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REVIEW

Recent advances in the bench-to-bedside translation of cancer nanomedicines



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Abstract Cancer remains a complex and challenging medical problem, driving extensive research efforts. Despite significant progress in understanding its genetic and molecular aspects, the quest for effective treatments continues. Nanomedicines have shown great potential for revolutionizing cancer treatment by offering targeted and controlled drug delivery, reducing side effects, and improving patient outcomes. Accordingly, nanomedicines have been the focus of extensive research and development for clinical translation. As of September 2024, a search on the ClinicalTrials.gov website using the term “nanoparticles” revealed numerous ongoing and planned clinical trials. Motivated by recent advances in the field, this review explores the current frontier of cancer nanomedicine. Nanomedicines have supported chemotherapy, phototherapy and sonodynamic therapy, nucleic acid therapy, and immunotherapy. However, translating nanomedicines into practice has been challenged by complex interactions between nanoparticles and biological systems, variable permeability and retention of nanoparticles in tumors, safety concerns, difficulty achieving targeted delivery, and issues with scaling up manufacturing. Perspectives on addressing these challenges are offered. Future opportunities for cancer nanomedicines, including modifying the tumor microenvironment, integrating artificial intelligence and big data, and targeting new medical areas, are also discussed. This review underscores the potential of cancer nanomedicines to revolutionize treatment from a clinical standpoint.

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1. Introduction

Cancer is a leading cause of death worldwide, posing a severe threat to human health. In 2022 alone, there were an estimated 20 million new cancer cases and nearly 10 million deaths globally¹. In China, cancer is the primary cause of death, with 5 million new cancer cases and approximately 3 million deaths reported in 2022. Both the incidence and mortality rates in China are among the highest in the world². With unhealthy lifestyles, environmental pollution, and changes in population structure, among other risk factors, the global incidence of cancer is expected to increase over the next 20 years significantly³. Therefore, effective medical interventions are urgently needed to reduce the overall mortality rate of cancer. While traditional cancer treatments such as surgery, chemotherapy, and radiotherapy (RT) have achieved some success in improving patient survival rates, their efficacy in treating advanced metastatic cancer remains limited. Immunotherapy has made significant breakthroughs in treating advanced cancer, yet its effectiveness is constrained by low response rates among patients^{4,5}. Moreover, both traditional chemotherapy and immunotherapy are non-targeted treatments that often result in significant damage to healthy cells, leading to serious or potentially fatal side effects⁶. As a result, researchers are actively pursuing targeted drug delivery systems (DDS) capable of explicitly accumulating in tumor tissue, selectively identifying and penetrating tumor cells, and accurately reaching subcellular sites of action. This precise delivery of drugs has become an urgent scientific challenge to address for targeted therapy^{7,8}.

Nanoparticles (NPs) have revolutionized drug delivery with their small size, large surface area, and customizable surfaces and compared to traditional methods, they have improved the pharmacokinetics and distribution of therapeutic agents. The development of NPs for biomedical applications began in the 1960s with liposomes, which encapsulated hydrophilic and hydrophobic drugs. This advancement led to further innovations like polymeric NPs, dendrimers, and micelles, enhancing drug solubility, stability, and targeting⁹. Over the past few decades, research in cancer nanomedicine has achieved significant milestones (Fig. 1). A variety of NPs, including lipid-based, polymeric, and inorganic NPs, have been developed for the targeted delivery of therapeutic nucleic acids, chemotherapeutic agents, and immunotherapeutics¹⁰ and have been evaluated in preclinical studies. Some of these nanomedicines have progressed to clinical trials^{11,12} (Table 1).

In recent years, integrating nanotechnology with biology, materials science, chemistry, biomedical engineering, pharmacology, and precision medicine has led to significant progress in cancer treatment¹³. Strategies based on nanomedicine have demonstrated outstanding potential for application and development in oncology¹⁴. Numerous preclinical studies have demonstrated that diverse nanocarriers can enhance drug accumulation in tumor tissues *via* active and/or passive targeting strategies, extend blood circulation time to improve the pharmacokinetic properties of biomacromolecules, shield bioactive substances from degradation in the bloodstream, effectively inhibit solid tumor growth by enhancing RT, photothermal therapy (PTT), photodynamic

therapy (PDT) and sonodynamic therapy (SDT); and mitigate the toxicity associated with chemotherapy drugs^{14,15}.

Recent research highlights the functionalization of mesoporous silica NPs (MSNPs) with cyclodextrin-grafted polyethylenimine (CP) to create a potent delivery system for small interfering RNA (siRNA)¹⁶. This MSNP-CP system enhances siRNA delivery by promoting endosomal escape and protecting siRNA from enzymatic degradation, showing strong potential in cancer therapy by targeting oncogenes such as pyruvate kinase M2 (PKM2) in breast cancer models. Nanoparticle development has led to hybrid systems like injectable nanoparticle generators (iNPGs), which self-assemble into nanometer-sized particles after release¹⁷. Designed to overcome barriers like poor tumor penetration and multidrug resistance, iNPGs enhance cancer treatment. For example, iNPG-pDox, loaded with a pH-sensitive doxorubicin conjugate, shows improved tumor accumulation, targeted drug release, and better outcomes in metastatic breast cancer models compared to standard treatments¹⁷. In addition to MSNPs and iNPGs, carbon-based nanomaterials, such as carbon nanotubes (CNTs) and graphene, are emerging as effective drug-delivery vehicles due to their unique structural properties¹⁸. CNTs excel at penetrating cellular membranes, aiding the delivery of drugs and genetic material, while graphene, with its high surface area and strength, is being investigated for the delivery of a variety of therapeutic agents, including anticancer drugs and genes¹⁸.

NPs utilize the enhanced permeability and retention (EPR) effect to accumulate in tumor tissues *via* leaky vasculature. However, the limitations of passive targeting have led researchers to develop active targeting strategies by modifying NP surfaces with ligands or antibodies for specific binding to tumor cells. Recent studies demonstrate that surface-engineered NPs enhance cellular uptake and improve therapeutic efficacy in various cancer models¹⁹. Additionally, advanced nanomedicine platforms have been designed to overcome multidrug resistance by delivering high concentrations of chemotherapeutics directly to cancer cells while minimizing off-target effects. This has been achieved through the use of liposomes, PNPs, and other nanostructures that can encapsulate drugs, protect them from premature degradation, and release them in a controlled manner within the tumor microenvironment (TME)²⁰. Incorporating stimuli-responsive elements into NPs advances targeted drug delivery by enhancing the precision and control of therapeutic release. These NPs respond to endogenous stimuli, such as acidic pH, high glutathione levels, elevated reactive oxygen species (ROS), and overexpressed enzymes, in pathological environments like tumors. Exogenous stimuli, including temperature, light, magnetic fields, ultrasound, and electric fields, further refine release profiles, enabling externally controlled, site-specific drug delivery (Fig. 2). For instance, pH-sensitive NPs release drugs in acidic tumor microenvironments, enhancing efficacy and reducing off-target effects²¹. Recent clinical and preclinical studies continue to demonstrate the potential of NPs for overcoming significant challenges in drug delivery. By enhancing the stability and bioavailability of poorly soluble drugs and enabling targeted delivery of biologics like siRNAs or CRISPR reagents, NPs are shaping the future of therapeutic strategies.

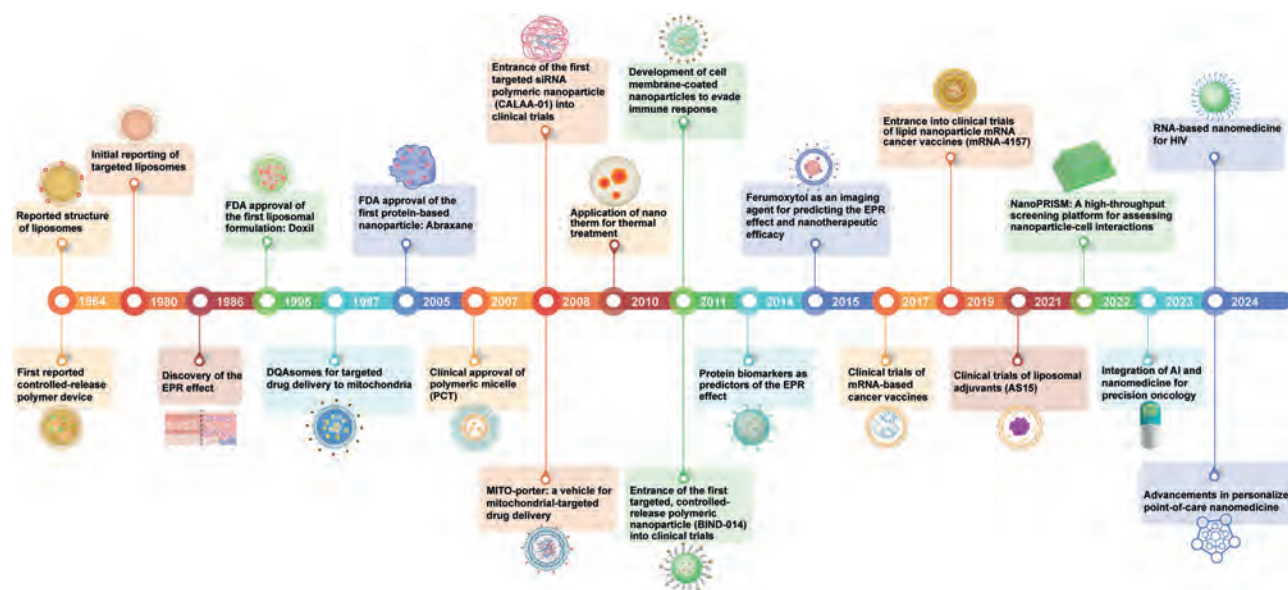


Figure 1 Historical timeline of major developments in cancer nanomedicine. EPR, enhanced permeability and retention; FDA, US Food & Drug Administration; RNA, ribonucleic acid; AI, artificial intelligence; HIV, human immunodeficiency virus.

