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Nanotherapeutics in the treatment of cancer: transforming cancer care

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Abstract

Nanotechnology is revolutionizing oncological interventions through nanotherapeutics, which employ nanoparticles (NPs) to significantly increase treatment precision and efficacy. These NP vectors deliver anticancer agents directly to tumors, reducing damage to healthy cells by utilizing the established enhanced permeability and retention (EPR) effect. In response to targeted biochemical signals, NPs ensure precise drug release within tumors. Additionally, they function as contrast agents to improve cancer imaging and diagnostics, facilitating early diagnosis and the development of personalized therapies. NP-based combination therapies effectively combat drug resistance by delivering multiple therapeutic agents targeting diverse molecular pathways. Nanomedicines provide accurate drug delivery in blood cancers, reducing side effects and potentially enhancing hematopoietic stem cell transplantation. Furthermore, NPs modulate intracellular signaling in hematological cancers, offering opportunities for pioneering treatments. This article highlights the multifaceted roles of NPs in advancing cancer treatment, pointing toward significant improvements and future research directions.

Keywords: Nanomedicine, Drug delivery systems, Antineoplastic agents, Nanoparticles, Targeted therapy, Molecular targeted therapy

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Introduction

Cancer remains one of the most formidable global health problems of the 21st century. In 2022, the International Agency for Research on Cancer recorded roughly 20 million new diagnoses and 9.7 million deaths, and epidemiological models predict both figures will continue to climb as populations age, urbanise, and adopt carcinogenic lifestyles[1–7]. Despite undeniable progress, the standard therapeutic arsenal—surgery, radiotherapy, cytotoxic chemotherapy, targeted antibodies, and immune-checkpoint inhibitors—still leaves many patients with refractory or relapsing disease. Dose-limiting toxicities restrict drug intensity, off-target tissue damage compromises quality of life, and intrinsic or acquired multidrug resistance has become a major cause of treatment failure. Consequently, the clinical community is actively searching for technologies that can deliver agents more precisely, overcome biological barriers, and engage tumours on multiple fronts without exacerbating systemic harm[8].

Nanotechnology offers a fundamentally new toolkit for addressing these challenges. When materials are engineered at dimensions between 1 and 100 nm, they display quantum and surface phenomena that bulk matter cannot: sizes comparable to biomacromolecules permit passage through fenestrated vasculature, a high surface-area-to-volume ratio supports dense functionalisation with targeting ligands, and tunable core–shell architectures enable controlled drug loading and release[9,10]. Nanoparticles (NPs) can therefore be designed not merely as passive drug carriers but as dynamic therapeutic systems that sense their environment, navigate complex physiological pathways, and discharge payloads on command[11]. The underlying principle, engineering matter from the bottom up, has already reshaped fields as diverse as micro-electronics and energy storage; its translation into oncology now appears similarly transformative[12–14].

The conceptual foundations of modern nanomedicine delivery systems were laid by pioneering work from groups led by Langer & Farokhzad[15,16], Park[17], and their collaborators, who established the principles of controlled drug release, polymer–drug interactions, and translational design constraints that continue to guide the field today. Langer's early demonstrations that polymeric matrices could safely and predictably modulate drug release kinetics transformed controlled delivery from a theoretical concept into a clinically viable strategy, enabling sustained, localized, and stimuli-responsive therapies[16]. In parallel, Park and colleagues critically articulated the biological and translational barriers facing nanoparticle-based drug delivery—particularly issues of burst release, reproducibility, scale-up, and the mismatch between *in vitro* performance and *in vivo* outcomes thereby shaping a more rigorous, mechanism-driven approach to nanocarrier design[18].

Over the past three years, momentum in translational nanomedicine has accelerated dramatically. The success of lipid-nanoparticle (LNP) platforms in delivering mRNA vaccines for COVID-19 validated large-scale, Good-Manufacturing-Practice production of clinically safe NPs and propelled a new wave of oncology vaccines and CRISPR-based gene editors into early-phase trials[19–22]. Stimuli-responsive hydrogels that transition from liquid to solid once injected now trap chemotherapeutics or immunomodulators inside surgical cavities and release them as pH, enzymatic activity, or reactive-oxygen-species (ROS) concentrations rise in the tumour micro-environment[23]. Exosome-mimetic vesicles, created by serial extrusion of donor cells, reproduce the protein corona of native extracellular vesicles and thereby evade phagocytic clearance while homing to metastatic niches. Metallic nanostructures, most notably 20- to 150-nm gold nanoshells, convert harmless near-infra-red light into localised thermal energy, achieving ablation of otherwise inoperable lesions, while superparamagnetic iron-oxide particles double as magnetic-resonance contrast agents and hyperthermia triggers. Even DNA-based nanorobots have reached proof-of-concept in animals: by carrying thrombin behind a strand-displacement gate that opens only on a tumour-specific membrane marker, these constructs occlude the feeding vasculature from within, starving malignant tissue without affecting healthy vessels[13].

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Yet the field still confronts critical knowledge gaps. Head-to-head comparisons that connect an NP's composition, shape, or surface chemistry to its pharmacokinetics, tumour penetration, immune profile, and long-term safety remain sparse[24,25]. While hydrogels, liposomes, and polymeric micelles dominate the existing literature, newer vehicles, ROS-generating carbon dots, metal-organic frameworks, dendrimers, and biological vesicles have introduced functions that go beyond payload delivery, actively modulating oxidative stress, metabolism, and the host immune response[26,27]. Understanding where each platform excels or fails is essential, because a carrier optimised for, say, siRNA transport across the blood–brain barrier will be suboptimal for photothermal ablation of a deep-seated sarcoma, and vice versa[28,29]. Furthermore, regulatory approval pathways are uneven: although several NP-containing new molecular entities won United States Food and Drug Administration clearance in 2024, others face delays due to manufacturability or toxicology concerns[30,31]. Systematic, comparative data can therefore accelerate translational decisions and de-risk clinical investment[19,32,33].

This work is presented as a narrative review aimed at providing a comprehensive and up-to-date synthesis of nanoparticle (NP) platforms applied to cancer therapy. The literature was identified through structured searches of major scientific databases, including PubMed, Scopus, Google Scholar, and ScienceDirect. Publications from January 2010 to December 2025 were considered, with particular emphasis placed on studies published within the last five years to capture recent technological advances and translational progress. Peer-reviewed original articles, review papers, and relevant clinical trial reports were included based on their relevance to nanocarrier design, physicochemical properties, biological interactions, preclinical performance, clinical evaluation, and regulatory status. In addition, clinical trial registries, regulatory databases, and publicly available industrial pipeline resources were consulted to provide an accurate overview of the current clinical and translational landscape of cancer nanomedicine.

The present review addresses this unmet need by providing a comprehensive, up-to-date synthesis of contemporary NP platforms used, or poised to be used, in cancer therapy. We first retrace the conceptual progression from classical liposomes to today's smart nanoconstructs, emphasising how incremental design choices have solved (or revealed) key biological bottlenecks. We then collate and evaluate evidence on eight major families, such as liposomes, polymeric micelles, nanoreinforced injectable hydrogels, dendrimers, metallic and carbon nanostructures, LNPs for nucleic acids, and biologically derived exosomes, highlighting for each the relationship between physicochemical parameters and *in vivo* behaviour. Special attention is given to ROS-generating nanocarriers and nano-robotic systems, which seek to turn oxidative stress and microvascular dynamics from liabilities into therapeutic assets. Clinical trial registries, regulatory databases, and industrial pipelines are mined to provide an objective snapshot of what has reached the bedside, what is in translation, and what remains conceptual.

By correlating design principles with pre-clinical and clinical outcomes, our goal is to deliver a practical framework that helps researchers and clinicians select or engineer the most suitable nanocarrier for a given oncologic challenge. In doing so, we hope to speed the transition from elegant nanoscale concepts to tangible patient benefit and to illuminate the pathways by which nanotechnology can convert cancer's biological complexity from an insurmountable hindrance into a map for precision intervention.

Characteristics and types of NPs

NPs exhibit distinct characteristics that make them highly effective carriers for anticancer therapies. Their small size allows for precise, targeted drug delivery, whereas their large surface area provides substantial drug-loading capacity. Additionally, NPs can be engineered to possess specific physicochemical properties, such as surface charge, size, or hydrophobicity, that optimize drug encapsulation and controlled release[34,35]. NPs are generally classified into two main categories: organic and inorganic. Organic NPs are derived primarily from carbon-based materials, whereas inorganic NPs are composed of noncarbon substances[36]. However, although they are carbon-based, certain materials, such as graphene, fullerenes, and carbon nanotubes, are sometimes classified as inorganic[37,38].

Organic NPs: liposomes

Organic NPs, particularly liposomes, have been widely investigated for their potential in drug delivery. Liposomes are structured entities composed of cholesterol and either natural or synthetic phospholipids. They feature a lipid bilayer that encases a core, which can encapsulate both hydrophobic and hydrophilic pharmaceutical compounds. This versatility makes liposomes ideal for targeted drug delivery. They can be administered orally or intravenously, with the latter being the more common route for cancer therapies. The drug delivery mechanism of liposomes involves accumulation at tumor sites, internalization by cancer cells, and the controlled release of the therapeutic agents. Two fundamental strategies are employed to target liposomes specifically to cancer cells: passive targeting, which exploits the EPR effect within the tumor microenvironment (TME), and active targeting, which involves surface modifications of liposomes. These modifications may include functionalization with antibodies, peptides, small molecules, or carbohydrates to improve targeting specificity. Liposomes have effectively delivered various anticancer drugs, including doxorubicin and paclitaxel, chemotherapeutic drugs, and nucleic acids. For example, paclitaxel-loaded liposomes have demonstrated superior efficacy and enhanced bioavailability compared with free paclitaxel, whereas liposomal doxorubicin has shown a reduction in cardiotoxicity without compromising efficacy in breast cancer treatment[35,39–49].

Organic NPs: extracellular vesicles

Extracellular vesicles (EVs), including exosomes (Exos), are membrane-bound particles secreted by prokaryotic and eukaryotic cells. EVs range in size from the nanoscale to the microscale and comprise lipids, proteins, and nucleic acids, including microRNAs. These vesicles hold considerable promise for targeted cancer therapies, as they can be engineered to enhance drug delivery and elicit specific anticancer effects. However, a key obstacle remains in scaling up the production of EVs for clinical application. Recent research indicates that EVs can act as carriers for conventional anticancer drugs and molecules designed to stimulate immune responses against tumors. For example, Exos loaded with A Disintegrin and Metalloprotease-10 inhibitors can prevent the release of decoy ligands that hinder tumor cell recognition, whereas NPs carrying aminobisphosphonates can stimulate an immune response via $\gamma\delta$ T cells, bridging innate and adaptive immunity[50–54].

A novel approach involving dual-targeted EVs (dtEVs) has been developed to deliver therapeutic RNA for treating pancreatic ductal adenocarcinoma (PDAC) in mice. These dtEVs, generated by transfecting cells with plasmid DNAs encoding RNA and protein, achieve high RNA loading. When combined with the chemotherapy agent gemcitabine, dtEVs, which include a tissue-targeting peptide and a

humanized monoclonal antibody, effectively suppressed PDAC tumors and metastasis, leading to increased survival rates in animal models. This approach offers considerable promise for scalable, efficient delivery of gene therapies targeting solid tumors, such as PDAC[55].

Organic NPs: nanoemulsions

Nanoemulsions are fine oil–water mixtures that efficiently deliver therapeutic agents to tumor sites. These systems use biocompatible oils as carriers, exploiting the EPR effect for passive tumor targeting. Additionally, surface modifications using peptides, small molecules, or antibodies specific to tumor-associated antigens (TAAs) are actively being investigated to increase targeting precision. Nanoemulsions show significant promise in overcoming multidrug resistance (MDR) and accommodating diverse drug combinations[56–59].

