undergo rapid renal clearance before substantial tumor uptake occurs.[71]

However, recent clinical experience has tempered initial enthusiasm about passive targeting.

The EPR effect shows marked heterogeneity among tumor types, individual patients, and even different regions within the same tumor.[72] Dense desmoplastic stroma characteristic of pancreatic cancer creates physical barriers that limit nanoparticle penetration despite vascular leakiness.[73] Elevated interstitial fluid pressure in many solid tumors opposes inward convective transport, reducing accumulation.[74] Clinical studies increasingly suggest that EPR-mediated delivery may be less reliable in humans than in experimental mouse models.[75]

Active targeting adds molecular specificity to tumor accumulation through ligand-receptor interactions. Surface-conjugated targeting moieties recognize and bind to molecules preferentially expressed on tumor cells or tumor-associated endothelium.[76] This approach operates through several sequential steps, each enhancing selectivity and cellular uptake.

Initial localization to tumor tissue may still depend partly on passive accumulation, as active

targeting cannot overcome absent vascular delivery.[77] Once nanoparticles reach the tumor microenvironment, targeting ligands engage their cognate receptors. For particles in tumor vessels, ligands may bind endothelial receptors like integrins or vascular endothelial growth factor receptors, facilitating transcytosis across the endothelial barrier.[78]

In tumor tissue, ligands recognize receptors overexpressed on cancer cell surfaces. The image depicts this process beginning with active-targeting nanoparticles encountering G-protein-coupled receptors on ovarian cancer cells. Ligand-receptor binding triggers internalization through receptor-mediated endocytosis.[79] The nanoparticle-receptor complex migrates laterally in the membrane until reaching clathrin-coated pits.[80] These specialized membrane regions invaginate and pinch off, forming endosomes that ferry nanoparticles into the cytoplasm.[81]

Following internalization, endosomes undergo progressive acidification as they mature.[82] This pH drop from neutral to acidic provides an opportunity for pH-sensitive nanoparticles to release their cargo.[83] However, drugs must often escape the endosomal compartment before fusion with lysosomes occurs, as lysosomal enzymes would degrade many therapeutics.[84] Various strategies including fusogenic peptides, pH-sensitive polymers, and cationic lipids have been developed to promote endosomal escape.[85]

The contrast between healthy and tumor tissue illustrated in the passive targeting image clarifies why combination approaches often prove most effective. In normal tissue, intact endothelium with tight epithelial junctions prevents nanoparticle extravasation. Functional lymphatic drainage efficiently removes any particles that do escape. This physiology protects healthy organs from nanoparticle accumulation.

Tumor tissue exhibits fundamentally altered architecture. Cancer cells display abnormal morphology and irregular arrangement. Defective vasculature with gaps in the endothelial layer allows nanoparticle extravasation. Impaired lymphatic drainage, visible as compressed or absent lymphatic vessels, prevents clearance. The combination enables progressive nanoparticle accumulation through passive mechanisms.

Optimal strategies frequently combine passive and active targeting. Passive accumulation increases local nanoparticle concentration in tumor tissue, improving the probability of ligand-receptor encounters. Active targeting then enhances binding to cancer cells and

promotes internalization, increasing intracellular drug delivery.[86] This complementary approach has demonstrated superior therapeutic efficacy compared to either mechanism alone in numerous preclinical studies.[87]

3. LIPID NANOPARTICLE-BASED mRNA DELIVERY

3.1 LNP Design and Mechanisms

LNPs have emerged as the leading platform for mRNA delivery. These particles typically contain ionizable lipids that are neutral at physiological pH but become positively charged in acidic endosomes, facilitating endosomal escape.[88] Helper lipids and cholesterol provide structural stability, while PEG-lipids prevent aggregation and reduce immune recognition.[89] Microfluidic mixing techniques enable reproducible formulation with consistent size and encapsulation efficiency.[90]

3.2 Cancer Vaccine Applications

Personalized neoantigen vaccines represent a major application of LNP-mRNA technology. Patient tumors undergo whole exome sequencing to identify mutations generating unique neoantigens.[91] mRNA encoding these neoantigens is formulated into LNPs and administered to stimulate T cell responses against tumor-specific targets.[92] Clinical trials have demonstrated safety and immunogenicity, with Moderna's mRNA-4157 showing promising results in combination with pembrolizumab for melanoma and other cancers.[93]