This progress emphasizes their crucial role in developing more effective, targeted, and personalized treatments^{22,23}.

Recent advances have also integrated nanotechnology with immunotherapy to enhance antitumor immune responses²⁴. NPs have been engineered to deliver immune modulators, such as checkpoint inhibitors and cytokines, thereby stimulating the body's own immune system to recognize and destroy cancer cells. Moreover, nanomedicine-assisted imaging strategies are being employed to better stratify patients for specific treatments and monitor therapeutic responses, which significantly improves the precision and efficacy of cancer therapies²⁵. Recent cancer treatments leveraging nanotechnology have exhibited promising advancements. Such advancements incorporate stimuli-responsive, convertible, or biomimetic coatings for cell membranes; integrate prodrugs, co-assembled drugs, or cell–nanocarrier complexes with innovations like nanorobots and *in vivo* nano catalytic reactions; and use nano vaccines to augment immunotherapy²⁶. These advancements have collectively enhanced therapeutic outcomes for malignant tumors²⁷.

However, compared to the number of ongoing preclinical studies, the number of clinical trials for nanotherapeutic drugs remains limited²⁸. Although cancer nanomedicines possess significant potential to revolutionize cancer treatment, only a limited number have received approval from regulatory agencies (Table 2). Obtaining approval from regulatory bodies such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Japan Pharmaceuticals and Medical Device Agency (PMDA), or the China National Medical Products Administration (NMPA) represents a critical milestone in transitioning nanomedicine technologies from the laboratory to clinical practice (Fig. 3). The rigorous approval process of these groups ensures the safety and efficacy of these therapies. However, the approval of targeted nanomedicines faces several bottlenecks: these nanomedicines have complex structures and a multi-step synthesis process, often resulting in poor reproducibility and compromised biological effects²⁹; *in vitro* and *in vivo* evaluation models inadequately replicate the human TME, leading to suboptimal therapeutic outcomes³⁰; equipment for scaling up

production of advanced nanotechnologies has challenges, restricting industrial production³¹; the safety and biocompatibility of new materials have been insufficiently researched, limiting clinical translation³²; and there are no clear guidelines or standards for the quality control and characterization of nanomedicines, causing inconsistent product quality, safety risks, and regulatory approval challenges³³.

In this review, we highlight recent clinical advancements in cancer nanomedicine and explore key challenges, case studies, and emerging opportunities in the field. Throughout the review, we provide perspective on how we can speed the translation of cancer nanomedicines to clinical settings, which can potentially revolutionize cancer treatment.

2. Common nanoparticles used in disease treatment and diagnostics

NPs have revolutionized modern medicine by improving drug delivery, imaging, and targeted therapies. Their customizable properties—such as size, shape, and surface functionalities—are crucial for diagnosing and treating various diseases. This section reviews recent research supporting the role of NPs, including polymeric, gold, and magnetic nanoparticles (MNPs), in advancing treatment for tumors, non-cancerous conditions, and other complex medical challenges (Fig. 4).

In oncology, NPs have been widely studied for enhancing drug delivery and precision in cancer therapies. Mieszkawska et al.³⁴ demonstrated that polylactic acid (PLA)- and poly(lactic-co-glycolic acid) (PLGA)-based NPs effectively delivered paclitaxel and doxorubicin, increasing drug accumulation in tumors while reducing toxicity to healthy tissues. Gold nanoparticles (AuNPs) also show promise, as Baranwal et al.³⁵ found they could be used in PTT to destroy cancer cells with minimal collateral damage and serve as contrast agents in computed tomography (CT) imaging. MNPs, particularly iron oxide nanoparticles (IONPs), significantly enhance cancer detection *via* magnetic resonance imaging (MRI). Chen et al.³⁶ showed that IONPs conjugated with tumor-targeting

Table 1 Recent advancements in cancer nanoformulations (adapted from Zhang et al., Med, 2022, <https://doi.org/10.1016/j.medj.2022.12.001>).

Therapeutic modality	Proprietary name (year)	Composition	Cancer indication	Registration number
Chemotherapy	MagNeo (2024)	Iron oxide NPs	Breast cancer	NCT05985551
	CNSI-Fe (II) (2023)	Injectable ferrous sulfate with nanoparticle carbon	Solid tumor	NCT06048367
	Ursolic acid nano-liposomes (2023)	Ursolic acid nano-liposomes for injection	Hepatocellular carcinoma	CTR20230593
	Nano-QUT (2022)	Quercetin-encapsulated PLGA-PEG NPs	Tongue squamous cell carcinoma	NCT05456022
	D3S-001 (2022)	D3S-001 monotherapy or combination therapy	Solid tumor with KRAS P.G12C mutation	NCT05410145
	Irinotecan hydrochloride (nano) micelles for injection (2021)	Irinotecan hydrochloride (nano) micelles for injection	Advanced colon cancer	CTR20212931
	ABI-009 (2018)	Albumin-bound rapamycin NPs	Glioblastoma	NCT03463265
	CPC634 (2018)	Docetaxel micellar	Ovarian cancer	NCT03742713
	EndoTAG-1 (2016)	Liposomal paclitaxel	Breast cancer	NCT03002103
	MM-302 (2014)	Human epidermal growth factor receptor 2 (HER2)-targeted liposomal doxorubicin hydrochloride	Breast cancer	NCT02213744
	CRLX101 (2012)	NPs consisting of camptothecin –cyclodextrin conjugate	Stomach, gastroesophageal, esophageal cancer	NCT01612546
	NK105 (2012)	Paclitaxel micelle	Breast cancer	NCT01644890
	NKTR-102 (2011)	Irinotecan PEG conjugate	Breast cancer	NCT01492101
	ThermoDox (2009)	Thermally sensitive liposomal doxorubicin	Breast cancer	NCT00826085
	NC-6004 (2009)	Cisplatin micellar	Pancreatic cancer	NCT00910741
	NKTR-102 (2008)	Irinotecan PEG conjugate	Breast cancer, glioma, ovarian cancer	NCT00802945, NCT01663012, NCT00806156
	CT-2106 (2006)	Camptothecin polymer conjugate	Colorectal cancer, ovarian cancer	NCT00291785, NCT00291837
	CT-2103 (2005)	Paclitaxel polymer conjugate	Ovarian, peritoneal cancer	NCT00108745
	Liposomal Annamycin (2005)	Liposomal annamycin	Leukemia	NCT00271063
	SPI-077 (2004)	Liposomal cisplatin	Ovarian cancer	NCT00004083
Radiotherapy sensitizer	Nano-SMART (2024)	AGuIX gadolinium-chelated polysiloxane	Non-small cell lung cancer, pancreatic cancer	NCT04789486
	NBTXR3 (2015)	Hafnium oxide NPs	Sarcoma	NCT02379845
	NVX-108 (2014)	DDFP liquid emulsion combined with radiation therapy	Glioblastoma multiforme	NCT02189109
Hyperthermia	ANCHIALE (2024)	Iron oxide NPs	Glioblastoma multiforme	NCT06271421
	NanoTherm (2021)	Iron oxide NPs	Prostate cancer	NCT05010759
	AuroLase (2009)	Silica core with a gold nanoshell	Primary and metastatic lung tumors	NCT01679470
Immunotherapy	AuroLase (2009)	Silica core with a gold nanoshell	Head and neck tumor	NCT00848042
	JS014(2021)	Recombinant interleukin-21 -human serum albumin nano antibody fusion protein	Advanced stage tumor	CTR20213180
	Personalized mRNA cancer vaccine (2018)	Personalized mRNA cancer vaccine against neoantigens	Melanoma, colon cancer, gastrointestinal cancer	NCT03480152
	CV9202 (2017)	mRNA cancer vaccine in combination with anti-PD-L1	Non-small cell lung cancer	NCT03164772
	DPX-survivac (2014)	Liposomal survivin-based synthetic peptide antigens	Lymphoma	NCT02323230
	PNT2258 (2012)	Liposomal DNA interference oligonucleotides PNT100	Lymphoma	NCT01733238
	Vaccination with mRNA-transfected DC (2011)	Vaccination with mRNA transfected DC	Prostate cancer	NCT01278914
	Tecemotide (2011)	Tecemotide (2011)	Prostate cancer	NCT01496131
	dHER2+AS15 (2009)	Truncated HER2 protein combined with the immunological liposomal AS15 adjuvant	Breast cancer	NCT00952692

Table 1 (continued)

Therapeutic modality	Proprietary name (year)	Composition	Cancer indication	Registration number
Nucleic acid nanodrug	MAGE A3+AS15 (2008)	Melanoma-associated antigen A3 protein in combination with AS15 adjuvant	Melanoma, non-small cell lung cancer	NCT00796445, NCT00480025
	SGT-53 (2015)	Liposomal p53 plasmid	Pancreatic cancer	NCT02340117
	DCR-MYC (2014)	Lipid NP containing MYC siRNA	Hepatocellular carcinoma	NCT02314052
	Atu027 (2013)	Liposomal protein kinase N3 siRNA	Pancreatic cancer	NCT01808638
	Pbi-shRNA STMN1 LP (2012)	shRNA against stathmin 1 using lipid NPs	Advanced and/or metastatic cancer	NCT01505153
	siRNA-EPHA2-DOPC (2012)	siRNA against EPHA2 using liposomes	Advanced neoplasm	NCT01591356
	ALN-VSP02 (2010)	siRNAs against KSP and VEGFA using lipid NPs	Solid tumor	NCT01158079
	TKM-PLK1 (2010)	Lipid NP containing PLK1 siRNA	Neuroendocrine tumors and adrenocortical carcinoma	NCT01262235
	CALAA-01 (2008)	siRNA targeting RRM2 using TfR-targeting polymeric NPs	Cancer, solid tumor	NCT00689065
	Allovectin-7 (2004)	Liposomal VCL-1005 plasmid	Melanoma	NCT00003646

NPs, nanoparticles; HER2, human epidermal growth factor receptor 2; PLGA, poly (lactic-co-glycolic acid); DC, dendritic cell; siRNA, small interfering RNA.