Moreover, nanoemulsions can be conjugated with antibodies or their fragments to facilitate highly specific and selective drug delivery. The antigen–antibody binding affinity enhances cancer cell-targeted delivery and uptake of drug-loaded nanoemulsions, thereby improving therapeutic efficacy. Furthermore, the nanocarrier–antibody complex can be designed to respond to specific stimuli, further increasing its precision in targeting cancerous tissues[60].

Although nanoemulsions can be combined with oligonucleotides, their use has been hindered by instability, rapid clearance from biological fluids, and limited intracellular penetration. However, substituting phosphodiester linkages with phosphorothionate bonds can improve resistance to enzymatic degradation. Conjugation with polyethylene glycol (PEG), cationic liposomes, micelle polyelectrolyte complexes (PEC), lipidic DNA, and pH-responsive nanocarriers has been investigated to mitigate these limitations and enhance the efficacy of cancer therapies[61–64].

In an innovative study, Moura et al. created lipid nanoemulsions that bind Low-density lipoprotein (LDL) receptors, facilitating targeted drug delivery to tissues exhibiting receptor overexpression, including tumor cells. They encapsulated methotrexate for leukemia therapy and demonstrated through *in vitro* assays that the nanoemulsion exhibited significantly higher cellular uptake and toxicity against cancer cells compared to the free drug[65]. Similarly, Winter et al. formulated chalcone-encapsulating nanoemulsions for leukemia treatment. Research conducted *in vitro* and *in vivo* revealed that chalcone-loaded nanoemulsions effectively triggered apoptosis in cancer cells, resulting in antileukemic effects comparable to free chalcones. However, they reported that free chalcones were more toxic to VERO cells compared to the nanoencapsulated chalcones, with *in vivo* tests showing that the free drug caused significant weight loss, liver damage due to oxidative stress, and inflammation[66].

Lycopene (LP), a compound with potential anticancer properties found in tomatoes, is often limited by poor stability and bioavailability[67]. A recent investigation aimed to overcome these obstacles by developing a nanoemulsion formulation containing LP and gold NPs. This formulation was tested on the human colon cancer cell line HT-29, and the results indicated that smaller gold NP sizes increased the cytotoxicity of the formulation. Additionally, increasing the LP content increased the percentage of early apoptotic cells. The simultaneous treatment and nanoemulsion formulation resulted in increased levels of apoptotic and necrotic cells. The emulsifier used did not significantly affect cell viability but played a role in enhancing the stability of the formulation. Ultimately, treatment with the nanoemulsion led to the downregulation of tumor markers and induced significant apoptotic effects in the cells[68,69].

The use of nanoemulsions as a potential approach for treating breast cancer has also been investigated, showing promising results. Periasamy et al. developed a nanoemulsion from *Nigella sativa* L. essential oil and showed that it could trigger apoptosis in MCF-7 breast cancer cells. This formulation could be an efficient carrier for targeted drug delivery in breast cancer treatment[70]. Another promising approach involves the local administration of C6 ceramide-loaded nanoemulsions. Researchers have developed bioadhesive nanoemulsions containing ceramide, which are surface-modified with chitosan. This modification enables localized targeting of tumors and pretumor lesions, reducing systemic toxicity. Compared with the free drug formulation, nanoencapsulation of C6 ceramide significantly lowered the concentration required to decrease the viability of MCF-7 cells. The inclusion of tributyrin in the oil phase further enhanced this reduction. *In vivo* studies revealed that administering the nanoemulsion intraductally led to extended drug retention in mammary tissues. Similarly, Natesan et al. used a chitosan-modified nanoemulsion to encapsulate camptothecin. The *in vitro* and *in vivo* results indicated that the nanoemulsion formulation was superior to the free drug in targeting and treating cancer[71,72].

Organic NPs: polymeric nanocarriers

Dendrimers are synthetic nanocarriers with a branched, tree-like structure, offering extensive surface customization and precise targeting capabilities. These NPs can be tailored for specific applications, allowing targeted drug delivery. Dendrimers can exploit the EPR effect for passive tumor targeting and can be combined with other nanocarriers. Owing to their high drug-loading capacity and versatile release mechanisms, these materials are adaptable to various therapeutic strategies. Surface modifications with antibodies, vitamins, or peptides have addressed common challenges in dendrimer-based drug delivery, including their rapid clearance from the body[73].

Solid lipid NPs (SLNs) are a colloidal drug delivery system that utilizes solid lipids instead of liquid ones. Common lipids employed in SLNs include fatty acids, steroids, and triglycerides. SLN models typically consist of solid solution and core–shell types. These nanoparticles can be administered through various routes, such as parenteral, oral, rectal, ophthalmic, and topical. Due to their large surface area, SLNs exhibit high drug release rates, supporting uniform distribution and controlled release. Passive targeting in SLNs relies primarily on the EPR effect, whereas active targeting involves the recognition of tumor-specific receptors or transporters that are overexpressed on cancer cell surfaces. Additionally, codelivery systems, which enable the concurrent delivery of two therapeutic agents, have been explored to increase treatment efficacy[74–77].

Various cancer cell lines treated with vorinostat-loaded SLNs have demonstrated improved pharmacokinetics and increased efficacy against MDR cancer cells. Table 1 summarizes the different NP types and their key characteristics.

Inorganic NPs

Inorganic NPs constitute a significant class of drug delivery systems in cancer therapy. These NPs include diverse materials, including gold and silver NPs, carbon quantum dots (CQDs), carbon nanotubes, metal oxide particles, and mesoporous silica NPs. They are known for their precise targeting ability, favorable pharmacokinetic profiles, capacity to encapsulate poorly soluble drugs, and utility in diagnostic applications. The development of drug delivery systems using these NPs requires careful consideration of their size and physicochemical properties[78].

Gold and silver NPs can effectively transport small and large drug molecules to tumor sites. Targeting strategies often take advantage of the EPR effect and the altered pH and redox potential of the TME. However, these metallic NPs are prone to aggregation and may exhibit

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Table 1. Summary of types of NPs and their key characteristics.

Nano-drug delivery system	Key characteristics	Liposomes	Extracellular vehicles	Nanoemulsions	Dendrimers	Inorganic NPs	Carbon quantum dots	Solid lipid NPs
General	Nanosized carriers are designed to improve drug solubility, stability, and delivery to target sites.	Biocompatible, versatile in drug loading	Natural origin, involved in cell communication	Enhances solubility, stable formulation	Highly branched, precise drug delivery	Targets specific cells, encapsulates poorly soluble drugs	Bright fluorescence for imaging, biocompatible	Solid at room temperature, controlled release
Targeting ability	Ability to deliver drugs specifically to tumor sites, increasing efficacy and minimizing side effects.	Active or passive targeting	Targeting based on cellular recognition and uptake	Passive targeting	Active targeting through specific surface ligands	Highly precise targeting mechanisms	Surface modification for targeting	Can be engineered for targeted release
Formulation stability	Physical stability of NPs under physiological conditions, preventing early release or degradation of the drug.	Stable in biological fluids	Stability influenced by lipid bilayer	Thermodynamically stable	Stable due to dendritic architecture	Good stability, but may require matrix stabilizers	Stable and resistant to photobleaching	Stability influenced by lipid matrix composition
Encapsulation ability	Ability to encapsulate a variety of therapeutic agents, including hydrophilic and hydrophobic drugs.	High encapsulation efficiency	Encapsulates proteins, RNA, DNA	Excellent for poorly soluble drugs	High versatility in drug loading	Capable of carrying various compounds, including genes	Effective for small molecules and drugs	Good encapsulation of hydrophobic and hydrophilic drugs
Therapeutic applications	Use in targeted therapy, imaging, and combination treatments for enhanced effectiveness against cancer.	Chemotherapy, vaccine delivery	Delivering proteins, biomolecules, and drugs	Delivery of lipophilic pharmaceuticals	Gene therapy, immunotherapeutics	Imaging, photothermal therapy, combination therapy	Bioimaging, drug delivery	Chemotherapy, anti-inflammatory agents, local anesthetics
Synthesis methods	Various techniques for NP preparation impact their size, shape, and stability.	Thin film hydration, reversed-phase evaporation	Isolation from biological sources, synthetic methods	High-energy emulsification, microfluidics	Divergent/convergent synthesis methods	Chemical vapor deposition, sol-gel, coprecipitation	Hydrothermal synthesis, chemical oxidation	High shear mixing, solvent evaporation
Size range	The size of NPs influences their biological behavior and interaction with cells.	50–500 nm	50–1,000 nm	100 –1,000 nm	1–10 nm	5–100 nm	2–10 nm	50–1,000 nm
Surface modifications	Modifying NP surfaces to improve biocompatibility and target specificity.	PEGylation, targeting ligands	Natural surface proteins, engineered ligands	Surfactants for stability	Surface functionalization with peptides	Coatings to enhance stability and targeting	Surface polymerization, functional groups	PEGylation, lipid coating
Biocompatibility	The compatibility of NPs with biological systems influences their safety and efficacy.	Generally, high biocompatibility	Biocompatible, derived from cells	Varies depending on the emulsifier	High, but depends on surface groups	Can vary; gold and silica are often biocompatible	Generally, high, minimal toxicity	High biocompatibility, ideal for drug delivery
Regulatory considerations	Regulations surrounding the approval and use of NPs in clinical settings.	FDA-compliant for certain formulations	Growing interest in regulation	Evolving regulations for emulsion products	FDA guidance for dendrimer applications	Must meet safety and efficacy standards	Emerging guidelines for nanomaterials	Regulatory scrutiny similar to liposomes
Future directions	Potential advancements and innovations in NP technology for improved cancer treatment.	Personalized medicine applications	Use in targeted therapies and diagnostics	Increasing applications in cosmetics	Expanding to include immune modulation	Development of multifunctional NPs	Advances in imaging applications	Enhanced targeting and formulation improvements

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increased toxicity to healthy cells, limiting their application unless they are conjugated with specific polymers such as PEG[79–81].

Magnetic NPs have proven to be especially beneficial in the treatment of cancer, especially in hyperthermic therapy. These particles can be composed of pure metals or composites with polymers and are typically delivered to the target site via a catheter or hypodermic needle injection. A heat source, such as microwave radiation, is then applied to induce hyperthermia at the tumor site, raising the local temperature to approximately 42 °C. This temperature increase induces cancer cell death by exploiting the leaky vascularity of tumors while sparing surrounding normal tissues. Moreover, magnetic NPs are employed in theranostics, photodynamic therapy, photothermal ablation, biosensing, drug delivery, and MRI owing to the superparamagnetic properties of iron oxide NPs[82–85].

CQDs are fluorescent carbon-based NPs crucial in cancer imaging and drug delivery. Their superior targeting capabilities are facilitated by their ability to undergo surface modifications, enabling attachment to multiple targeting molecules. The fluorescence properties of CQDs make them particularly valuable for bioimaging, increasing their potential in theranostic applications. CQDs are characterized by low toxicity, high biocompatibility, efficient targeting, and additional diagnostic functionality, positioning them as promising emerging platforms for nanodrug delivery[86–88].

The role of NPs in cancer therapy

NPs derived from organic and inorganic materials are instrumental in advancing cancer treatment. Their unique properties, such as size, shape, and surface characteristics, are critical in determining the efficacy of nanobased drug delivery systems. These properties directly influence therapeutic outcomes by enhancing drug solubility, facilitating selective tumor targeting, and improving bioavailability[89–91]. NPs in the optimal size range of 10–100 nm are particularly effective for cancer therapy. This range allows for efficient drug transport while exploiting the EPR effect, facilitating accumulation at tumor sites. NPs smaller than 10 nm can leak from blood vessels and potentially harm healthy cells, whereas kidneys rapidly excrete particles less than 1–2 nm in size. Conversely, the immune system quickly clears NPs larger than 100 nm. The surface properties of these NPs, such as charge, hydrophobicity, and functionalization, are pivotal in enhancing their stability, increasing their targeting precision, and minimizing off-target effects[92–95].