Shared tumor antigen vaccines target antigens expressed across multiple patients' tumors, enabling off-the-shelf production.[94] Clinical development is advancing for antigens including NY-ESO-1, MAGE-A3, and carcinoembryonic antigen.[95]

3.3 Cytokine Delivery

mRNA encoding immunostimulatory cytokines offers advantages over recombinant protein administration. Interleukin-12 (IL-12) potently activates anti-tumor immunity but causes severe toxicity when given systemically as a protein.[96] LNP-delivered IL-12 mRNA enables local production within tumors, achieving therapeutic effects with reduced systemic exposure.[97] Preclinical studies have reported tumor elimination rates exceeding 80% in mouse models.[98] Clinical trials are evaluating safety and efficacy in patients with advanced solid tumors.[99]

Similar approaches are being explored for IL-15, which supports T cell and NK cell

proliferation, and IL-21, which enhances effector function.[100]

3.4 Antibody Production In Vivo

mRNA encoding therapeutic antibodies enables sustained in vivo production, potentially overcoming the short half-life and high cost of recombinant proteins.[101] BioNTech's BNT142 delivers mRNA encoding bispecific antibodies targeting tumor antigens and CD3, redirecting T cells to cancer cells.[102] Phase I/II trials have demonstrated feasibility and early signs of efficacy.[103]

3.5 Targeting Innovations

First-generation LNPs accumulate predominantly in liver following systemic administration.[104] Recent advances have achieved tumor-selective delivery through surface modification with targeting ligands. Antibody-conjugated LNPs demonstrate over 100-fold selectivity for tumors expressing specific antigens such as prostate-specific membrane antigen (PSMA) or HER2.[105] Organ-specific targeting to spleen and lymph nodes has been accomplished by modulating lipid composition and surface charge.[106]

4. BIOMIMETIC NANOPARTICLE PLATFORMS

4.1 Cell Membrane Coating Technology

Biomimetic nanoparticles leverage cell membranes as natural camouflage to evade immune clearance and enhance tumor targeting.[107] The fabrication process involves extracting and purifying cell membranes, then coating them onto synthetic nanoparticle cores through extrusion or sonication.[108] This approach preserves membrane proteins and glycans that mediate biological interactions.[109]

4.2 Cancer Cell Membrane-Coated Systems

Coating nanoparticles with cancer cell membranes enables homotypic targeting, where particles preferentially bind to tumors of the same origin.[110] This mechanism exploits adhesion molecules that mediate tumor cell interactions.[111] Applications include delivery of photosensitizers for photodynamic therapy, with some formulations achieving nearly 50% light-to-heat conversion efficiency.[112] Chemotherapy drugs encapsulated in cancer membrane-coated nanoparticles show improved tumor accumulation and reduced toxicity compared to free drugs.[113]

4.3 Immune Cell Membrane-Coated Systems

Macrophage membrane-coated nanoparticles inherit inflammation-homing properties, facilitating delivery to the immunosuppressive TME.[114] These particles can deliver agents that reprogram tumor-associated macrophages from immunosuppressive M2 to anti-tumor M1 phenotypes.[115] Neutrophil membranes confer tumor-homing abilities and can induce pyroptosis, an immunogenic form of cell death.[116]

Platelet membrane coating enables targeting of circulating tumor cells, potentially preventing metastasis.[117] T cell and NK cell membranes enhance recognition of tumor cells while protecting therapeutic cargo from degradation.[118]

4.4 Clinical Translation Challenges

Despite promising preclinical results, biomimetic nanoparticles face significant translation hurdles. Standardizing membrane isolation and coating procedures across batches is technically challenging.[119] Source cell availability and quality control remain concerns, particularly for autologous cancer cell membranes.[120] Regulatory pathways for these hybrid biological-synthetic systems are still being defined.[121] Scaling production to clinical doses while maintaining membrane protein functionality requires further development.[122]

5. STIMULI-RESPONSIVE NANO-DELIVERY

5.1 pH-Responsive Systems

The acidic TME, with pH values around 6.5-6.8 compared to physiological 7.4, provides an opportunity for selective drug release.[123] pH-sensitive nanoparticles incorporate acid-cleavable linkers or charge-reversal polymers that become unstable or change properties at tumor pH.[124] Recent innovations include systems that clear excess potassium from the TME, promoting macrophage repolarization from M2 to M1 phenotypes.[125]