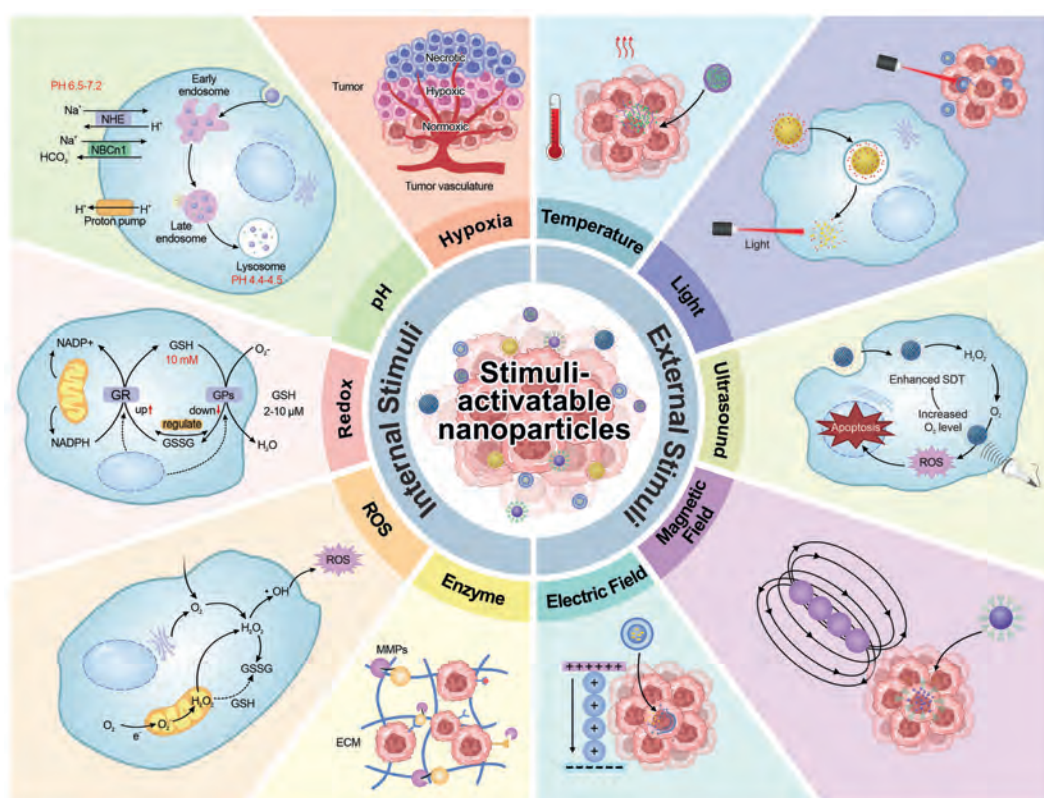


Figure 2 Overview of stimuli-activatable nanoparticles in tumor therapy. ECM, extracellular matrix; GPs, glutathione peroxidases; GR, glutathione reductase; GSH, glutathione; GSSG, glutathione disulfide; MMPs, matrix metalloproteinases; NHE, Na^+/H^+ exchanger; ROS, reactive oxygen species; SDT, sonodynamic therapy.

ligands improved imaging of breast and glioblastoma cancers. Additionally, the application of magnetic hyperthermia therapy (MHT) and RT using MNPs has proven effective in sensitizing tumor cells to therapeutic interventions³⁷.

NPs show significant promise beyond oncology, playing a key role in treating various non-cancerous diseases³⁸. Guo et al.³⁹ highlighted the role of NPs in the treatment of Alzheimer's disease, showing that NPs can cross the blood–brain barrier

Table 2 Approved cancer drug therapies based on nanotechnology.

Approval (year)	Product	Company	Nanoparticle material	Drug/mechanism	Indication
2024	Irinotecan hydrochloride liposome injection (II)	Jiangsu hengrui medicine co., Ltd.	Liposome	Irinotecan	Second-line treatment of pancreatic cancer
2023	Doxorubicin hydrochloride liposome injection	Shanghai fudan-zhangjiang bio-pharmaceutical co., Ltd.	Liposome	Doxorubicin	Kaposi's sarcoma, breast and ovarian cancer
2022	Mitoxantrone hydrochloride liposome injection	CSPC pharmaceutical group limited	Liposome	Mitoxantrone	Patients with relapsed or refractory peripheral T-cell lymphoma who have had at least one prior line of standard treatment
2020	Paclitaxel liposome for injection	Luye pharma group Ltd.	Liposome	Paclitaxel	Ovarian cancer, non-small cell lung cancer
2020	BNT162b2 (Comirnaty)	Pfizer/BioNTech	Lipid nanoparticle	mRNA	COVID-19 (included because of its significant impact on oncology research)
2019	Onpattro (Patisiran)	Alnylam pharmaceuticals	Lipid nanoparticle	siRNA	Hereditary transthyretin-mediated amyloidosis
2019	Hensify (NBTXR3)	Nanobiotix	Hafnium oxide nanoparticle	Radiotherapy	Locally advanced soft tissue sarcoma (STS)
2019	Pazenir	Ratiopharm GmbH	Nanoparticle-bound albumin	Paclitaxel	Metastatic breast cancer, metastatic adenocarcinoma of the pancreas, non-small cell lung cancer
2018	Vyxeos	Celator/Jazz pharma	Liposome	Cytarabine/Daunorubicin	Acute myeloid leukemia
2018	Apealea®	Elevar therapeutics	Paclitaxel micelles	Active paclitaxel	Cancer of the ovary or surrounding structures
2015	Onivyde	Merrimack pharma	Liposome	Irinotecan	Pancreatic cancer, colorectal cancer
2013	NanoTherm	MagForce nanotechnologies AG	Iron oxide NPs	Thermal ablation with magnetic field	Glioblastoma, prostate, and pancreatic cancer
2012	Marqibo	Talon therapeutics/Spectrum pharmaceuticals	Liposome	Vincristine	Acute lymphoblastic leukemia
2009	Mepact	Takeda pharmaceuticals	Liposome	Mifamurtide MTP-PE	Osteosarcoma
2007	Genexol-PM	Samyang Biopharmaceuticals	PEG-PLA polymeric micelle	Paclitaxel	Breast, lung, ovarian cancer
2006	Oncaspar	Enzon-sigma-tau	Polymer protein conjugate	Pegaspargase/L-asparaginase	Acute lymphoblastic leukemia
2005	Abraxane	Abraxis/Celgene	Nanoparticle-bound albumin	Paclitaxel	Breast and pancreatic cancer, non-small cell lung cancer
1999	DepoCyt	Pacira pharmaceuticals	Liposome	Cytarabine	Neoplastic meningitis
1996	DaunoXome	Gilead sciences	Liposome	Daunorubicin	Kaposi's sarcoma
1995	Doxil	Johnson & johnson	Liposome	Doxorubicin	Kaposi's sarcoma, ovarian cancer, multiple myeloma

NPs, nanoparticles; STS, soft tissue sarcoma; PLA, polylactic acid.

(BBB) and interact with amyloid plaques, a key feature of the disease pathology. Zinc oxide NPs (ZnO NPs), as noted by Anjum et al.⁴⁰, are being developed for cardiovascular conditions, leveraging their antioxidant properties to reduce oxidative stress and promote tissue recovery in heart disease. Another noteworthy application of NPs is in wound healing, particularly in treating bacteria-infected wounds and difficult-to-treat ulcers.

For example, Xiang et al.⁴¹ demonstrated the use of cuttlefish ink nanoparticle—reinforced hydrogels for treating oral ulcers in diabetic patients. Similarly, Zeng et al.⁴² found that polydopamine NPs (PDA NPs) in hydrogels accelerated the healing of bacteria-infected wounds through photothermal effects, while the hydrogels' strong adhesive properties promoted rapid re-epithelialization⁴³.