In addition to determining targeting efficiency, the physicochemical characteristics of nanoparticles critically govern their biological fate following systemic administration. Nanoparticle size strongly influences circulation time, biodistribution, and clearance, with particles in the 10–100 nm range demonstrating prolonged blood residence and enhanced tumor accumulation[96]. Particle shape further modulates vascular margination and cellular internalization, as rod-shaped or disk-like nanoparticles often exhibit improved adhesion to endothelial surfaces compared with spherical counterparts. Surface properties, including charge, hydrophobicity, and chemical functionalization, dictate interactions with plasma proteins, leading to protein corona formation that can alter nanoparticle identity and biological behavior[97]. These surface-mediated interactions influence opsonization, uptake by the mononuclear phagocyte system, and subsequent clearance. At the cellular level, nanoparticles enter tumor and immune cells through multiple endocytic pathways, including clathrin-mediated endocytosis, caveolae-dependent uptake, and macropinocytosis, with the dominant pathway determined by nanoparticle size and surface chemistry[98]. Following internalization, intracellular trafficking through endosomal and lysosomal compartments regulates drug release, degradation, and therapeutic efficacy. Consequently, rational nanoparticle design must integrate size, shape, and surface engineering to optimize systemic stability, cellular uptake, and intracellular drug availability in cancer therapy[99].

Significant efforts are directed toward understanding how to avoid toxic effects in vital organs while ensuring effective drug distribution. Therapeutic NPs (TNPs) offer adaptable characteristics, such as customizable sizes and surface features, which allow for conjugation with tumor-specific molecules, enabling more targeted treatments[100,101]. As the understanding of cancer progresses, TNPs are becoming increasingly integral to personalized cancer therapies. However, challenges remain, including limited drug-loading capacity, the need for regulated drug release, and difficulties in ensuring accurate intracellular and tissue distributions. Additionally, the concurrent targeting of both tumor cells and the TME presents further hurdles. Overcoming these challenges will require structural refinement, the design of multiligand targeting systems, extensive pharmacokinetic and pharmacodynamic analyses, and thorough quantification of tissue distribution[65,101–104]. Various nanocarrier formulations utilize distinct strategies to address these issues. For example, some nanocarriers generate reactive oxygen species (ROS) upon entering the bloodstream, leading to DNA damage and tumor cell apoptosis[105–107].

Active targeting, a promising approach for cancer therapy, leverages the overexpression of specific receptors on tumor cells. Nanocarriers can be engineered with ligands or antibodies that bind to these receptors, increasing the specificity of drug delivery. For example, the epidermal growth factor receptor (EGFR) is often overexpressed in various cancers, leading to the development of EGFR-targeted nanocarriers to improve delivery efficiency. While active targeting provides increased specificity and reduces systemic toxicity, challenges remain, such as receptor heterogeneity across different cancer types and the potential for receptor downregulation or mutation during treatment[108–113].

In contrast, passive targeting exploits the inherent properties of tumor sites, including the EPR effect and unique TME characteristics, to concentrate nanocarriers at the tumor site. In tumors, abnormal blood vessel formation and poor lymphatic drainage lead to enhanced particle retention and EPR. However, the high interstitial fluid pressure within the TME can hinder uniform NP distribution, resulting in particle accumulation primarily around blood vessels and the tumor periphery. To address this, many nanocarriers are designed to exploit TME features such as acidic pH, increased redox potential, and enzyme variations, enabling more consistent drug delivery throughout the tumor[114–117].

Targeting the TME remains a critical area of research. Nanocarriers can be functionalized with specific ligands to guide their accumulation in cancerous tissues, leveraging the EPR effect. However, the effectiveness of this approach may be limited in smaller tumors with less developed vasculature. For example, the chemotherapeutic agent Abraxane accumulates in tumors via albumin binding to the gp60 receptor and secreted protein acidic and rich in cysteine (SPARC). Additionally, various targeting ligands, such as lymphatic peptide 1 (LyP-1), Cys-Arg-Glu-Lys-Ala (CREKA), Arg-Gly-Asp (RGD), and urokinase-type plasminogen activator (uPA), have been utilized to enhance drug delivery by targeting endothelial cells in the tumor vasculature[118–120].

Reducing systemic toxicity is a significant benefit of NP-based drug delivery. Targeted strategies facilitate accurate delivery of drugs to cancerous locations, thus limiting contact with healthy tissues and decreasing off-target effects. This targeted approach allows higher drug doses at the tumor site, improving therapeutic efficacy while protecting normal cells from toxic effects. Additionally, NPs can protect encapsulated drugs from premature degradation and enzymatic breakdown, further enhancing the therapeutic potential of cancer treatments[24,121].

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NPs also hold promise for advancing cancer biomarker discovery and diagnostics. NPs can be engineered to detect circulating tumor cells, identify prognostic markers, and assess treatment efficacy. For example, fluorescent silver or dendrimer-based nanocomposites can label cells for imaging, whereas quantum dots are used to detect early-stage cancers. Magnetic NPs can capture circulating tumor cells, enabling tumor detection that is often not possible with traditional imaging techniques[122–125].

The molecular structure of NPs significantly influences their toxicity and stability. Key factors, including size, shape, surface charge, and chemical composition, determine their interactions with biological systems, which can result in toxicological effects such as oxidative stress, inflammation, and genetic damage[126–128]. Metallic NPs, including silver, gold, and iron oxides, induce cellular damage by crossing membranes and affecting organelles such as mitochondria and nuclei. This can lead to the disruption of metabolic processes and mutagenic changes[126,127,129]. Additionally, the bioaccumulation of NPs in critical organs such as the liver, kidneys, and brain raises concerns about long-term health effects[129]. As a result, comprehensive studies are needed to assess the toxicokinetic behavior of these particles. Strategies such as surface modification or encapsulation can help mitigate these risks while preserving the therapeutic efficacy of NPs in cancer treatment[130,131].

Nanoparticle targeting of apoptosis pathways: maximizing efficacy

Cancer cells often develop resistance to therapeutic agents through the dysregulation of proteins such as B-cell lymphoma 2 (Bcl-2) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). The overexpression of Bcl-2, in particular, contributes to resistance, making it a target for NP-based therapies. One promising strategy is the use of NPs to deliver small interfering RNAs (siRNAs) that target Bcl-2, often in combination with chemotherapeutic agents[132]. Similarly, inhibitors of NF-kB, such as pyrrolidine dithiocarbamate (PDTC) and curcumin, have been incorporated into NP-based combination therapies to overcome drug resistance[133,134]. Another strategy is to activate proapoptotic factors directly. For example, combining ceramide with paclitaxel has enhanced therapeutic efficacy in drug-resistant tumor models[135]. Furthermore, NP-mediated ceramide delivery has been shown to restore p53 expression, a critical tumor suppressor that can potentially reverse drug resistance[136].

NP-based gene therapy targeting p53 has shown promise in treating lung and breast cancers by promoting apoptosis and inhibiting tumor proliferation[137–139]. Several NP-based drug delivery systems work by blocking drug efflux pumps while promoting apoptosis, thus overcoming both pump-mediated and non-pump-mediated resistance mechanisms[140]. For example, an amphiphilic cationic NP complex encapsulating paclitaxel along with the Bcl-2 convertor gene has demonstrated the ability to effectively inhibit the growth of drug-resistant cancer cells[141]. Additionally, the codelivery of doxorubicin and resveratrol using NPs has demonstrated substantial cytotoxicity in doxorubicin-resistant breast cancer cells by downregulation of Bcl-2 and NF-kB expression and inhibiting efflux transporter expression[142,143]. Folic acid-conjugated NPs containing resveratrol and docetaxel have also proven effective in treating MDR prostate cancer[144,145].

Mitochondrion-targeted NPs, which influence efflux transporters and apoptotic pathways, reduce ATP production and disrupt the mitochondrial outer membrane, ultimately leading to cell death[146]. NP-based strategies collectively present promising solutions for overcoming drug resistance in cancer by simultaneously targeting multiple molecular pathways (Fig. 1).

Nanoformulations of drugs to enhance the antitumor immune response

Antitumor immunotherapy aims to modulate or activate the immune system to target cancer cells while minimizing damage to healthy tissue. NPs are vital in drug delivery, providing a targeted, controlled drug release platform, improving pharmacokinetics and biodistribution, and mitigating the risks of systemic toxicity. This is achieved through their ability to protect drugs from degradation, facilitate controlled release, and target specific tissues[147,148]. Chitosan-based NPs, for example, are nontoxic, biodegradable, and mucoadhesive, enabling precise cancer cell targeting[148]. In cancer vaccines, NPs act as delivery vehicles and adjuvants, increasing immunogenicity by efficiently delivering antigens and adjuvants to immune cells. Lipid NPs, for example, improve mRNA vaccine stability and the immune response, which is crucial for antitumor immunity[149,150]. NPs also enable the codelivery of peptide neoantigens and adjuvants such as STING and TLR4 agonists, enhancing $CD8^+$ T-cell activation and improving immune checkpoint blockade therapy efficacy[151].

Despite its potential, significant clinical challenges remain in the context of tumor immunotherapy. A major hurdle is the immune system's difficulty in distinguishing between malignant and normal cells owing to their molecular similarities. For example, in chimeric antigen receptor T-cell (CAR-T) therapy, managing 'off-target effects', unintended attacks on healthy cells, remains a substantial challenge[152]. Moreover, immune cells or cytokines delivered intravenously often fail to reach tumor sites because of the immunosuppressive microenvironment of solid tumors. As a result, immunotherapy tends to be more effective against hematological cancers, with limited efficacy against solid tumors[153].

Immunotherapy targeting cellular mechanisms via nanotechnology

Dendritic cells (DCs) are key antigen-presenting cells (APCs) that initiate immune responses and ensure self-tolerance. Nanotechnology enhances cancer therapy by improving antigen delivery to DCs, triggering a stronger immune response against tumor cells. However, regulatory T cells (Tregs) within the TME suppress cytotoxic T lymphocytes (CTLs), dampening overall T-cell activity. Targeted nanodelivery systems designed to reduce Treg numbers at the tumor site can help mitigate this suppression[154,155].

Tumor cells often evade immune detection by overexpressing immune-evasive proteins such as programmed death-ligand 1 (PD-L1) and CD47, which block T-cell functions[156,157]. Nanocarriers engineered to deliver inhibitors targeting these proteins can enhance immunotherapy efficacy. In addition to direct tumor cell death, NP drugs can trigger immunogenic cell death (ICD) through ROS production, further amplifying the immune response. Thus, integrating nanotechnology into cancer immunotherapy holds significant promise by stimulating immune responses and overcoming tumor-mediated immune evasion[158,159].

Nanocarrier systems for augmenting tumor immunotherapy

Nanocarriers enhance tumor immunotherapy by delivering a range of agents, including TAAs, immune checkpoint inhibitors, mRNA-based vaccines, immunomodulatory cytokines, and natural polysaccharides. These strategies aim to improve the ability of the immune system to recognize and eliminate cancer cells, contributing to both cancer prevention and treatment[160,161].