5.2 Enzyme-Responsive Systems

Matrix metalloproteinases (MMPs) are overexpressed in many tumors and can trigger drug release from nanoparticles containing MMP-cleavable peptides.[126] Cathepsin-responsive systems exploit lysosomal enzyme activity within cancer cells.[127] Dual enzyme-responsive designs enhance tumor specificity by requiring multiple enzymatic activities for full activation.[128]

5.3 Redox and Hypoxia-Responsive Systems

Elevated reactive oxygen species in tumors can trigger drug release from nanoparticles containing thioketal or selenium-based linkages.[129] Glutathione-responsive systems utilize the higher intracellular glutathione concentrations in cancer cells.[130] Hypoxia-responsive nanoparticles incorporate nitroimidazole derivatives that undergo reduction in low-oxygen environments.[131] Some platforms generate oxygen to overcome hypoxia-mediated resistance while delivering therapy.[132]

5.4 Externally-Triggered Systems

Photoresponsive nanoparticles enable spatiotemporal control of drug release using near-infrared light, which penetrates several centimeters into tissue.[133] Photothermal and photodynamic therapies can be integrated with drug delivery for synergistic effects.[134] Magnetic nanoparticles allow guided delivery to specific sites and can generate heat under alternating magnetic fields.[135] Ultrasound-responsive systems offer deep tissue penetration and have shown promise for opening the blood-brain barrier.[136]

6. CHECKPOINT INHIBITOR DELIVERY

6.1 Nanoformulation Strategies

While checkpoint inhibitor antibodies have revolutionized cancer treatment, systemic administration causes immune-related adverse events in many patients.[137] Nanoparticle encapsulation or conjugation enhances tumor accumulation while reducing systemic exposure.[138] Various platforms have been developed for anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies.[139]

6.2 siRNA-Mediated Checkpoint Blockade

Small interfering RNA (siRNA) targeting checkpoint molecules offers an alternative to antibody therapy.[140] Nanoparticle delivery of PD-L1 siRNA has demonstrated superior tumor growth inhibition compared to anti-PD-L1 antibodies in preclinical studies.[141] CTLA-4 silencing in regulatory T cells can enhance anti-tumor immunity while avoiding systemic suppression.[142]

6.3 Combination Delivery

Co-delivery of checkpoint inhibitors with chemotherapy, phototherapy, or other agents in single nanoparticles enables synergistic effects.[143] Chemotherapy-induced immunogenic cell death releases tumor antigens that enhance checkpoint blockade efficacy.[144] Phototherapy

generates local inflammation that sensitizes tumors to immune attack.[145] Careful sequencing and ratio optimization are critical for maximizing therapeutic benefit.[146]

7. TUMOR MICROENVIRONMENT MODULATION

7.1 Immunosuppressive Cell Targeting

The TME contains multiple immunosuppressive cell populations. Tumor-associated macrophages (TAMs) promote cancer progression through growth factor secretion and immune suppression.[147] Nanoparticles delivering CSF-1R inhibitors or PI3Kγ inhibitors can deplete TAMs or reprogram them toward anti-tumor phenotypes.[148] Combining TAM modulation with checkpoint blockade shows enhanced efficacy in preclinical models.[149]

Myeloid-derived suppressor cells (MDSCs) suppress T cell function through multiple mechanisms.[150] Nanoformulated MDSC-depleting agents or functional inhibitors restore anti-tumor immunity.[151] Regulatory T cells maintain immunological tolerance but suppress anti-tumor responses.[152] Targeted delivery to Tregs can selectively deplete this population within tumors.[153]

7.2 Stromal Remodeling

Cancer-associated fibroblasts (CAFs) create physical barriers and secrete immunosuppressive factors.[154] Nanoparticles targeting fibroblast activation protein (FAP) enable CAF-selective drug delivery.[155] Enzymes that degrade extracellular matrix components improve nanoparticle penetration and T cell infiltration.[156] Vascular normalization strategies reduce interstitial pressure and enhance drug delivery.[157]

7.3 Metabolic Modulation

Tumor hypoxia and altered metabolism impair immune cell function.[158] Oxygen-generating or oxygen-carrying nanoparticles alleviate hypoxia and enhance therapy.[159] Inhibiting glycolysis or other metabolic pathways can reprogram the TME to favor immune attack.[160] Metabolic interventions may improve T cell function and persistence.[161]