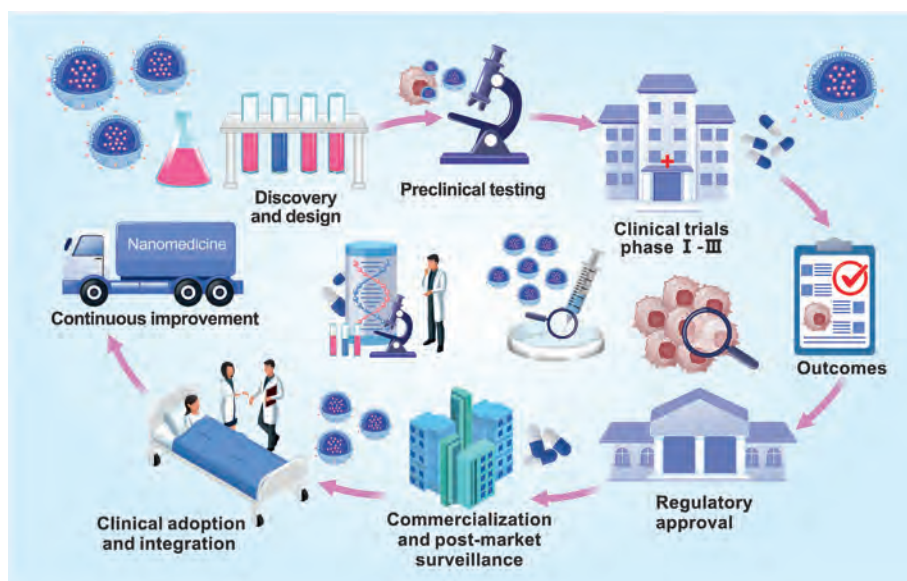


Figure 3 The process of nanomedicine from discovery to clinical adoption.

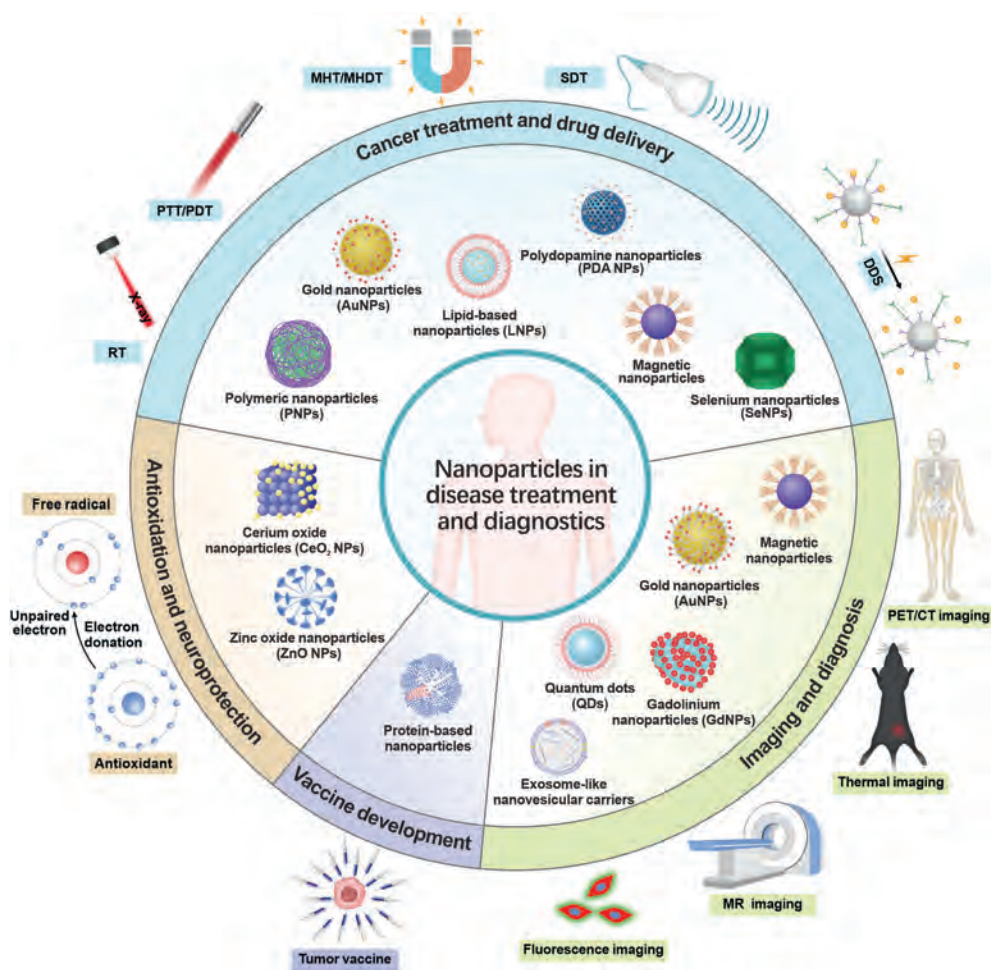


Figure 4 Applications of common nanoparticles. DDS, drug delivery system; MHT/MHDT, magnetic hyperthermia therapy/magnetic hyperthermia-directed therapy; PDT, photodynamic therapy; PTT, photothermal therapy; RT, radiotherapy; SDT, sonodynamic therapy.

In summary, NPs are versatile tools in modern medicine, offering innovative solutions for diagnosis and treatment across various diseases⁴⁴. They can be precisely engineered for targeted delivery and multifunctionality, holding promise for advancing personalized medicine. As research progresses, optimized NP designs are expected to play a vital role in tackling complex medical challenges, especially in oncology, as highlighted in the next section.

3. Advancements in the clinical application of cancer nanomedicines

Many of the latest advancements in the clinical application of cancer nanomedicines involve NPs, which have considerably enhanced six broad areas of cancer nanomedicine: chemotherapy drug delivery, PTT, PDT, SDT, nucleic acid therapy, and immunotherapy. These types of cancer nanomedicines are summarized in Fig. 5 and discussed in the following sections.

3.1. NP DDS for chemotherapy

NP-based DDS have been a significant technological breakthrough in cancer treatment, offering fundamental improvements in therapeutic methods through the unique advantages of nanotechnology. These systems enable precise control over drug release and distribution, significantly enhancing treatment efficacy while minimizing damage to healthy cells, thereby effectively reducing patient side effects⁴⁵. Various types of NPs, including liposomes, polymeric NPs, and inorganic NPs, have been developed for cancer treatment, each displaying distinct characteristics and offering unique advantages⁴⁶ (Table 3).

Liposome NPs, consisting of small vesicles made from natural or synthetic lipids, have been successfully applied in various drug delivery scenarios. For instance, encapsulating the chemotherapy drug doxorubicin into liposomes (*i.e.*, Doxil) effectively improves drug stability and bioavailability while reducing cardiotoxicity⁴⁷.

The APPROVE trial found that combining liposomal doxorubicin (PLD) with apatinib for platinum-resistant ovarian cancer significantly improved progression-free survival (PFS) (by reducing disease progression risk by 56%) and was well tolerated without new safety concerns²⁶. A meta-analysis of randomized clinical trials highlighted that compared to combining carboplatin with paclitaxel (C + P), combining carboplatin with PLD (C + PLD) for ovarian cancer resulted in superior PFS (hazard ratio [HR]: 0.87, 95% confidence interval [CI]: 0.78 to 0.96) and similar overall survival (OS) (HR: 0.95, 95% CI: 0.84 to 1.07), with a distinct but generally more tolerable safety profile, including less neutropenia and neuropathy but increased gastrointestinal toxicity and mucositis/stomatitis⁴⁸.

Dendrimers, characterized by their branched structure and customizable surface functionalities, serve as highly specific targeted DDS. Modifications targeting specific receptors are capable of delivering drugs precisely to tumor cells, maximizing the concentration of drugs in cancer cells, reducing harm to healthy cells, and lowering side effects⁴⁹. Kędra et al.⁵⁰ reviewed self-immolative domino dendrimers (SIDendr) for anticancer drug delivery, highlighting their capability to enhance the pharmacological effectiveness of both novel and traditional drugs, showcasing their significant clinical potential. In another study, Chittasupho et al.⁵¹ explored CXCR4-targeted dendrimers for breast cancer treatment, finding that these dendrimers effectively inhibited cancer cell migration by more than 60% and enhanced drug delivery specificity beyond that of non-targeted therapies.