The use of TAAs is crucial for reactivating immune responses. NP-based delivery systems offer advantages over direct antigen injections by protecting antigens from degradation and ensuring targeted delivery to DCs for efficient antigen presentation and CTL activation. Several nanogel and nanovaccine formulations, such as those incorporating long peptide antigens or recombinant MUC4β subunits, have

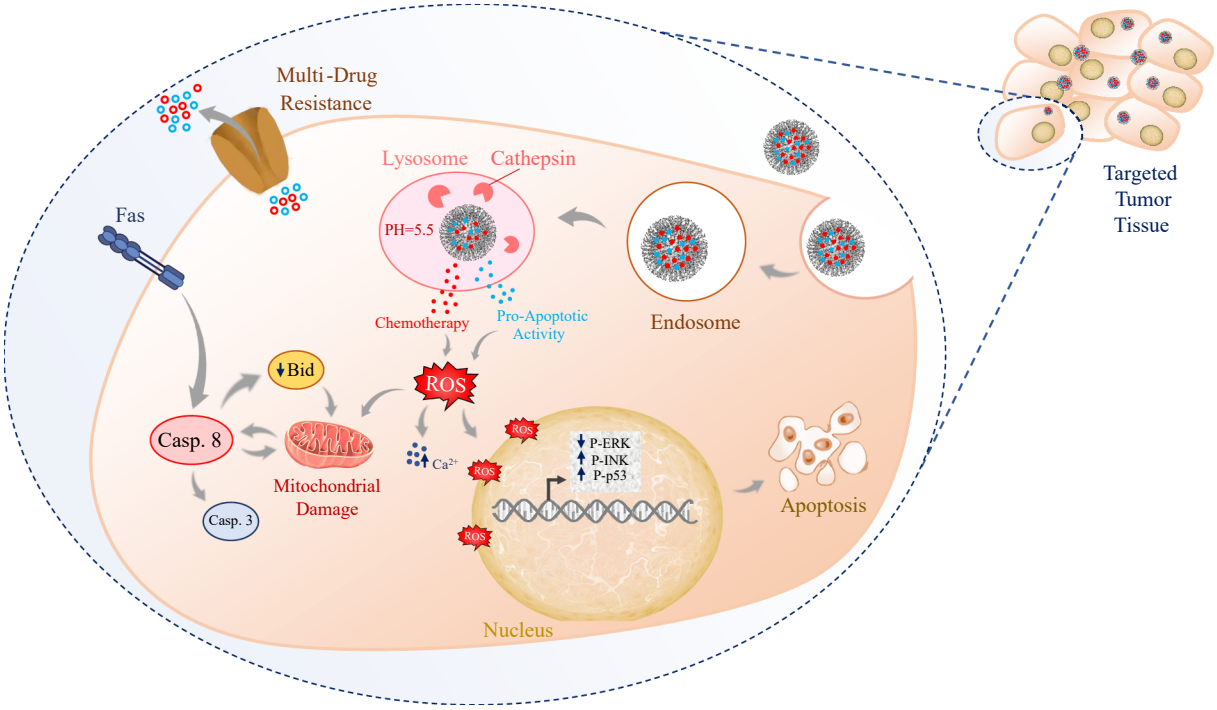

Fig. 1 The diagram depicts the sequential process by which targeted nanoparticles are delivered to tumor cells to induce apoptosis with optimal efficacy. Initially, nanoparticles penetrate the cell via endocytosis, circumventing MDR channels. Once inside the cell, the nanoparticles engage key caspase cascade elements, initiating apoptotic signaling pathways. This interaction promotes the production of ROS within the apoptosis pathway, further amplifying cellular death. The nanoparticles ultimately trigger apoptosis in tumor cells through precise targeting and efficient delivery. This highlights the potential of nanoparticle-based drug delivery systems to counteract drug resistance mechanisms, thereby improving the effectiveness of cancer therapies. Reactive oxygen species (ROS), caspase-8 (Casp. 8), caspase-3 (Casp. 3), extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), tumor protein p53 (P53), and multi-drug resistance (MDR).

demonstrated potent antigen-specific T-cell responses[162]. Additionally, targeted delivery of antigens to APCs combined with immunostimulatory agents such as Toll-Like Receptor 4 (TLR4) agonists can further enhance antitumor immunity. The delivery of antigens to local lymph nodes via nanocarriers promotes both CTL and humoral immune responses, underscoring the therapeutic potential of these systems in cancer immunotherapy[163–165].

Monoclonal antibodies (mAbs) have revolutionized cancer immunotherapy by targeting tumor cells with high specificity. However, their poor pharmacokinetics often limit their efficacy, which can be improved by encapsulating them in nanocarriers. NPs can deliver immune-modulating agents such as anti-programmed cell death protein 1 (PD-1) or anti-CD47 antibodies, increasing immune responses and attacks on cancer cells. These NPs can also play multiple roles in the cancer immune cycle, including antigen presentation, T-cell activation, and tumor eradication. Furthermore, combining CAR-T-cell therapy with bispecific antibodies in NP formats has shown significant antitumor efficacy in preclinical models[166–170].

Despite promising results from nucleic acid-based immunotherapy in preclinical studies, clinical trials have underperformed due to nucleic acid delivery challenges. Biocompatible, cell-targeting nanomaterials, such as lipid NPs, have improved the delivery of mRNA-based vaccines, leading to robust $CD8^+$ T-cell responses and tumor shrinkage in animal models. Moreover, combining mRNA therapies with cytokines or immunoadjuvants in NPs has further enhanced immune activation and improved tumor responses[171–173].

Polysaccharides, such as lentinan and Ganoderma lucidum glycopeptides, have long been recognized for their ability to modulate immune responses. While their clinical use has been limited by stability and bioavailability issues, recent advances in NP carriers have increased their stability and delivery[174–177]. Studies have shown that polysaccharide-loaded nanocarriers can stimulate immune cell activation, expand T-cell populations, and synergize with chemotherapy, offering significant potential in cancer immunotherapy[178–181].

Nanoparticle-based immunotherapy leveraging adoptive T-cell transfer

Adoptive T-cell transfer (ACT) has shown substantial efficacy in cancer treatment, but several challenges remain, including poor tumor infiltration, limited functional persistence, and suboptimal targeting. Recent advances in nanotechnology offer strategies to overcome these barriers. Traditional *ex vivo* T-cell expansion using natural APCs can be time-consuming and inconsistent, leading to efforts to develop artificial APCs (aAPCs) to improve antitumor T-cell expansion[182–185].

For example, Zhang et al. engineered biomimetic magnetosomes and magnetic nanoclusters coated with leukocyte membrane fragments and functionalized them with T-cell stimulatory components. These aAPCs enhanced antigen-specific CTL expansion and guided CTL migration to tumor sites via MRI, significantly inhibiting tumor growth in mouse models[186]. Similarly, Li et al. designed polymer NPs that delivered cytotoxic T-lymphocyte antigen 4 (CTLA-4) siRNA to T-cells, leading to enhanced T-cell activation and proliferation within the TME[187].

Additionally, Demento et al. developed poly(lactic-co-glycolic acid) (PLGA)-based NPs modified with lipopolysaccharides to promote DC maturation, further enhancing T-cell responses and boosting both humoral and cellular immunity[188].

Role of stimulus-responsive NPs in immunotherapy

Tumor tissues exhibit unique microenvironments characterized by acidity, hypoxia, and enzyme overexpression, which distinguish them

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from normal tissues[189,190]. These factors contribute to the low immunogenicity of cancer cells and the immunosuppressive nature of the TME. Enhancing the effectiveness of anticancer therapies necessitates remodeling the TME and enhancing immune cell infiltration. Multifunctional nanodrug delivery systems are being developed to target tumor tissues, improve drug uptake and release, and modulate the immunosuppressive TME. For example, microenvironment-responsive systems that respond to specific signals within the tumor can improve drug retention and penetration. Examples include systems that codeliver PD-L1 antibodies and photosensitizers, resulting in significant tumor growth inhibition[191–194]. Additionally, systems that exploit the acidic TME to activate prodrugs or inhibit immunosuppressive enzymes have shown promise in enhancing local and systemic antitumor effects[195–198].

Immune checkpoint inhibitors, including anti-PD-1 and anti-CTLA-4 antibodies, have revolutionized melanoma and non-small cell lung cancer (NSCLC) treatments by restoring the body's antitumor immune response. This approach functions by counteracting the inhibitory effects of PD-1 and CTLA-4, which normally suppress the activity of $CD8^+$ $\alpha\beta$ T lymphocytes, thereby restoring their antitumor capabilities[199–205]. However, these therapies have been less effective for other tumors, including colorectal and ovarian cancers. In murine models, liposomal doxorubicin targeted PD-L1-expressing tumor cells via specific peptides, disrupting the PD-L1/PD-1 interaction and enhancing $CD8^+$ T-cell-mediated antitumor activity[206]. NK cells and $\gamma\delta$ T cells, key components of the innate immune system, exhibit reduced expression of immune checkpoint molecules, which enhances their cytotoxic activity against tumors. Consequently, nanoformulated activators targeting these immune cells may constitute an ideal strategy for treating tumors that do not respond to anti-PD-1 and/or anti-CTLA-4 therapies. Further investigation is necessary to understand how NP-based drugs can effectively trigger $\gamma\delta$ T cells[207,208].

The effective delivery of immunomodulatory agents to targeted cells is essential for the development of nanovaccines, NP-based formulations designed to induce antigen-specific immune responses[209]. NPs confer numerous advantages, including protection of payloads, extended half-life, reduced toxicity, and enhanced delivery to APCs or TAAs[210]. Some NPs possess inherent immunostimulatory properties, provoking robust T-cell and antibody responses against tumors. The size of the NPs significantly influences their efficacy, and they can be used to deliver DC stimulatory molecules that activate APCs in tumor-draining lymph nodes. Combining antigens with adjuvants in NPs has demonstrated potential, with particle size playing a crucial role in immunogenicity. Moreover, targeting specific subsets of DCs with tailored NPs can enhance cytotoxic T-cell responses. The combination of distinct NP types with complementary functionalities remains an intriguing avenue for future exploration[211–213].

Nanotechnology-assisted adoptive cell therapies (ACTs), such as CAR-T-cell therapy, also hold promise for enhancing cancer treatment outcomes. Strategies involving the incorporation of NPs or cytokines into CAR-T cells have shown potential for increasing their cytotoxic activity, improving treatment outcomes[214–216]. However, challenges such as side effects, high costs, and limited efficacy remain[217–219]. Research into combination therapies and alternative immune cells, such as CAR-NK cells or CAR-macrophages, could further improve the clinical efficacy of ACT (Fig. 2)[220–222].