8. IMMUNOGENIC CELL DEATH INDUCTION

Cancer cell death pathways influence immune responses. Immunogenic cell death (ICD) releases damage-associated molecular patterns including calreticulin, ATP, and HMGB1 that activate dendritic cells and initiate adaptive immunity.[162] Certain chemotherapeutics including doxorubicin, oxaliplatin, and paclitaxel induce ICD when delivered at appropriate

doses.[163]

Nanoformulated ICD inducers achieve higher intratumoral concentrations with reduced systemic toxicity.[164] Photosensitizers for photodynamic therapy are potent ICD inducers, with combinations such as chlorin e6 plus sorafenib demonstrating strong dendritic cell activation.[165] Photothermal therapy can also trigger ICD through controlled hyperthermia.[166]

Combining ICD-inducing treatments with checkpoint inhibitors or cancer vaccines enhances therapeutic efficacy.[167] The released tumor antigens serve as an *in situ* vaccine that primes anti-tumor T cell responses.[168]

9. PERSONALIZED CANCER NANOVACCINES

9.1 Neoantigen Discovery

Advances in next-generation sequencing and computational biology enable identification of patient-specific neoantigens.[169] Whole exome sequencing identifies somatic mutations in tumor DNA.[170] Algorithms predict which mutations generate peptides that bind MHC molecules and stimulate T cell responses.[171] Artificial intelligence approaches such as LinearDesign optimize mRNA sequences for enhanced translation and immunogenicity.[172]

9.2 Vaccine Platforms

LNP-mRNA vaccines enable rapid manufacturing, with production timelines of weeks rather than months.[173] Peptide or protein nanovaccines require chemical synthesis or recombinant production.[174] Virus-like particles and exosome-based vaccines provide alternative platforms with distinct advantages.[175]

9.3 Adjuvant Integration

Co-delivery of vaccine antigens with adjuvants enhances immune responses. STING agonists activate innate immunity and promote T cell priming.[176] Combination of STING agonists with HPV antigens achieved 71% tumor elimination in animal models.[177] Toll-like receptor agonists including CpG oligodeoxynucleotides are commonly used adjuvants.[178] Multi-adjuvant formulations may provide superior immunity compared to single agents.[179]

9.4 Clinical Development

Several personalized neoantigen vaccines are in clinical trials.[180] Manufacturing timelines and costs remain challenges for widespread adoption.[181] Patient stratification based on tumor

mutational burden, microsatellite instability, and PD-L1 expression may identify those most likely to benefit.[182]

10. CLINICAL TRANSLATION

10.1 FDA-Approved Nanomedicines

Multiple nanomedicines have received regulatory approval for cancer treatment. Doxil, the first approved liposomal drug in 1995, delivers doxorubicin with reduced cardiotoxicity.[183] Abraxane uses albumin nanoparticles to deliver paclitaxel without toxic solvents.[184] Onivyde is a liposomal irinotecan approved for pancreatic cancer.[185] Vyxeos is a dual-drug liposomal formulation for acute myeloid leukemia.[186] These approvals have validated nanomedicine while revealing challenges in demonstrating superiority over conventional therapies.[187]

Table 2: FDA-Approved Nanomedicines for Cancer Treatment (1995-2024).

Drug Name	Formulation Type	Active Pharmaceutical Agent	Cancer Indication	FDA Approval Year	Key Clinical Benefit	Ref
Doxil/Caelyx	PEGylated liposome (85-100 nm)	Doxorubicin HCl	Ovarian cancer; AIDS-related Kaposi's sarcoma; Multiple myeloma	1995	Significantly reduced cardiotoxicity; Extended circulation half-life (>55 hours vs 0.2 hours)	[123]
DaunoXome	Non-PEGylated liposome	Daunorubicin citrate	HIV-associated Kaposi's sarcoma	1996	Improved therapeutic index; Reduced systemic toxicity	[15]
Myocet	Non-PEGylated liposome	Doxorubicin HCl	Metastatic breast cancer (combination with cyclophosphamide)	2000 (Europe)	Reduced cardiotoxicity when combined with trastuzumab; Maintained efficacy	[123]
Abraxane	Albumin-bound Nanoparticle (130 nm)	Paclitaxel	Metastatic breast cancer; Non-small cell lung cancer; Pancreatic adenocarcinoma	2005	Elimination of toxic Cremophor solvent; Enhanced tumor accumulation via SPARC/gp60	[124]