Polymeric NPs, made from synthetic or natural polymers, can be optimized for drug delivery with immense flexibility and customization. Adjustments to their size, shape, and surface modifications can maximize drug release and targeting properties⁵². For instance, Xu et al.⁵³ discussed the potential of poly (N-isopropylacrylamide) (PNIPAM)-based thermosensitive hydrogels for biomedical applications. Despite their low mechanical strength, these hydrogels show great promise for drug delivery,

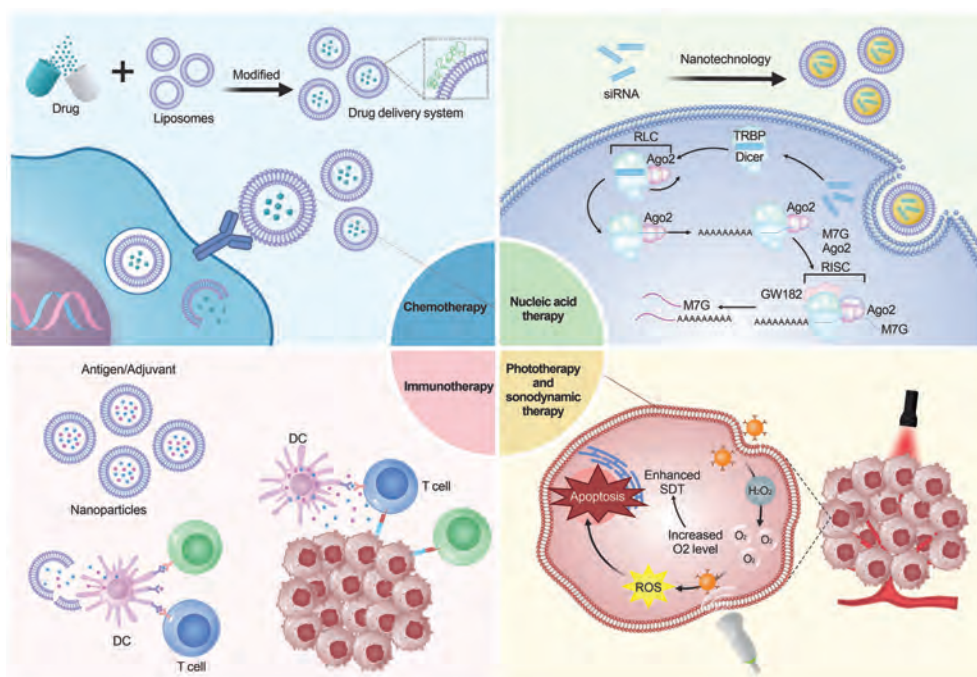


Figure 5 Various therapies involving cancer nanomedicines. DC, dendritic cell; ROS, reactive oxygen species; SDT, sonodynamic therapy.

Table 3 Types of NPs for cancer nanomedicine with pros and cons.

Type	Pros	Cons
Liposomes	• Biocompatibility • Biodegradability • Drug delivery • Targeted delivery • Controlled release	• Stability issues • Higher production costs • Short half-life • Storage challenges
Dendrimers	• High drug loading capacity • Controlled release • Surface modification • Multifunctionality	• Toxicity concerns • Complex synthesis • Aggregation • Limited clinical use
Inorganic NPs	• Optical properties • High stability • Easy functionalization • Multimodal imaging	• potential toxicity • Clearance issues • Higher production costs • Regulatory hurdles
Nucleic acid-related NPs	• precision medicine • Targeted therapy • Versatility • Biocompatibility	• Delivery challenges • Stability issues • Immune response • Complex manufacturing
Nanovaccines	• Enhanced immunogenicity • Targeted delivery • Dose sparing • Stability	• Regulatory challenges • Complex manufacturing and quality control • Potential toxicity • Higher production costs

NPs, nanoparticles.

tissue engineering, and wound dressing. To enhance their properties, materials such as graphene oxide nanosheets, chitosan, and dextrin can be incorporated into PNIPAM hydrogels. Graphene oxide nanosheets improve cell attachment and proliferation, facilitating better cell sheet harvesting. Chitosan contributes to biocompatibility and biodegradability, while dextrin can be degraded by amylase for complete biodegradation in drug delivery applications.

Inorganic NPs, such as those made from gold, silver, and silicon, leverage their unique optical and electrochemical properties to not only act as drug carriers but also enhance PTT and PDT effects⁵⁴. For instance, Kim et al.⁵⁵ demonstrated that AuNPs can serve as both photothermal agents and drug carriers, utilizing surface plasmon resonance effects to facilitate strong light absorption and heat generation at specific wavelengths. Recent clinical trials have shown the effectiveness of these NP-based therapies. For example, in a phase I clinical trial (NCT05268718), a composite nanogel of gold, silver, and cuprous oxide was combined with PTT and evaluated for treating severe drug-resistant bacterial keratitis in human eyes. The clinical evidence suggested that for corneal diseases, the NP-based approach was safer and more effective than traditional antibiotic therapy, offering promise for translational applications⁵⁶.

One key advantage of NP systems lies in their targeted delivery capabilities. By decorating these NPs with targeting molecules, such as antibodies, peptides, or small molecule ligands, the NPs can precisely identify and lock onto tumor cells⁵⁷. A recent study demonstrated enhanced specificity and efficacy in treating colorectal cancer using AuNPs conjugated with cellular prion protein aptamers for targeted delivery of doxorubicin. The treatment increased the percentage of early and late apoptosis, which was 67% in the treatment group but only 27% in the group with free doxorubicin⁵⁸. In another study, AuNPs coated with peptides containing isoAsp-Gly-Arg, TNF- α , and IL-12 significantly

enhanced the anticancer activity of doxorubicin through vascular targeting. Specifically, the treatment extended the survival time (indicated by tumor volume) in tumor-bearing mice from 22 days (doxorubicin alone) to 42 days⁵⁹. These decorated NPs allow for the direct delivery of drugs to cancer cells, greatly improving treatment efficiency and reducing harm to healthy cells⁶⁰.

Another key advantage of NP systems lies in their controlled-release capabilities. Controlled-release technology enables drugs to be released at a predetermined rate over a specific period, maintaining an effective concentration, optimizing therapeutic effects, and reducing dosing frequency⁶¹. For instance, Price et al.⁶² demonstrated that the controlled release of antibiotics from coated orthopedic implants resulted in sustained drug release over 14 days, significantly reducing infection rates post-surgery compared to those after conventional antibiotic treatments. Similarly, Kim et al.⁶³ observed that sustained-release formulations can maintain consistent drug levels over time, which is particularly beneficial for chronic conditions requiring long-term medication adherence. In their study, they compared the pharmacokinetic characteristics of sustained-release and immediate-release formulations of cilostazol. They found that the sustained-release formulation provided more stable drug concentrations, reducing peak-trough fluctuations and potentially minimizing side effects associated with high peak levels of the drug. This controlled release not only enhances therapeutic outcomes but also improves patient compliance by decreasing the frequency of dosing, making it a crucial aspect of modern pharmaceutical development. Moreover, Candiotti Keith highlighted the effectiveness of liposomal bupivacaine in managing postsurgical pain, noting that patients required 60% fewer opioid analgesics and reported 35% lower pain scores over a 72-h period compared to those receiving standard bupivacaine⁶⁴.

In response to the common issue of drug resistance in chemotherapy, NP systems offer an effective strategy. By co-delivering

multiple drugs within a single nanoparticle, it is possible to reach multiple therapeutic targets simultaneously, thereby disrupting cancer cell resistance mechanisms and enhancing therapeutic efficacy⁶⁵. For example, Zhang et al.⁶⁶ demonstrated that multifunctional NPs co-loaded with adriamycin and siRNAs targeting multiple drug resistance mechanisms, designed for active targeting and pH-responsive protonation, effectively treated chemotherapy-resistant esophageal cancer by exhibiting significant tumor-specific targeting and high intracellular delivery efficiency.

The development of NP-based DDS not only opens new avenues for cancer treatment but also lays a solid foundation for more personalized and precise treatment strategies⁶⁷.

3.2. Nanomedicine for phototherapy and sonodynamic therapy

Nanomedicines have led to significant technological advancements in cancer treatment, particularly in advanced therapeutic techniques such as PTT, PDT, and SDT⁶⁸. These methods have demonstrated the revolutionary potential of nanotechnology in medicine, providing cancer patients with more effective and precise treatment options⁶⁹. PTT, PDT, and SDT have all been enhanced by NPs. In PTT, NPs absorb specific wavelengths of light, converting them into thermal energy to directly destroy cancer cells or tumor tissues. In PDT, several types of NPs can act as photosensitizers, generating ROS under light irradiation to induce cell death^{70,71}. In SDT, several types of NPs can act as sonosensitizers, which, in response to ultrasound waves, generate high localized temperatures and/or ROS to destroy cancer cells. SDT can penetrate deeper tissues, making it an effective approach for treating deep-seated tumors⁷². All three techniques offer localized therapy, causing minimal damage to healthy tissues. The pros and cons of each technique are listed in Table 4.

Combining PTT, PDT, SDT, and chemotherapy can produce significant synergistic effects, markedly improving treatment outcomes⁵³. Such a multimodal treatment strategy leverages the advantages of each therapy to address the complex biological characteristics and resistance mechanisms of cancer, enabling a comprehensive attack on cancer cells. While chemotherapy reduces the overall tumor burden, PTT and PDT target local tumor areas, and SDT treats deeper tumors, thereby increasing treatment efficiency and reducing the development of drug resistance⁷³.

Preclinical studies and clinical trials have demonstrated the significant advantages of combining these nanomedicine-mediated treatment methods for enhancing efficacy and reducing side effects. Sun et al.⁷⁴ developed gold nanorods coated with cancer cell membranes (GNR@Mem) for treating oral squamous cancer with PTT and RT. GNR@Mem showed excellent photothermal transfer ability and radio-sensitizing effects under near-infrared light and X-ray irradiation, significantly increasing tumor cell apoptosis *in vivo* without noticeable systemic toxicity. The tumor volume suppression rate reached 95.6%, with 4 out of 5 tumors completely destroyed. GNR@Mem also demonstrated selective targeting, with an intracellular gold concentration in KB cancer cells 4.7 times higher than in other cells after 24 h of incubation. Wang et al.⁵⁶ designed a tumor-targeted and enzyme-responsive gold nanorod platform combining PTT with protein therapy. It efficiently induced localized hyperthermia and released therapeutic proteins in the presence of tumor-specific enzymes, causing significant apoptosis of A549 cancer cells and outperforming single treatments. Zhang et al.⁷⁵ proposed a novel design of heterogeneous palladium-gold nanorods (Pd–Au NRs) for photothermal therapy (PTT) in the second near-infrared (NIR-II) region,

Table 4 Pros and cons of photothermal, photodynamic, and sonodynamic therapy.