Therapeutic effects of NPs on solid tumors

NMs, defined by at least one dimension in the nanoscale range (1–100 nm), exhibit unique mechanical, optical, electrical, and catalytic properties that distinguish them from bulk materials. NMs are

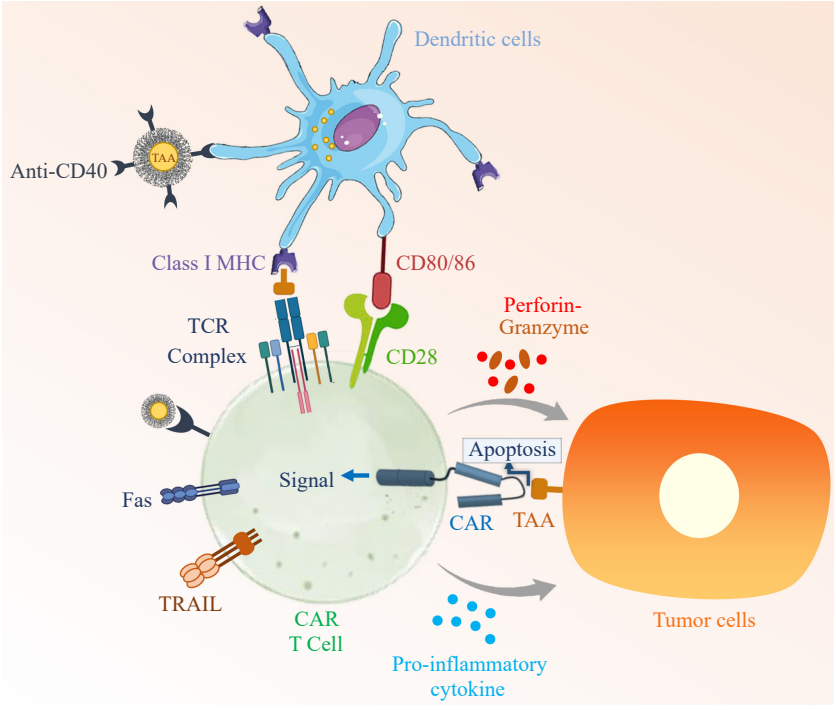

Fig. 2 The diagram illustrates the enhanced delivery of DC stimulatory molecules via nanoparticles, facilitating the activation of APCs or TAAs within the tumor-draining lymph nodes. This mechanism can amplify the cytotoxic potential of nanotechnology-assisted ACT, exemplified by CAR-T cells. The figure shows that DCs interact with nanoparticles through their receptors, initiating CAR-T-cell activation via class I and additional receptors. CAR-T cells, in turn, recognize and bind to tumor cells via a specific receptor, leading to their destruction through the release of perforin and granzyme. Chimeric antigen receptor (CAR), tumor-associated antigens (TAA), major histocompatibility complex class I (Class I MHC), T cell receptor (TCR), and TNF-related apoptosis-inducing ligand (TRAIL).

categorized on the basis of their dimensionality into zero-dimensional (0D), one-dimensional (1D), two-dimensional (2D), and three-dimensional (3D), including structures such as nanospheres, nanotubes, and nanosheets. Their properties can be fine-tuned through modifications in size, shape, synthesis, and functionalization, and they can be composed of both inorganic materials (e.g., metals and oxides) and organic materials (e.g., polymeric NPs and nanofilms)[223–225].

The resistance of solid tumors to traditional systemic treatments is a multifaceted challenge influenced by multiple biological and environmental factors. A significant challenge is heterogeneity within tumors, which includes subpopulations of cells, such as polyploid giant cancer cells (PGCCs), that can survive treatment and repopulate the tumor, contributing to therapy resistance[226]. Additionally, the TME plays a crucial role in supporting tumor survival through factors such as hypoxia and acidity, which protect the tumor and facilitate its adaptation to treatment, presenting further barriers to effective therapy[227]. Traditional chemotherapy often fails due to mechanisms such as drug inactivation, efflux, and DNA repair, which are further complicated by the presence of cancer stem cells (CSCs) that exhibit inherent resistance to many treatments[228,229]. Furthermore, systemic chemotherapy struggles to deliver high concentrations of drugs at the tumor site, leading to limited effectiveness and significant side effects[230]. Although monoclonal antibodies are more targeted, their poor tissue penetration and heterogeneous distribution contribute to acquired resistance[231]. Nanocarriers provide an effective approach to overcoming the resistance of solid tumors to traditional treatments by targeting key resistance mechanisms, such as the overexpression of apoptosis inhibitors (e.g., Bcl-2, IAPs, and Akt) and drug efflux proteins such as P-gp, which are commonly observed in resistant tumors. These NP-based systems increase the solubility, stability, and targeted delivery of anticancer drugs via the EPR effect, concentrating them in tumor tissues to improve efficacy and reduce off-target toxicity[232]. Moreover, nanocarriers can codeliver autophagy regulators and anticancer drugs, offering a synergistic effect that increases treatment efficacy while reducing systemic toxicity[233]. Designed for precise targeting, deep penetration, and controlled drug release, nanocarriers help overcome MDR, minimize side effects, and improve biocompatibility[234,235]. The codelivery of multiple drugs and MDR reversal agents also shows promise in inhibiting tumor metastasis and recurrence (Table 2)[236].

The delivery of NMs to solid tumors has been a central research focus for over a decade. Early studies emphasized improving delivery via passive or active targeting strategies, primarily leveraging the EPR effect. The EPR effect takes advantage of the abnormal vascular structures found in tumors, allowing NMs to extravasate from blood vessels and penetrate tumor tissues[29,237]. However, recent studies indicate that the EPR effect is often less effective than previously thought, with some researchers proposing that NMs may enter tumors through active mechanisms rather than solely relying on leaky blood vessels[114,238–240].

A meta-analysis by Wilhelm et al. revealed that only 0.7% of intravenously administered organic and inorganic NPs accumulate in solid tumors in preclinical models, irrespective of the targeted strategy used. While this low accumulation may suffice for small tumors, it is insufficient for larger tumors because of size and cellular composition variations. These findings emphasize that therapeutic success depends on the precision of targeting mechanisms and the proficiency of drug release processes. Despite the low accumulation rate, this figure is still higher than the efficacy seen with conventional therapies, although it does not account for tumor size, dosage, or variability in the EPR effect across different models[237].

The size of gold-based NMs is particularly important for optimizing delivery efficiency. The thickness and permeability of the stromal barrier, directly related to tumor size, can affect the penetration of NMs into the tumor. Tailoring the size of NMs to match the specific dimensions of individual tumors may improve therapeutic outcomes by enhancing diagnostic and therapeutic efficiency. However, the biological heterogeneity of tumors complicates the prediction of NM effectiveness[241–243]. The variability in tumor perfusion, vessel permeability, and angiogenesis further challenges the reliable prediction of outcomes from NP-based treatments[244,245].

Therapeutic effects of NPs on hematological malignancies

Current chemotherapeutic and molecularly targeted agents have improved outcomes in treating hematological malignancies (HMs), but long-term remission or complete remission remains achievable in only a subset of patients. This limited success can be attributed to the nonspecific nature of these therapies, which inadvertently affect healthy tissues and cause off-target side effects[252]. To sustain therapeutic concentrations at the tumor site, high drug doses and frequent administrations are frequently required, exacerbating these adverse effects[253]. Consequently, there is a growing need for drug-delivery systems that minimize healthy tissue exposure while ensuring precise and effective delivery to malignant cells[254].

HMs, particularly lymphomas, often involve the spleen, which plays a key role in immune regulation and can accumulate intravenously administered NPs. The targeting of inflammatory monocytes in the spleen via NPs loaded with siRNA has shown promise in reducing tumor growth in lymphoma models[255,256].

Several formulations have been developed and tested in nanomedicine for drug delivery in blood cancers. These include PEGylated liposomal doxorubicin (PLD) and non-PEGylated liposomal doxorubicin (NPLD), which are used in treating various HMs. For example,

Table 2. Utilizing NPs to promote antitumor immune reactions.

Approach	Tumor model(s)	Key outcome(s)	Ref.
Delivery of TAAs to APCs	OVA-expressing melanoma, thymoma, T-cell lymphoma, colon adenocarcinoma	- Efficient internalization of TAAs by dendritic cells (DCs). - Potent cellular and humoral immune responses. - Enhanced immune response of tumor-specific T cells against antigens. - Tumor growth slowed down.	[246,247]
Delivery of adjuvants to TDLNs (Tumor-Draining Lymph Nodes)	Melanoma, B-cell lymphoma	- Efficient internalization of adjuvants by dendritic cells. - Strong cellular and humoral immune responses. - Reduction in tumor size. - Prolonged survival time. - Immune stimulation of DCs through TLR-ligand modulation.	[248,249]
Codelivery of antigen and adjuvant	Melanoma, OVA-expressing	- Immune responses from both CD4 and CD8 T cells. - Strong CD8 T-cell response independent of additional stimuli. - Production of INF-gamma. - Balanced antibody response (IgG1 and IgG2). - Reduced regulatory T-cell count, enhancing vaccine effectiveness. - Vigorous production of antigen-specific cytotoxic T lymphocytes (CTLs).	[250,251]

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PLD in combination with the proteasome inhibitor bortezomib has shown encouraging results in multiple myeloma treatment[257–259]. Additionally, liposomal daunorubicin has been explored as a treatment option for HM[260]. Liposomal vincristine has also been approved for treating Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL)[261,262]. Recently, approved combinations, such as liposomal cytarabine + daunorubicin (CPX-351/VYXEOSTM), have demonstrated efficacy in high-risk secondary acute myeloid leukemia (AML)[263]. Moreover, polymer-based nanomedicines, including polymeric micelles, have emerged as tailored solutions to enhance drug stability, circulation, and targeting, offering considerable potential in hematological cancer treatment.

In addition to optimizing drug delivery, nanotechnology has also been investigated to improve hematopoietic stem cell transplantation (HSCT), a critical treatment for blood cancers such as leukemia. However, challenges such as recurrence and graft-vs-host disease (GVHD) remain. Nanomaterials are being investigated to expand hematopoietic stem cells (HSCs) *ex vivo*, addressing the issue of limited donor cell availability. Hydrogels, microcavity arrays, and NPs have shown promise in supporting HSC expansion in laboratory settings, suggesting that they may improve HSCT outcomes[264–266].

Additionally, NPs have been engineered to target signaling pathways involved in blood cancers[254,267,268], with promising results in animal models. NPs have also been studied for their ability to modulate intracellular pathways related to epigenetics, cell death, and metabolism, potentially opening new treatment options. These advancements in nanomedicine could enhance therapeutic outcomes while minimizing side effects in blood cancer treatment[268–271]. Furthermore, NP-based delivery systems can stimulate immune responses by promoting the release of antitumor cytokines. For example, recombinant granulocyte–monocyte colony stimulatory factor (rGM-CSF) delivered through nanoformulations has been designed to enhance tumor cell clearance by macrophages[272]. NPs loaded with siRNAs have been utilized to target tumor-associated macrophages, indicating their promising role in cancer immunotherapy, although potential side effects remain a concern[273,274]. Peptide- and protein-based nanoformulations have been explored for their ability to enhance the efficacy of cancer vaccines[275], and NP-based drug formulations have demonstrated promise in stimulating antitumor immune effector cells[187,276].

Challenges and limitations of nanocarrier utilization in cancer treatment

Nanocarriers demonstrate significant potential in cancer therapy; however, several challenges impede their successful translation into clinical application. A considerable challenge in oncology is tumor biology's complex and heterogeneous nature, which poses substantial obstacles to effectively targeting and delivering chemotherapeutic agents. MDR, driven by mechanisms such as the overproduction of efflux pumps or alterations in drug targets, further reduces the effectiveness of nanocarriers[277,278]. This issue, coupled with the varied molecular profiles of tumor cells, makes selective targeting difficult while sparing healthy tissue.

Nanocarriers must be able to target and infiltrate diverse tumor cell types, but inconsistent receptor expression across different tumor types limits their specificity. This variability reduces the success of receptor-targeted therapies[279]. Additionally, the TME, with factors such as hypoxia, elevated interstitial fluid pressure, and acidic pH, presents significant obstacles to drug release and distribution. Hypoxia can reduce drug sensitivity, whereas interstitial fluid pressure can limit the penetration of nanocarriers into deeper tumor regions[280–282].

Off-target toxicity is another major concern. Despite efforts to improve nanocarrier selectivity, unintended accumulation in healthy tissues may lead to harmful side effects. Nanomaterials may provoke immune responses or accumulate in organs such as the liver, spleen, or kidneys, resulting in chronic toxicity[283]. Moreover, the long-term fate of nanocarriers is not well understood, and interactions with the immune system could cause immunogenicity or impair immune function. Therefore, controlling nanocarrier distribution and clearance is crucial for reducing off-target effects. Comprehensive preclinical evaluations of pharmacokinetics, biocompatibility, and long-term safety are essential.

The scalability of nanocarrier production also presents challenges. Manufacturing nanocarriers requires precise control over size, shape, and surface properties to ensure consistent therapeutic outcomes[284]. Even small deviations in these parameters can impact biodistribution, uptake, and efficacy. Ensuring consistent quality at a commercial scale is vital for successful clinical use. Furthermore, regulatory approval of nanomedicines remains slow, with few products approved due to the challenges in proving their safety and efficacy. Regulatory agencies require extensive data on physicochemical properties, pharmacokinetics, toxicity, and efficacy, which is often time-consuming and expensive[285].