Marqibo	Sphingomyelin/ Cholesterol liposome	Vincristine sulfate	Philadelphia chromosome-negative acute lymphoblastic leukemia	2012	Improved maximum tolerated dose; Extended exposure duration	[15]
Onivyde	Liposomal Irinotecan (PEGylated, 110 nm)	Irinotecan	Metastatic pancreatic adenocarcinoma (after gemcitabine failure)	2015	Prolonged drug exposure; Overall survival improvement (6.1 vs 4.2 months)	[125]
Vyxeos	Dual-drug liposome (100 nm)	Daunorubicin + Cytarabine (5:1 molar ratio)	Therapy-related AML; AML with myelodysplasia-related changes	2017	Synergistic fixed-ratio delivery; Improved median overall survival (9.56 vs 5.95 months)	-

10.2 Current Clinical Trials

Phase III trials are evaluating ThermoDox, a thermosensitive liposomal doxorubicin, in combination with radiofrequency ablation.[188] Phase II trials of mRNA cancer vaccines from Moderna and BioNTech are showing encouraging safety and immunogenicity data.[189] BNT142, encoding bispecific antibodies, is in Phase I/II testing.[190] Trial designs increasingly incorporate biomarker-driven patient selection and adaptive randomization.[191]

Table 3: Selected Clinical Trials of Nano-Immunotherapy (2020-2025).

Trial Identifier	Platform/Investigational Agent	Cancer Type(s)	Phase	Current Status	Primary Endpoint / Key Findings	Ref
NCT03313778	mRNA-4157 (individualized neoantigen vaccine) + Pembrolizumab	Resected solid tumors (melanoma, NSCLC)	Phase II	Active, recruiting	Recurrence-free survival; Early data show improved RFS in melanoma patients	[33, 129]
NCT04486378	BNT122 (FixVac) individualized neoantigen LNP-mRNA vaccine	Advanced melanoma	Phase II	Recruiting	Objective response rate; Immunogenicity assessment ongoing	[129]
NCT03739931	BNT142 (mRNA encoding bispecific anti-CLDN6/CD3 antibody)	CLDN6-positive solid tumors	Phase I/II	Active	Safety and tolerability; Preliminary data show acceptable	[42, 130]

					safety profile	
NCT02112656	ThermoDox (thermosensitive liposomal doxorubicin) + RFA	Hepatocellular carcinoma	Phase III	Completed	Overall survival; Primary endpoint not met (median OS: 2.8 vs 2.4 years, p=0.359)	[128]
NCT04534205	mRNA-5671 (KRAS vaccine) + Pembrolizumab	KRAS-mutant NSCLC, CRC, pancreatic cancer	Phase I	Active, recruiting	Safety, immunogenicity; Dose escalation ongoing	[129]
NCT03897881	SAR441000 (liposomal TLR9 agonist)	Advanced solid tumors	Phase I/II	Active	Safety and preliminary efficacy; Intratumoral administration	[118]
NCT04163094	MEDI1191 (STING agonist formulation) + Durvalumab	Advanced solid tumors and lymphomas	Phase I	Active	Maximum tolerated dose; Tumor response with anti-PD-L1 combination	[116]
NCT03788083	Nanoplatin (liposomal cisplatin)	Recurrent ovarian cancer	Phase II	Recruiting	Progression-free survival; Reduced nephrotoxicity vs free cisplatin	[127]
NCT04526899	BNT111 (FixVac melanoma vaccine, RNA-LPX)	Advanced melanoma	Phase I	Active	Safety and immunogenicity; RNA lipoplex platform evaluation	[43]

10.3 Translation Challenges

The EPR effect, fundamental to many nanomedicine designs, shows high variability among patients.[192] Tumor heterogeneity influences nanoparticle accumulation and therapeutic response.[193] Biomarkers predicting nanomedicine efficacy remain elusive.[194] Manufacturing reproducibility at clinical scales presents technical and regulatory challenges.[195]

11. MANUFACTURING AND REGULATORY CONSIDERATIONS

Good manufacturing practice (GMP) production of nanomedicines requires stringent quality control.[196] Batch-to-batch consistency in size distribution, surface properties, drug loading, and stability must be demonstrated.[197] Characterization techniques including dynamic light scattering, electron microscopy, and chromatography are essential.[198]

The FDA has issued guidance documents for liposomal products and mRNA therapeutics.[199]