Therapy	Pros	Cons
PTT	• High precision • noninvasive • Synergistic effects • Real-time monitoring	• Heat distribution • Limited penetration • Thermal resistance
PDT	• Selective targeting • Minimal invasiveness • combination potential • Immune response activation	• Photosensitivity • Depth limitation • Reactive oxygen species
SDT	• Deep penetration • noninvasive • Targeted activation • Enhanced permeability	• Limited sonosensitizers • complex mechanism • Ultrasound heating

PTT, photothermal therapy; PDT, photodynamic therapy; SDT, sonodynamic therapy.

achieving a high photothermal conversion efficiency of 52.07%. This method effectively eradicated tumors with safer NIR-II levels, eliminated most tumor cells in a single treatment, and enhanced the conversion of chemotherapeutic agents.

Recent clinical trials have demonstrated PDT's efficacy in treating various cancers⁷⁶. For head and neck cancer, RM-1929, a conjugate of IR700 dye with an epidermal growth factor receptor (EGFR) receptor-targeting antibody, showed significant antitumor activity (NCT02422979). Photosensitizers such as porfimer sodium (Photofrin) and mono-L-aspartyl chlorin e6 (NPe6) have been used in PDT to effectively treat early-stage lung cancer. Specifically, the results of a phase II clinical study using NPe6 showed a complete response rate of 84.6% per lesion and 82.9% per patient, demonstrating significant tumor reduction and improved survival rates⁷⁷. Several ongoing clinical trials are investigating the use of SDT for various cancers. For example, the NCT04559685 trial is evaluating the safety and feasibility of combining SDT with intravenous aminolevulinic acid (SONALA-001) and a magnetic resonance-guided focused ultrasound device for the treatment of high-grade glioma⁷⁸. Hadi et al.⁷⁹ reported that combining nanomedicine with SDT not only reduced tumor size but also triggered immune-mediated effects, highlighting the potential of SDT to enhance immune responses against tumors. Viala Garcia et al.⁸⁰ discovered that oxygen nanobubbles improve the efficacy of SDT by alleviating tumor hypoxia. The nanobubbles significantly enhanced mitochondrial function increased ATP production, and reduced oxidative stress; and in preclinical models, they reduced pancreatic tumor volume by 45% and increased intra-tumoral oxygen in nasopharyngeal carcinoma 6-fold. These findings underscore the versatility and potential of phototherapy and SDT in oncology, paving the way for its integration into standard cancer treatment protocols.

3.3. Nanotechnology for nucleic acid therapy (RNA and DNA therapies)

Nanotechnology has greatly improved RNA and DNA therapies, particularly for cancer treatment. Traditional DDSs are unstable and have difficulty crossing biological barriers, but NPs can overcome these challenges, creating new treatment possibilities⁸¹.

Nanotechnology protects siRNAs from degradation, facilitates their crossing of cell membranes, and ensures effective delivery to target cells, making RNA interference more effective in inhibiting cancer cell growth. Liposomal siRNAs reduced gene expression by 65% in ovarian cancer models within 48 hs, and cyclodextrin NPs (~50 nm) enhanced cellular uptake and gene silencing⁸². Such advancements protect siRNAs and improve targeted delivery, boosting their therapeutic potential in cancer treatment. Similarly, nanoparticle carriers significantly enhance the stability and delivery efficiency of CRISPR/Cas9, a precise gene editing tool, making gene editing therapies feasible⁸³. For example, studies have shown that lipid NPs can encapsulate Cas9 mRNA and single guide RNA, achieving transfection efficiencies of up to 87% in target cells, which is significantly higher than traditional delivery methods⁸⁴. Additionally, mRNA vaccines and microRNA therapies show great potential for regulating gene expression or activating specific immune responses⁸⁵. Jackson et al.⁸⁶ showed that an mRNA vaccine for SARS-CoV-2, encapsulated in lipid NPs, elicited a robust immune response. Lipid NPs protect the mRNA from degradation and enhance cellular uptake. After the first dose, the geometric mean titers were 40,227 for the 25- μ g group, 109,209 for the 100- μ g group, and 213,526 for the 250- μ g group. This represents a 171.5% increase from 25 μ g to 100 μ g and a 95.5% increase from 100 to 250 μ g. Ning et al.^{87,88} used a rapid on-chip interferon-gamma release assay to evaluate T-cell activation, demonstrating that the main SARS-CoV-2 vaccines were effective against all variants. This assay, incorporating a nanolayer of polylysine on the microfluidic chip, effectively detected T-cell responses in vaccinated or previously infected individuals. The nanolayer enhanced cell capture, allowing for sensitive, rapid, and cost-effective, high-throughput analysis.

The integration of nanotechnology with RNA- and DNA-based therapies has also significantly advanced precision and personalized medicine⁸⁹. Preclinical studies and clinical trials have demonstrated the potential of NPs in cancer treatment, showing improved therapeutic efficacy and laying the groundwork for personalized treatments⁹⁰. Hafez Ghoran et al.⁹¹ showed that nanoformulations of curcumin greatly improved its stability and bioavailability, enhancing its antitumor effects. Nanocurcumin was 9 times more effective than free curcumin and had better oral bioavailability, making it a promising cancer treatment. After analyzing a patient's genetic background, physicians can design targeted treatment plans that use these advanced therapies, offering precise and effective treatment options with reduced side effects⁹². Choi, Ha Yeong, and Ji-Eun Chang highlighted that FDA-approved drugs osimertinib and crizotinib target EGFR mutations and anaplastic lymphoma kinase (ALK) rearrangements, respectively⁹³. Osimertinib improved PFS (18.9 vs. 10.2 months) and 18-month survival rates (83% vs. 71%) over first-generation EGFR tyrosine kinase inhibitors, with fewer adverse events. Crizotinib achieved a median PFS of 10.9 months for ALK-positive non-small cell lung cancer, compared to 7.0 months with chemotherapy. Thus, these drugs enhance survival and quality of life for patients with specific genetic alterations. Similarly, the GC0301/TOP002 phase III trial demonstrated that genomic predictors enhanced chemotherapy efficacy for advanced gastric cancer, resulting in better outcomes and fewer side effects. S-1 is a combination oral anticancer agent composed of tegafur, gimeracil, and oteracil⁹⁴. Patients on irinotecan and S-1 (IRI-S) had a median OS of 12.8 months compared to 10.5 months with S-1 alone, and IRI-S was particularly effective for those with diffuse-type histology and Eastern Cooperative Oncology Group (ECOG)

performance status 1 or 2, suggesting that these genomic predictors could be crucial for tailoring treatment plans and improving survival outcomes⁹⁴. By leveraging these advanced therapeutic strategies, researchers are revolutionizing precision medicine and expanding therapeutic strategies for personalized medicine.

3.4. Nanomedicine for immunotherapy (tumor vaccines)

In cancer immunotherapy, nanomedicine has driven the development of tumor vaccines that precisely activate the immune system to target cancer cells while minimizing harm to healthy cells⁹⁵. These tumor vaccines have been combined with other immunotherapy methods and have also been adapted for personalized medicine.

Tumor vaccines have benefitted from precisely engineered NPs. These NPs can optimize antigen presentation and enhance immune responses by improving DC intake, thus activating T cells and B cells more effectively^{96,97}. Additionally, NPs can be engineered to release antigens and adjuvants under specific physiological conditions, ensuring precise immune activation⁹⁸. Butreddy et al.⁹⁹ developed long-acting depot injections using biodegradable PLGA or PLA microspheres for controlled protein/peptide delivery, which improved therapeutic effects by maintaining constant drug plasma concentrations over extended periods. NPs have been engineered with optimized shapes, sizes, and surface properties for efficient delivery of therapeutic agents and interaction with immune cells¹⁰⁰. A “Trojan horse” approach using T cells delivered 90 times more chemotherapeutics to lymph nodes than free drugs systemically injected at 10-fold higher doses. This approach significantly reduced tumor burden and improved survival compared to that from free drug or drug-loaded NPs alone¹⁰¹.

Combining tumor vaccines with other immunotherapy methods, such as immune checkpoint inhibitors, further enhances their therapeutic effects¹⁰². Zhang et al.¹⁰³ demonstrated that the combination of a nano vaccine with an antibody therapy targeting the checkpoint inhibitor programmed cell death protein 1 (anti-PD-1) increased the tumor suppression rate by more than 20% and significantly increased the survival rate in a mouse model of melanoma. Such a multimodal treatment strategy aims to overcome the immune system's suppressive mechanisms, boosting the immune attack on tumors and providing a more comprehensive and effective treatment approach¹⁰⁴.