Researchers are developing stimuli-responsive nanocarriers to increase the precision of drug delivery triggered by ultrasonic, light, or temperature factors. These systems can potentially regulate drug release specifically at the tumor site, minimizing systemic exposure and reducing associated side effects. However, designing such systems is complex, and practical limitations, such as the depth of stimulus penetration, must be addressed. For example, light-responsive nanocarriers face limitations in terms of tissue penetration, whereas ultrasound and magnetic fields, which allow deeper penetration, require optimized protocols[284,286]. Furthermore, the possibility of inadvertently damaging healthy tissues remains a concern, and achieving uniform activation within heterogeneous tumors remains challenging.

Despite these obstacles, innovative strategies are emerging. Functionalizing nanomaterials, such as graphene oxide, is a promising approach to improving nanocarrier targeting and cytotoxicity. With its large surface area and capacity to absorb near-infrared light, graphene oxide emerges as an ideal candidate for drug delivery and photothermal therapy. Furthermore, developing multifunctional, 'smart' nanocarriers that can respond to multiple stimuli or deliver combination therapies may increase the precision and effectiveness of cancer treatments[60,287].

One promising approach to mitigate the challenges of nanocarrier-based cancer treatment is the development of multifunctional nanocarriers. These specialized carriers are designed with distinct characteristics that allow them to navigate the complex TME and efficiently deliver therapeutic agents to the tumor site[288–291]. Several strategies can be utilized to enhance the performance of nanocarriers: (1) Targeting specificity: Nanocarriers can be altered with targeting ligands (such as antibodies or peptides) that recognize specific receptors on cancer cells, increasing their selectivity for tumor cells. This modification enhances the accumulation of therapeutic agents at the tumor site, improving their effectiveness while reducing systemic toxicity[292–294]. (2) Stimuli-responsive behavior: Nanocarriers can be engineered to respond to specific conditions in the TME, such as acidic pH, elevated enzyme levels, or hypoxia. For example, pH-sensitive nanocarriers exploit the acidic microenvironment of tumors to trigger the release of drugs directly at the tumor site, reducing the impact on healthy tissues[198,295,296]. (3) Enhanced imaging capabilities and theranostics: Nanocarriers can be integrated with imaging agents, allowing noninvasive tracking of their distribution in the body. These real-time data can help optimize treatment regimens and enable personalized treatment approaches. Furthermore, the development of theranostic nanocarriers, which combine therapeutic agents with diagnostic imaging tools,

holds promise for real-time monitoring of treatment responses and adaptive management (Table 3)[297–300].

Despite extensive preclinical success, only a limited number of nanocarrier-based formulations have successfully translated into clinical practice, underscoring the gap between experimental promise and clinical reality. Examining both successful and unsuccessful clinical cases provides critical insight into the factors governing nanomedicine efficacy, safety, and translational feasibility.

Among the most successful examples is Doxil®, a PEGylated liposomal formulation of doxorubicin approved for the treatment of ovarian cancer, multiple myeloma, and Kaposi's sarcoma. Doxil® demonstrated reduced cardiotoxicity and improved pharmacokinetics compared with free doxorubicin, largely due to prolonged circulation time and controlled drug release. This formulation highlights the importance of surface modification and size optimization in minimizing off-target toxicity while maintaining therapeutic efficacy[48,301]. Similarly, Abraxane®, an albumin-bound paclitaxel nanoparticle, achieved clinical success by eliminating the need for toxic solvents and exploiting endogenous albumin transport pathways to enhance tumor accumulation. Abraxane® showed improved tolerability and efficacy in breast, pancreatic, and lung cancers, illustrating how simplified nanocarrier design and biologically inspired targeting can facilitate clinical translation[302,303].

Another notable success is CPX-351 (Vyxeos®), a liposomal formulation co-encapsulating cytarabine and daunorubicin at a fixed synergistic ratio for the treatment of high-risk acute myeloid leukemia. By maintaining optimal drug ratios *in vivo*, CPX-351 significantly improved overall survival compared with conventional chemotherapy, demonstrating the advantage of nanocarriers in combination drug delivery[304]. In addition, although not developed for cancer, Onpattro® (patisiran)—a lipid nanoparticle–delivered siRNA therapeutic—provides strong clinical validation for nucleic acid delivery platforms that are now being adapted for oncological applications[305].

In contrast, several nanocarrier systems have shown limited or unsuccessful outcomes in clinical trials, highlighting persistent translational challenges. BIND-014, a prostate-specific membrane antigen (PSMA)-targeted polymeric nanoparticle delivering docetaxel, failed to demonstrate superior efficacy in Phase II trials despite promising preclinical data. This failure has been attributed to insufficient tumor accumulation and heterogeneous receptor expression, emphasizing the limitations of active targeting strategies in complex tumor environments[306]. Similarly, MM-302, a HER2-targeted liposomal

Table 3. Some recent advancements in nanoparticle-based imaging and targeted drug delivery for solid tumor types.

Tumor type	NPs type	NPs feature	Key advancements	Ref.
Breast cancer (MCF-7)	Oleic acid-Fe_3O_4 NPs (OA-Fe_3O_4) incorporated into PLA-PEG-PLA copolymer (BMNPs/EPPT/drug)	- Spherical morphology (179–203 nm) - Magnetic - Drug-loaded - pH-sensitive release - Targeted delivery via EPPT peptides	- Increased drug release at lower pH - Enhanced *in vitro* cytotoxicity (lower IC_{50}) - Selective interaction with breast cancer receptors - Significant tumor volume reduction *in vivo*.	[310]
HER-2-positive breast cancer	Generation 5 poly(amidoamine) dendrimers conjugated with gold NPs, chelated gadolinium, and anti-HER-2 antibody	- Bimodal imaging (CT and MRI) - HER-2 specific targeting - Encapsulated gold NPs - Gadolinium for MRI	- Enhanced MRI signal intensity (~20%) - Improved CT resolution and contrast (2-fold) - Specific targeting and internalization in HER-2 positive cells - Potential for early detection and therapeutic monitoring.	[311]
HER2-positive breast cancer	cRGD-modified RBC membrane-coated multidrug nanocomplexes	- Coated with red blood cell membrane (RBCm) - Cyclic Arg-Gly-Asp (cRGD) modification for targeting - Combinational delivery of Polo-like kinase 1 siRNA (siPlk1) and neratinib - Enhanced drug stability and tumor accumulation	- Overcomes challenges of *in vivo* codelivery of oligonucleotide drugs and chemotherapy agents - Combination therapy significantly improved antitumor efficacy in HER2-positive breast cancer, both *in vitro* and *in vivo*.	[312]
Breast cancer	Biologically produced Gold NPs (AuNPs)	- Round AuNPs (13 ± 1.3 nm) - Zeta potential of −35.8 ± 1.3 mV - Conjugated with multiple cargoes (Paclitaxel, Transferrin, and anti-miR-135b)	- Multicargo delivery system with effective tumor targeting - Higher *in vitro* cytotoxicity - Enhanced tumor-specific toxicity - Suppression of miR-135b expression - Superior to current drug carriers.	[313]
Breast cancer	Polymeric siRNA NPs (PRNs)	- NPs (50–200 nm) made using rolling circle transcription (RCT) - Coated with biopolymers (PLL, PLG, HA)	- Size- and surface-tuned PRNs improve systemic delivery and anticancer effects - HA-layered NPs (~200 nm) exhibit the best targeting and therapeutic efficacy due to CD44 receptor targeting.	[314]
Breast cancer	Lipid-substituted polyethyleneimine (PEI) polymers (lipopolymers)	- siRNA/lipopolymer nanocomplexes - Optimized with anionic additives (phosphate buffer and N-Lauroylsarcosine Sodium Salt) for gene silencing	- Achieved > 80% gene silencing and > 70% cell killing with minimal cytotoxicity in MDA-MB-231 breast cancer cells - > 95% cell uptake - Persistent effects for at least 6 d.	[315]
Lung cancer (NSCLC)	Superparamagnetic iron oxide NPs (SPIONs) combined with Exos derived from NSCLC cells	- Dual-targeting system using SPIONs for magnetic targeting - Exos for homing and targeted delivery - Doxorubicin (DOX) loaded for tumor suppression	- Developed a 'dual-targeting' drug delivery platform - Exosome-SPIONs loaded with DOX provide optimal tumor tissue delivery - Effective tumor suppression in NSCLC models - Reduced toxicity to normal tissues.	[316]
Lung cancer (EGFR-mutant, PC-9 cells)	Silk peptide NPs (CUR/ERL@SP)	- Dual-drug coloaded (curcumin and erlotinib) - 150 nm in size - Enhanced cell internalization	- Codelivery of curcumin and erlotinib enhances drug efficiency - Improved cellular uptake - Downregulation of EGFR and proteins involved in tumor invasion - More effective therapeutic strategy for EGFR-mutant lung cancer.	[317]

(to be continued)

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Table 3. (continued)