European Medicines Agency requirements are generally aligned but with some regional differences.[200] Accelerated approval pathways are available for serious conditions with unmet needs.[201] Chemistry, manufacturing, and controls documentation must demonstrate process control and product consistency.[202]

Manufacturing costs significantly impact accessibility.[203] Strategies to reduce production expenses include process optimization, continuous manufacturing, and economies of scale.[204] Global access disparities remain substantial, particularly for personalized therapies requiring patient-specific manufacturing.[205]

12. SAFETY AND TOXICOLOGY

Nanoparticle size and composition influence toxicity profiles.[206] Very small nanoparticles may cross biological barriers including the blood-brain barrier, raising concerns about unintended biodistribution.[207] Immunotoxicity including hypersensitivity reactions can occur, particularly with lipid-based formulations.[208] Complement activation-related pseudoallergy (CARPA) causes infusion reactions in some patients.[209]

Anti-PEG antibodies develop in a subset of patients receiving PEGylated nanomedicines, potentially accelerating clearance upon repeat dosing.[210] This accelerated blood clearance (ABC) phenomenon may reduce therapeutic efficacy.[211] Alternative stealth coatings are being investigated.[212]

Clinical trials have reported manageable safety profiles for most nanomedicines, though Grade 3/4 toxicities occur.[213] Long-term safety data remain limited for many platforms.[214] Predictive toxicology models and dose optimization can mitigate risks.[215] Patient monitoring protocols should be tailored to the specific nanoformulation and therapeutic agents.[216]

13. ARTIFICIAL INTELLIGENCE IN NANOMEDICINE

Machine learning algorithms are accelerating nanoparticle design and optimization.[217] High-throughput screening combined with computational modeling can predict formulation performance.[218] Biodistribution and pharmacokinetic predictions inform rational design.[219]
In clinical applications, AI enables patient stratification based on genomic, proteomic, and imaging data.[220] Response prediction algorithms may identify patients likely to benefit from specific nanotherapies.[221] Adaptive trial designs use accumulating data to optimize dosing and patient selection.[222] Multi-omics integration provides comprehensive understanding of

treatment effects.[223]

14. FUTURE PERSPECTIVES

14.1 Emerging Technologies

Integration of gene editing technologies with nanoparticle delivery could enable correction of oncogenic mutations.[224] CRISPR-Cas9 delivery to tumor cells is being actively developed.[225] Circular RNA therapeutics offer enhanced stability compared to linear mRNA.[226] Two-dimensional materials and metal-organic frameworks provide novel carrier options.[227]

The intersection of microbiome research and nanomedicine may yield new therapeutic strategies.[228] Engineered bacteria combined with nanoparticles could target specific tumor environments.[229] Sustainable nanomedicine approaches addressing environmental impacts are gaining attention.[230]

14.2 Short-Term Goals

Improving tumor targeting specificity remains a priority.[231] Simplified manufacturing processes would reduce costs and improve accessibility.[232] Biomarker-driven patient selection could increase response rates and justify healthcare expenditures.[233] Combination strategies rationally designed based on mechanisms of action show promise.[234]

14.3 Long-Term Vision

AI-designed personalized nanoformulations tailored to individual patient tumors represent an ambitious goal.[235] Real-time theranostic systems combining diagnostics and therapeutics could enable treatment monitoring and adaptation.[236] Achieving curative outcomes for metastatic disease through optimized nano-immunotherapy combinations would transform cancer care.[237]

15. CONCLUSION

Nanotechnology has emerged as a powerful tool for enhancing cancer immunotherapy. The successful clinical translation of mRNA-LNP vaccines has validated the potential of nanomedicine while highlighting remaining challenges. Biomimetic and stimuli-responsive systems show promise in preclinical studies but require further development for clinical use.

Critical gaps persist in standardization, reproducibility, and predictive models for human translation. Long-term safety data are needed for most platforms. Manufacturing scalability

and cost-effectiveness must improve for widespread adoption. Regulatory pathways continue to evolve as novel platforms emerge.

The path forward requires interdisciplinary collaboration among engineers, immunologists, clinicians, and regulators. Patient-centric outcome measures should guide development priorities. With continued innovation and rigorous clinical validation, nano-delivery systems have the potential to substantially improve outcomes for patients with cancer, particularly those with difficult-to-treat solid tumors. The convergence of nanotechnology, immunotherapy, and personalized medicine may finally realize the promise of curative cancer treatment.

CRediT Author Statement

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Conflict-of-interest

The authors declare that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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