Several recent clinical trials have showcased the potential of this combination approach for treating various types of cancer. The interim analysis of one phase I trial (NCT02410733) demonstrated that a melanoma mRNA cancer vaccine (FixVac), alone or in combination with blocking PD-1, mediates durable objective responses in checkpoint inhibitor-experienced patients with unresectable melanoma¹⁰⁵. A phase I clinical trial (NCT03047928) demonstrated that combining personalized neo-antigen vaccines (IO102/IO103) with PD-1 inhibitors significantly improved outcomes in melanoma treatment¹⁰⁶. The vaccines induced robust T-cell responses, leading to tumor regression in multiple patients. Similarly, a phase II trial (NCT03897881) highlighted the efficacy of a personalized mRNA-based vaccine (mRNA-4157) in conjunction with the PD-1 inhibitor pembrolizumab for patients with high-risk melanoma. The study showed a marked 44% reduction in the risk of recurrence or death (HR: 0.561, 95% CI: 0.309 to 1.017) compared to that after standard treatments. Additionally, the trial reported a statistically

significant improvement in distant metastasis-free survival (DMFS) for the combination therapy; At a median follow-up of 23 months, the 18-month DMFS rate was 91.8% for the combination therapy group and 76.8% for the pembrolizumab monotherapy group (HR: 0.347, 95% CI: 0.145 to 0.828)¹⁰⁷. The phase I AMPLIFY-201 trial (NCT04853017) showed that a neoantigen vaccine (ELI-002 2P) targeting KRAS mutations in pancreatic and colorectal cancers, combined with standard chemotherapy, elicited a strong immune response and was well tolerated, offering a promising new treatment avenue¹⁰⁸.

In addition to mRNA vaccines, several innovative approaches are being explored to improve cancer treatment outcomes. Personalized RNA mutanome vaccines target unique cancer mutations, showing promising results¹⁰⁹. One patient with multiple progressing metastases unresponsive to local RT achieved complete remission with blockade of cytotoxic T-lymphocyte associated protein 4 (CTLA-4), remaining relapse-free for 26 months. Another patient had an 80% reduction in melanoma lesions within 2 months of combining the neo-epitope vaccine with PD-1 blockade therapy, with T cells from the vaccine persisting for up to 9 months.

Nanomedicine has also driven the development of personalized cancer vaccines. These vaccines are tailored to each patient's unique tumor antigens, enhancing treatment specificity and providing bespoke plans for superior outcomes¹¹⁰. Recent clinical trials have demonstrated promising results, showing that these vaccines can induce robust immune responses and improve clinical outcomes in various cancers. A melanoma trial combining a personalized mRNA vaccine with immunotherapy showed enhanced T-cell responses and significant tumor regression¹¹¹. Compared to patients receiving pembrolizumab alone, patients receiving mRNA-4157 and pembrolizumab had a 44%-reduced risk of recurrence or death. Nanomedicine's personalized approach offers new hope for cancer treatment by providing precise and effective tumor immunotherapy vaccines¹¹². This technology increases treatment success rates and improves patients' quality of life, showcasing nanotechnology's potential in advancing medical development.

4. Challenges and countermeasures in translating cancer nanomedicine from the bench to the bedside

While significant progress has been achieved in the development of antitumor nanomedicines, their advancement and clinical translation still encounter numerous challenges (Fig. 6). These challenges include the complex nature of tumor biology, interactions between NPs and biological systems, and difficulties in nanomedicine characterization, such as ensuring precise, reproducible physicochemical properties. Delivery and targeting obstacles, like tumor-specific accumulation and penetration, complicate clinical use. Additionally, production, scalability, and quality control standards further hinder the widespread application of cancer nanomedicines¹¹³. The complexity of tumor biology arises from tumor heterogeneity, which can exist not only between patients but also within a single tumor, making it challenging to design nanomedicines that are universally effective¹¹⁴. Moreover, the TME, characterized by conditions such as hypoxia, abnormal vasculature, and variable pH levels, further complicates the targeted delivery and efficacy of nanomedicines¹¹⁵. Interactions between NPs and biological systems are complex because of protein corona formation, which alters the surface characteristics

of NPs and affects their biodistribution, targeting efficiency, and detection by the immune system¹¹⁶. Understanding and managing these interactions is crucial for the successful design and application of nanomedicines in clinical settings¹¹⁷.

Precise NP characterization is vital for safety, efficacy, and regulatory approval, but current techniques often miss key features like size, surface charge, stability, and drug release¹¹⁸. This leads to inconsistencies between preclinical and clinical results and challenges in reproducibility. Manufacturing variations can further alter NP properties, complicating batch consistency. Regulatory bodies require robust data, but the lack of standardized methods hinders approval. Developing advanced, reliable, and standardized techniques is crucial for overcoming these challenges and ensuring successful clinical translation of nanomedicines¹¹⁹.

Failure to achieve active targeted delivery in antitumor nanomedicines is due to tumor heterogeneity, the complex tumor microenvironment, rapid mononuclear phagocyte system (MPS) clearance, inefficient extracellular matrix (ECM) penetration, and suboptimal receptor binding¹²⁰. Innovative strategies are needed to enhance nanoparticle stability, circulation, and specificity to improve therapeutic outcomes.

Scaling up the production of nanomedicines poses challenges related to maintaining consistency in NP size, charge, surface modification, and drug loading, all of which are critical for ensuring the safety, efficacy, and stability of NPs¹¹⁷. Achieving uniformity across large batches is essential for clinical application but remains difficult because of the intricate processes involved in NP synthesis and drug encapsulation¹²¹. Quality control of nanomedicines entails rigorous and comprehensive testing to guarantee their safety and efficacy. The complexity of nanomedicine formulations, which may incorporate active pharmaceutical ingredients, carriers, and targeting ligands, necessitates advanced analytical techniques for thorough characterization and quality assessment¹²². This increases the cost and time of development, impacting the feasibility of clinical translation.

Overcoming these challenges requires collaboration across multiple disciplines and strategies, such as advancing nanotechnology, gaining deeper insights into tumor biology and the immune system, innovating manufacturing techniques, and establishing standardized quality control protocols¹²³. The following sections explore challenges confronting the clinical translation of cancer nanomedicines and discuss strategies to address them.

4.1. Complex interactions with biological systems and crossing biological barriers

The application of nanomedicines in cancer treatment has unveiled their unique value and potential for interacting with biological systems and traversing biological barriers. Research in this field not only explores the physicochemical properties of NPs, such as size, shape, surface charge, and chemical composition but also delves into how these properties influence complex interactions with biological systems¹²⁴. A critical focus of the study is the interaction between NPs and the immune system. Surface modifications, such as incorporating targeting molecules or applying polyethylene glycol (PEG) "stealth" coatings, play a pivotal role in reducing immune recognition, prolonging circulation time in the bloodstream, and enhancing the likelihood of reaching target tissues¹²⁵.

Overcoming challenges like crossing the BBB and targeting specific biological barriers within the TME requires innovative

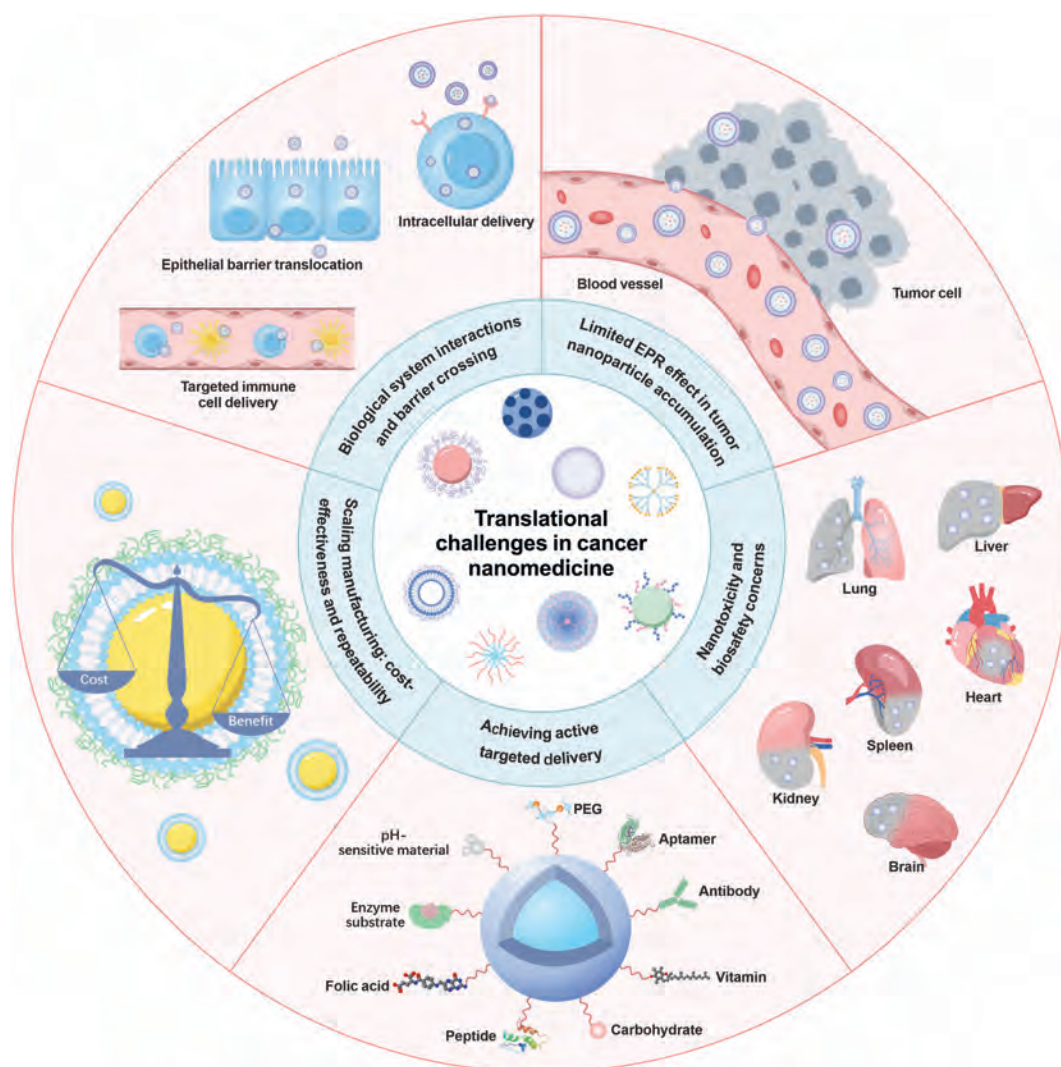


Figure 6 Challenges in the clinical translation of cancer nanomedicine.