Tumor type	NPs type	NPs feature	Key advancements	Ref.
Lung cancer (A549 cells)	Paclitaxel-loaded PLGA NPs (AM@PTX-NPs)	- A549 cell membrane biomimetic NPs - 10.90% drug loading efficiency - Spherical shape	- A549 cell membrane camouflaged NPs significantly enhanced targeting - Tumor growth inhibition: 73% vs 37.39% for unmodified PTX-NPs - Improved strategy for targeted cancer treatment.	[318]
Lung cancer (A549 cells)	Collagenase-loaded AcMD nanostructured microparticles (MPs)	- Hollow, corrugated morphology - Median volume diameters: 2.58 ± 1.35 to 3.01 ± 0.68 μm - MMAD: 1.93 ± 0.06 to 2.80 ± 0.10 μm - FPF: 68.02 ± 6.86% to 69.62 ± 2.01% - Enzymatic stability: 89.5 ± 6.7%	- Collagenase-loaded microparticles improved nanoparticle penetration into tumor spheroids (A549/MRC-5 coculture) - Enhanced delivery of therapeutic NPs - ECM-modulation for better intratumoral penetration.	[319]
Lung cancer (A549 cells)	Niosomes containing gold NPs (Nio-AuNPs)	- Hydrodynamic diameter of AuNPs: 38.85 ± 0.85 nm - Nio-AuNPs diameter: 127.8 ± 2.92 nm - Spherical shape (confirmed by TEM and FE-SEM)	- Combination of Nio-AuNPs with X-ray radiation (XRT) showed a synergistic effect - Increased cytotoxicity and apoptosis induction in A549 cells - Superior to XRT or AuNPs alone.	[320]
Metastatic prostate cancer (PCa)	Au/Mn nanodots-luteinizing hormone-releasing hormone (AMNDs-LHRH) nanosystem	- Multimode imaging (FL/CT/MR) - Targeted drug delivery - Photothermal therapy - Fluorescence-guided surgery	- Targeting GnRH-R positive PCa and metastases for accurate preoperative CT/MR diagnosis - Fluorescence visualization for surgery - Improved photothermal therapy for metastatic PCa - Enhanced diagnostic accuracy and therapeutic effect.	[321]
Bone metastatic prostate cancer (PCa)	Au/Gd nanodots	- Multimode imaging (optical and X-ray) - Good biocompatibility - High biosafety	- High-precision detection of metastatic prostate cancer - Complementary multimode imaging for accurate diagnosis and treatment guidance - Enhanced biosafety and biocompatibility *in vitro* and *in vivo*.	[322]
Colorectal cancer	Functionalized mesoporous silica NPs (MSN-NH_2 and MSN-COOH)	- Spherical shape - Mesoporous structure - pH-responsive drug release - Surface functionalization with amino (positive charge) and carboxyl groups (negative charge)	- Controlled release of doxorubicin at physiological pH (7.4) to reduce systemic toxicity - Enhanced drug release at acidic pH (5.5), targeting TME - Improved therapeutic efficacy by exploiting pH-sensitive drug release.	[323]
Colon cancer	Poly(lactide-co-glycolide)-block-poly(ethylene glycol)-carboxylic acid endcap NPs (PLGA-PEG-COOH NPs)	- CASIN encapsulated in PLGA-PEG-COOH NPs - Targeted delivery system - Improved bioavailability - Reduced drug elimination	- Development of a nanoparticle-based delivery system for CASIN - Overcomes rapid drug elimination and low bioavailability - Enables targeted inhibition of Cdc42 in colon cancer.	[324]
Colorectal cancer	Salmonella membrane-coated bacilliform gold nanorods (SM-AuNRs)	- Gold nanorods coated with Salmonella membrane proteins - Mimics Salmonella morphology and surface - Targeted tumor cell internalization - Mucus barrier penetration	- Development of biomimetic SM-AuNRs for enhanced tumor targeting and penetration - Superior photothermal and chemotherapeutic effects for colorectal cancer treatment.	[325]
Colorectal cancer	GOx@FeNPs (glucose oxidase-loaded iron NPs)	- Dual-targeted NPs with cRGD peptide and anisamide (AA) - Combines photothermal therapy (PTT), ferroptosis, immune checkpoint blockade (αPD-L1), and MRI	- Combination of PTT, ferroptosis, and *α*PD-L1 blockade for enhanced CRC treatment - Dual-targeting (cRGD and AA) improves tumor targeting - Induces immunogenic cell death (ICD) and enhances immune response - Achieves over 90% tumor inhibition - MRI capability for integrated diagnosis and therapy.	[326]
Colorectal cancer	Hyaluronidase-responsive MSN-HA/DOX, DOX/SLN-PEG-Biotin, Galactosylated chitosan-functionalized MSNs	- Functionalized mesoporous silica NPs (MSNs) - Surface modifications with hyaluronic acid (HA), polyethylene glycol (PEG), biotin, and galactosylated chitosan - Dual-stimulus release (hyaluronidase-responsive)	- Enhanced tumor inhibition via dual-stimulus release and biotin-targeting for CRC cells - Controlled release through asialoglycoprotein receptors - Significant *in vitro* and *in vivo* efficacy improvements over conventional chemotherapy.	[327]
Gastrointestinal cancer	Poly(lactic-co-glycolic acid) (PLGA)-based NPs	Biodegradable, biocompatible, and tunable properties such as the ratio of PLA to PGA, molecular weight, crystallinity, and preparation process	- Diagnosis - Chemotherapy - Radiotherapy - Novel treatments like immunotherapy, gene therapy, and photothermal therapy	[328]
Gastric cancer	pH-responsive NPs with TPGS-conjugated fucoidan	- pH-responsive - Targeted delivery to P-selectin protein	- Demonstrated enhanced antigastric tumor efficacy - Reduced expression of malignant proteins - Promising clinical therapeutic potential	[329]
Gastric and colon cancer	Glucose oxidase-loaded manganese-based mesoporous silica NPs (MSN@Mn-GOx)	- Solid spheres (~100 nm) - Fenton-like properties - pH-responsive (stronger at pH 6.0) - Zeta potential: -35 mV	- Enhanced ROS production - Inhibition of gastric and colon cancer cell proliferation - MRI-based tumor imaging enhancement - Potential therapeutic option for gastric cancer	[330]
Gastric cancer	Arginine-chitosan and fucoidan NPs	- Protects postbiotic (SGMNL-133) from gastric acid degradation - Facilitates mucus penetration - Enhances interaction with cancer cells	- Successful isolation and optimization of GMNL-133 (SGMNL-133) to inhibit gastric cancer cell proliferation - Development of NP formulation to improve *in vivo* delivery of SGMNL-133 - Enhanced anti-gastric tumor efficacy and reduced tissue inflammation.	[331]

(to be continued)

Table 3. (continued)

Tumor type	NPs type	NPs feature	Key advancements	Ref.
Pancreatic adenocarcinoma	AuNPs (Gold NPs)	- Coated with hyaluronic acid and oleic acid (HAOA-AuNPs) - Coated with bombesin peptides (BBN-AuNPs) - Spherical shape - Size: 83 ± 20 nm (HAOA-AuNPs) - Size: 49 ± 12 nm (BBN-AuNPs)	- Significant reduction in cell viability when combined with Radiation Therapy (RT) - Improved therapeutic effect when RT was combined with AuNPs - AuNPs at different concentrations (200-400 μM for HAOA-AuNPs, 50-200 μM for BBN-AuNPs) showed varying reductions in cell viability (up to 37%) - RT + AuNPs combination showed up to a 26% reduction in viability at 72 h postirradiation	[332]
Pancreatic cancer (MIAPaCa-2 and PANC-1 cell lines)	Titanium dioxide NPs (H_2O_2-modified)	- Modified with hydrogen peroxide - Used in combination with ultrasound-stimulated microbubbles (USMB) and X-rays	- USMB + X-rays showed a significant radiation enhancement effect and increased ROS in MIAPaCa-2 cells - No enhancement effect observed in PANC-1 cells - USMB did not improve nanoparticle-induced radiosensitization in either cell line when combined	[333]
Pancreatic adenocarcinoma	AuNPs (Gold NPs)	- Coated with hyaluronic acid and oleic acid (HAOA-AuNPs) - Coated with bombesin peptides (BBN-AuNPs) - Spherical shape - Size: 83 ± 20 nm (HAOA-AuNPs) - Size: 49 ± 12 nm (BBN-AuNPs)	- Significant reduction in cell viability when combined with Radiation Therapy (RT) - RT + AuNPs showed up to 37% reduction in cell viability - Combination of RT and AuNPs led to improved therapeutic efficacy, with up to 26% reduction in cell viability at 72 h postirradiation - Improved effect observed with both HAOA-AuNPs and BBN-AuNPs compared to RT alone	[334]
Pancreatic cancer (PANC-1 cell line)	Silver NPs (AgNPs)	- Functionalized with IgG molecules - NIR light absorption (808 nm, 2 W) - Used for photothermal therapy	- Photo-excitation of IgG-functionalized silver NPs induced dysfunction in the Golgi apparatus - Activated caspase-3 apoptotic pathway, leading to cellular apoptosis - Demonstrated as a potential novel therapy for pancreatic cancer via photothermal treatment using a laser	[335]
Pancreatic cancer	Gelatin-based NPs	- Fabricated via radiation-induced crosslinking - Size: 5–20 nm - Labeled with 64Cu - Negative surface potential	- Developed as a novel imaging agent for PET - *In vivo* evaluation showed accumulation of NPs in pancreatic tumors - 64Cu-labeled gelatin NPs show promise for next-generation PET imaging in pancreatic cancer	[336]
Pancreatic cancer	Hyaluronic acid (HA)-displaying NPs	- Composed of positively charged chitosan (CS) - Complexed with small interfering RNA (siRNA) - Two formulations: low molecular weight (LMW) CS and high molecular weight (HMW) CS	- Targeted siRNA therapy to downregulate HIF-1α and enhance treatment outcomes - Both LMW and HMW CS formulations showed an ability to knock down HIF-1α *in vitro* and *in vivo* - LMW CS showed faster uptake kinetics, while HMW CS was more effective in gene knockdown - Potential to enhance treatment in the hypoxic TME, a characteristic of pancreatic cancer	[337]
Ovarian cancer	Polymeric-based NPs	siRNA delivery, serum stability enhancement, targeted delivery	- Developing polymeric NPs for siRNA delivery to target specific genes involved in OC prognosis and overcoming chemo-resistance.	[338]
Ovarian cancer	Honokiol (HK)-based polyprodrug NPs	- Glutathione (GSH)-sensitive HK polyprodrug - Conjugated with EpCAM-specific aptamer and polyethylene glycol (PEG) - High drug loading and GSH-responsive drug release	- Developed a GSH-sensitive HK polyprodrug for targeted ovarian cancer therapy - A/P-PHK NP40 (aptamer-modified and PEG-modified prodrug) showed the highest targeting ability for EpCAM-overexpressing ovarian cancer cells - Exhibited enhanced cell growth inhibition compared to free HK and control HK NPs - Novel strategy for improving the delivery and targeting of HK in ovarian cancer treatment	[339]
Ovarian cancer	Arsenic-manganese complex NPs (ATO-Mn)	- Arsenic trioxide (ATO) and manganese (Mn^{2+}) complexed in NPs - pH-sensitive release of arsenic (As^{3+}) and manganese (Mn^{2+}) ions - SKOV3 cell membrane-encapsulated NPs for homologous targeting - Glucose oxidase-based starvation therapy - MR imaging for real-time ATO dose distribution monitoring	- Achieved synergistic effects combining starvation therapy, chemodynamic therapy, and chemotherapy - ATO and Mn^{2+} release triggered by tumor acidity, generating reactive oxygen species (ROS) through Fenton-like reaction - Improved biocompatibility and therapeutic efficacy compared to free ATO administration - Self-enhanced chemodynamic therapy with glucose oxidase supporting H_2O_2 restoration and reducing cellular acidity - Innovative approach for multimodal diagnosis and treatment of ovarian cancer	[340]
Ovarian Cancer	HA@PFG NPs	- Cisplatin prodrug (Pt-COOH) - Fe^{3+} and natural polyphenols (Gossypol) - Stable structure - Controllable drug release behavior - High drug loading capacity - pH-sensitive release at tumor sites - Ferroptosis promotion	- Combined MRI imaging with cisplatin-based chemotherapy for improved diagnosis and therapy - Synergistic effect of Pt-COOH (chemotherapy) and Gossypol (pro-apoptotic) for tumor cell killing - Fe^{3+} release at tumor sites facilitates ferroptosis and MRI imaging of ovarian cancer - Improved therapeutic efficacy in patient-derived tumor xenograft (PDX) model - Ameliorated OC symptoms through IL-6 signaling pathways	[341]

(to be continued)

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Table 3. (continued)

Tumor type	NPs type	NPs feature	Key advancements	Ref.
Hepatocellular carcinoma	- Solid lipid NPs (SLN) - PEGylated galactose-conjugated SLN (GAL-SSLN)	- Targeted delivery - Enhanced cytotoxicity - Apoptosis induction - Improved pharmacokinetics	- GAL-SSLN demonstrated superior targeting and therapeutic efficacy compared to traditional Sorafenib-loaded SLN in HCC. - Enhanced liver-specific drug delivery and efficacy.	[342]
Hepatocellular carcinoma	Nano Zinc Oxide (nZnO)	- Aged nZnO with physicochemical transformation - Investigated for promotional effects on liver cancer progression	- Studied the promotional effects of aged nano zinc oxide (nZnO) on HCC cell progression (HepG2) - Focused on the impact of long-term exposure to subtoxic doses of NPs - Explored how NMs, specifically nZnO, may influence liver cancer progression, highlighting the challenges in assessing chronic exposure to NPs	[343]
Hepatocellular carcinoma	Inorganic NPs	- Accumulate in the liver due to EPR effect - Enhanced accumulation in HCC tumors with leaky vasculature	- Explored the use of inorganic NPs in liver cancer therapy, leveraging their ability to accumulate in HCC tumors through the EPR effect - Identified the potential of inorganic NPs to overcome the challenge of liver accumulation and enhance therapeutic effects in HCC treatment - Highlighted the use of low- and high-LET radiation from the same radionuclide for enhanced treatment strategies in HCC	[344]
Liver cancer	Silica NPs (DOX-loaded)	- Loaded with doxorubicin (DOX) and MRI contrast agent - Coated with pH-responsive and tumor cell-targeting polymers - Targeted delivery with controlled drug release in acidic environments	- Achieved integrated diagnostic and therapeutic strategy for liver cancer - pH-responsive polymer coating enables controlled release of DOX in the tumor's acidic environment - Inhibited autophagic flux by targeting the autophagy–lysosome pathway and regulating TFEB nuclear translocation - Promoted tumor cell death and enhanced therapeutic efficacy in liver cancer treatment	[345]
Hepatocellular carcinoma	siCD24-Lenvatinib-MnO@PLAP nanomedicine	- Incorporates manganese oxide (MnO), lenvatinib (Len), and siRNA against CD24 (siCD24) - Micelles composed of methoxypolyethylene glycol (mPEG), poly-L-lysine (PLLys), and polyasparagyl (PAsp(PIP)) triblock copolymer - Responsive to TME (TME) - MRI contrast agent (Mn^{2+})	- Synergistic effect of siCD24 and lenvatinib reduces CSC stemness and enhances therapeutic efficacy - Inhibited CD24 expression and HIF-1α, reducing drug resistance in CSCs - Improved lenvatinib therapy for HCC with enhanced tumor-targeting and reduced stem cell resistance - In situ production of Mn^{2+} for MRI monitoring of therapeutic progress	[346]
Hepatoblastoma	Vincristine-loaded polycaprolactone NPs with carbon dots (Vin@PCL-CDs)	- Carbon dots encapsulated with vincristine sulfate - Polycaprolactone (PCL) biodegradable NPs - Spherical, uniformly sized (~200 nm) - Excellent colloidal stability	- Improved vincristine pharmacokinetics and targeted delivery to liver cancer cells - Prolonged release of both vincristine and carbon dots, enhancing the therapeutic effect - Enhanced cancer cell inhibition and targeted delivery compared to free vincristine - Carbon dots enabled bioimaging with clear fluorescence, not cytotoxic, offering potential in imaging and cancer research	[347]
Kidney cancer	ICG-PEG45 (Indocyanine Green conjugated with PEG)	- Renal-tubule-secreted near-infrared-emitting fluorophore - Effluxed via P-glycoprotein transporter in normal tissues - Retained in cancerous tissues with low P-glycoprotein expression	- Enhanced kidney cancer targeting through renal tubular secretion - Hyperfluorescence imaging for better detection and visualization of tumors.	[348]
Renal cell carcinoma	ZnPP@G-PP NPs (ZnPP@PLGA-PFP NPs)	- Sound-sensitive, multifunctional nanoplatform - Sonosensitizer (ZnPP) loaded in NPs - G250-targeting ligand for tumor specificity - Encapsulation efficiency and good stability - Multimodal imaging (PA/US) capabilities	- Designed for targeted sonodynamic therapy (SDT) and multimodal imaging - Effective tumor targeting via G250 ligand - LIFU (low-intensity focused ultrasound) irradiation enhances $^1O_2$ production, improving the SDT effect - *In vitro* and *in vivo* studies showed significant therapeutic effects with effective tumor penetration and suppression - Real-time diagnostic and therapeutic monitoring with PA/US imaging - Excellent biocompatibility and therapeutic potential for RCC treatment	[349]
Bladder cancer	Silver NPs (AgNPs)	- Biogenic synthesis from Fusarium sp. - Dose- and time-dependent cytotoxicity - Induces apoptosis - Inhibits cell migration and proliferation	- AgNPs demonstrated antitumoral activity in NMIBC models - Tumor regression (57.13%) and benign lesions observed in animal studies - Potential as a cost-effective alternative for bladder cancer treatment	[350]
Bladder cancer	PAMAM-modified Mesoporous Silica NPs (MSNPs)	- Modified with poly(amidoamine) (PAMAM) dendrimers - Mucoadhesive properties - Controlled drug release triggered by acidic pH	- PAMAM-modified MSNPs exhibited enhanced mucoadhesion, particularly with two-generation PAMAM - Sustained doxorubicin release - Demonstrates potential as a mucoadhesive drug delivery system to improve bladder cancer chemotherapy.	[351]

(to be continued)

Table 3. (continued)

Tumor type	NPs type	NPs feature	Key advancements	Ref.
Bladder cancer	Lipid-coated Mesoporous Silica NPs (Silicasomes)	- Combination of cisplatin (chemotherapy) and tirofiban (antiplatelet agent) - TME-targeted - Prevents LVI formation and enhances drug delivery	- Developed a nanodrug that targets the TME, combining chemotherapy and antiplatelet therapy - Silicasomes enable targeted delivery and synergistic treatment - Inhibition of platelet function to prevent LVI formation, reduce metastasis, and enhance cisplatin efficacy - Demonstrated improved antitumor activity without significant adverse effects, offering a promising strategy for bladder cancer treatment	[352]
Bladder cancer	CTMF NPs (Cascading Transformative Multifunctional Nanotransformer)	- Composed of CuS NPs (photothermal agent) - Encapsulated perfluoro-15-crown-5-ether (PFCE, 19F MRI agent) - Coated with Mn^{2+}-polyphenol shell (signal quencher and therapeutic agent) - TME-activatable - Dual imaging (19F MRI and photoacoustic) for tumor tracking	- Stepwise morphologic transformation to enhance drug penetration and overcome transport barriers - TME-activatable, zero-background 19F MRI for tumor imaging and ratiometric photoacoustic imaging for guidance - Polyphenol-enhanced cell adhesion and in situ generation of quinones for efficient tumor targeting and internalization - Laser-triggered decomposition, oxidative stress amplification, and mitochondrial damage leading to cuproptosis and immunogenic cell death - Synergistic tumor therapy, providing a versatile, precise, and efficient bladder cancer treatment strategy with imaging-guided capabilities	[353]
Bladder Cancer	Iron oxide nanoparticle coated with hyaluronic acid (HA)	- HA coating for mucosa penetration - DBCO for bioorthogonal reaction with azide receptor on bladder cancer cells - Labeled with 177Lu for internal irradiation - Magnetic resonance imaging (MRI) for targeted imaging	- Multifunctional nanodrug that integrates mucosa penetration, targeting, and internal irradiation for bladder cancer therapy - Facilitates bladder cancer downstaging and bladder-preserving therapy - Improved cellular internalization through bioorthogonal reaction - Targeted MRI for visualizing both nonmuscle-invasive and muscle-invasive bladder cancer - Demonstrated inhibition of metastasis and potential for preserving the bladder during treatment	[354]
Bladder Cancer	Wrinkled silica NPs (WSNs)	- WSNs used as microreactors for multiplex miRNA analysis - Conjugated with S9.6 antibody for DNA/miRNA duplex binding - ssDNA labeled with quantum dots (QDs) for miRNA identification - Fluorescence-based detection	- Enables multiplex miRNA detection without enzymes or nucleic acid amplification - Achieves high sensitivity (down to 5 fM) and wide dynamic range (six orders of magnitude) - High specificity to distinguish single-base mutation sequences - Effective for clinical serum specimen analysis, improving the accuracy and reliability of BC diagnosis	[355]
Non-Muscle Invasive Bladder Cancer	Sodium Chloride NPs (NaCl-NPs)	- Intravesical instillation of NaCl-NPs for local treatment - No systemic or local toxicity at high doses - Treatment administered posttransurethral resection of bladder tumors (TURBT)	- Safe and effective alternative to traditional therapies (e.g., BCG, intravesical chemotherapy) - 2.55-fold reduction in tumor development compared to saline, similar to gemcitabine - Improved overall survival (70% at 60 d vs 40% for saline group) - Potential for safer, more tolerable treatment regimens to prevent recurrence of NMIBC	[356]
Bladder Cancer (Drug-resistant)	Doxorubicin (DOX)/COOH-mesoporous silica nanoparticle (MSN)/Polyethylenimine (PEI)/Nucleic acid chimeras	- COOH-mesoporous silica NPs (MSN) with PEI coating - Controlled drug release for over 48 h - Targeted delivery of DOX and siRNA	- DOX/MSN/Chimera significantly inhibits PI3K expression and promotes apoptosis in drug-resistant bladder cancer cells - Reduces tumor volume *in vivo* - Improved reduction in chemotherapy-induced toxicity to normal tissues - Potential for personalized and targeted therapy for drug-resistant bladder cancer	[357]
Bladder Cancer	Lipid-Polymer hybrid NPs (LPHNP) loaded with Solasonine (SS) and Solamargine (SM)	- Average size: 130 nm - Polydispersity index: 0.22 - Positive zeta potential (indicating chitosan coating) - High encapsulation efficiency (91.08% for SS, 88.35% for SM) - Mucoadhesive properties	- Nanoencapsulated SS/SM showed enhanced anticancer effects compared to free SS/SM, with twofold lower IC50 in 3D bladder cancer cell culture - *In vivo* antitumoral effect with significant reduction in bladder volume - High encapsulation efficiency and stability - Identified systemic toxicity and liver damage at high doses, suggesting the need for further safety evaluations	[358]

doxorubicin, did not improve survival in metastatic breast cancer, likely due to poor tumor penetration and variability in HER2 expression[307].

Stimulus-responsive nanocarriers have also encountered clinical challenges. ThermoDox®, a heat-sensitive liposomal formulation of doxorubicin designed for localized drug release during hyperthermia, failed to meet primary endpoints in Phase III trials. Inconsistent heat application, limited control over stimulus activation, and tumor heterogeneity were identified as major barriers[308]. Furthermore, CALAA-01, a cyclodextrin-based siRNA nanoparticle, was discontinued in early-phase trials due to immune activation and safety concerns, illustrating the difficulties associated with systemic nucleic acid delivery[309].

These clinical cases underscore that successful nanomedicine translation depends not only on innovative design but also on robust control of pharmacokinetics, tumor penetration, safety, and manufacturability. They reinforce the need for realistic preclinical models, improved patient stratification, and simplified, scalable nanocarrier systems to overcome the biological and regulatory challenges limiting the clinical impact of nanotechnology in cancer therapy.

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Conclusions

Nanotherapeutics, especially via engineered NPs, are revolutionizing cancer treatment, offering significant advantages over traditional therapeutic modalities. Nanotechnology enables more effective drug delivery and reduces systemic toxicity, a longstanding limitation of conventional therapies. Owing to their small size and large surface area, NPs facilitate targeted drug delivery, improving the transport of therapeutic agents to tumor sites through the EPR effect. Furthermore, these particles can be engineered for controlled drug release, promoting sustained and targeted drug delivery that optimizes therapeutic efficacy. Beyond their function in drug delivery, NPs are pivotal in cancer imaging and diagnostics, enabling earlier detection and supporting the development of personalized treatment strategies. The versatility of NPs extends to combination therapies, where they can help overcome drug resistance by concurrently delivering multiple agents that target distinct molecular pathways. In the context of HMs, nanomedicines have demonstrated promise in improving treatment specificity while minimizing adverse side effects. Nanocarriers, such as liposomes and polymeric NPs, are particularly notable for their potential in this domain. Advancements in NP-based stem cell expansion and the modulation of intracellular signaling pathways further expand the therapeutic potential of NPs, offering new strategies for treatment. The potential of nanotechnology in oncology remains substantial, with ongoing efforts aimed at enhancing the drug-loading capacity of NPs, optimizing release mechanisms, and refining tumor targeting. Integrating nanotechnology with emerging immunotherapies, such as CAR-T-cell therapies, also holds considerable promise for improving treatment efficacy and patient outcomes.

Ethical statements

Not applicable.

Author contributions

The authors confirm their contributions to the paper as follows: figure, table and draft manuscript preparation: Rad MK, Razani E; manuscript review and editing: Bashash D. All authors reviewed the results and approved the final version of the manuscript.

Data availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflict of interest

The authors declare that they have no conflict of interest.

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