nanotechnological strategies^{126,127}. NPs can be engineered with surface modifications to promote binding to BBB receptors, thus facilitating drug delivery across this selective barrier¹²⁸. For example, Hoyos-Ceballos et al.¹²⁹ designed PLGA-PEG NPs conjugated with Angiopep-2 (Ang-2), which crossed the BBB and accumulated in neuronal cells in an animal model, highlighting their potential as a promising approach for brain drug delivery and the treatment of central nervous system diseases. Rabanel et al.¹³⁰ studied the transport of PEGylated-PLA NPs across a BBB model, their neuronal cell entry, and their *in vivo* brain bioavailability. The research identified optimal surface parameters that facilitated the endocytosis of NPs into vascular endothelial cells primarily through micropinocytosis, revealing that smaller NPs and longer PEG chains (PEG5000) enhanced endocytosis and *in vivo* brain bioavailability more than larger NPs and shorter PEG chains (PEG2000). Simultaneously, the distinct physical and chemical properties of the TME promote the accumulation of carefully designed nanomedicines in tumor tissue. In a glioma model, compared to non-choline formulations, BBB-crossing anti-PD-L1-MP-3 NPs reduced tumor size 20-fold, significantly suppressing tumor growth and prolonging survival. Their pH-responsive release mechanism in the acidic TME

further enhanced efficacy and minimized side effects, holding great promise for cancer immunotherapy¹³¹.

In nanomedicine research, customizing nanoparticle properties like size, shape, and surface modifications is crucial for optimizing therapeutic effects and minimizing nonspecific actions¹³². Tailoring these parameters enhances drug targeting, bio-distribution, and excretion, making targeted disease treatment possible¹³³. NPs starting at 80 nm can shrink to ~10 nm in slightly acidic tumor environments (pH ~6.7), improving penetration and drug delivery. In BxPC-3 pancreatic tumor models, this size transition increased drug delivery efficiency from 2.5- to 3.5-fold and tumor accumulation from 4.5- to 7.0-fold compared to traditional treatments. Incorporating pH-responsive polymers like PEG-b-PAEMA allows NPs to disassemble into smaller units in acidic conditions, enhancing penetration depth from 25 μ m to 85 μ m in multicellular spheroids. This modification increased drug uptake 2.9-fold after 4 h and 2.6-fold after 12 h in acidic conditions (pH 6.7) compared to non-modified NPs¹³⁴. These advancements highlight nanomedicine's potential in oncology as well as the interdisciplinary collaboration required to develop efficient and safe therapies.

4.2. Limited EPR effect for nanoparticle accumulation in tumors

In the field of nanomedicine, particularly in the design and application of NPs for tumor treatment, the EPR effect is considered a key mechanism¹³⁵. Nanomedicines target tumor tissue by exploiting the EPR effect, which utilizes the permeability of tumor vasculature and defects in the lymphatic system for passive accumulation in solid tumors. Discovered in 1986, the EPR effect has been crucial in cancer nanotherapy¹³⁶. However, it varies because of the complexity and heterogeneity of the tumor microenvironment, with its abnormal structure of tumor blood vessels, high interstitial pressure, and uneven blood flow. The EPR effect also varies significantly among patients, tumor types, and even between primary tumors and metastases within the same patient¹³⁷. This leads to uneven distribution of NPs within the tumor, thereby limiting their therapeutic effects¹³⁸. This variability results in cancer nanomedicines having different levels of accumulation and therapeutic effects in different tumors and patients¹³⁹. Therefore, to enhance the accumulation of nanomedicines in tumors with low EPR effects, researchers have proposed several alternative targeting strategies, including tumor vasculature targeting, cell-mediated tumor targeting, tumor-penetrating peptides, iRGD (internalizing arginine-glycine-aspartate, CRGDK/RGPD/EC)-facilitated *trans*-endothelial extravasation, improved tumor penetration, and local delivery methods¹⁴⁰.

A key challenge in translating the EPR effect from animal models to human clinical applications stems from significant differences between animal and human vasculature. For instance, animal models, particularly rodent tumors, often show stronger EPR effects because of higher blood flow and distinct vascular architecture. Studies have shown that rodent tumors have an average blood flow of 5.4 mL/100 g/min, while human tumors range between 30 and 64.8 mL/100 g/min, leading to less efficient NP accumulation in human tissues. Additionally, higher interstitial fluid pressure and solid stress in human tumors further limit drug penetration. Overcoming these barriers is crucial for improving the clinical efficacy of EPR-based nanomedicines¹⁴¹.

Therefore, researchers have focused on improving permeability and retention to enhance NP accumulation within tumors¹⁴². One strategy is to optimize the size and surface properties of NPs. Studies have shown that adjusting NPs to a specific size range (approximately 10–100 nm) and modifying their surface hydrophilicity or adding specific targeting molecules can increase their specificity and accumulation in tumors¹⁴³. Another strategy is pretreatment with vascular normalizing agents or drugs to modify the TME. These pretreatments can optimize blood flow dynamics within the tumor and reduce interstitial pressure, thereby enhancing the permeability of tissues and the retention of NPs¹⁴⁴. Recent research by Cho et al.¹⁴⁵ revealed that using RGD-modified lipid NPs to silence vascular endothelial growth factor receptor 2 (VEGFR2) enhanced vascular normalization and T-cell infiltration, boosting the efficacy of anti-PD-1 antibodies. When compared to monotherapy, this combination therapy increased CD8⁺ T-cell infiltration 5.5-fold, suppressed tumor growth with an interaction index of -0.90 (95% CI, -1.55 to -0.26) on Day 12, and significantly reduced average tumor volume.

These strategies can achieve two goals simultaneously: they not only enhance permeability and retention, increasing drug accumulation in tumors, but also mitigate toxicity to normal tissues.

4.3. Nanotoxicity and biosafety concerns

The sustainable progress of nanomedicine relies on addressing nanotoxicology and biosafety concerns¹⁴⁶. As nanomaterials are incorporated into medical applications for drug delivery, diagnosis, and treatment, both the scientific community and the public have become increasingly concerned about the safety and biocompatibility of these nanomaterials. Thus, researchers are implementing measures to assess and improve the safety of nanomaterials. Firstly, they are studying the long-term safety and toxicity of NPs and their degradation products¹⁴⁷. Compared to traditional materials, NPs interact differently with biological systems because of their unique size, shape, and surface properties. They can cross biological barriers and enter cell nuclei, which, in addition to providing new therapeutic possibilities, can potentially pose risks of toxicity¹⁴⁸. Therefore, comprehensive studies on the distribution, metabolism, and clearance of NPs are imperative, as are studies on possible cytotoxicity, genotoxicity, and carcinogenicity¹⁴⁹. Conducting these studies *in vivo* and *in vitro* will help ensure safe utilization¹⁵⁰.

A major challenge in translating these findings from animal models to humans is the difficulty in mimicking human physiology, as animals and humans have differences in metabolism, immune function, and cellular interactions with NPs. These differences raise concerns about the reliability of animal studies in predicting human outcomes, emphasizing the urgent need for alternative methods like organ-on-a-chip and advanced *in vitro* models. These technologies offer more accurate predictions of NP behavior in humans, reducing reliance on animal testing and improving safety assessments¹⁵¹. Secondly, to mitigate potential toxicity, researchers are exploring novel biocompatible and biodegradable materials¹⁵². Materials such as PLGA, liposomes, and natural biopolymers are being researched extensively. These materials can safely degrade and be cleared by the body after fulfilling their intended functions, thereby reducing long-term burdens¹⁵³.

Evaluating NP biosafety involves assessing factors like size, shape, surface charge, and chemical composition, as these influence cellular uptake, biodistribution, and toxicity. Smaller NPs (<100 nm) typically have higher cellular uptake but may evade immune detection, resulting in prolonged retention and unexpected effects. Surface modifications, such as PEGylation, can alter interactions with biological environments, reducing toxicity by minimizing protein adsorption and improving circulation time. It's essential to balance therapeutic efficacy with potential risks, as protein coronas on NP surfaces can impact biological behavior¹⁵⁴. Thus, designing NPs with controlled protein interactions is crucial for enhancing biosafety without compromising efficacy, while understanding their interactions with the immune system is vital for minimizing adverse effects and improving therapeutic outcomes¹⁵⁵.

Advancing nanomedicine also relies on establishing standardized safety testing protocols and guidelines. This involves analyzing the physicochemical properties of nanomaterials, assessing biocompatibility, and conducting evaluations for long-term toxicity and ecotoxicity¹⁵⁶. The resulting protocols provide a scientific framework for the safe clinical integration of nanomaterials¹⁵⁷. As new materials and technologies continually emerge, these testing protocols and guidelines need to be continuously updated to ensure their accuracy and relevance¹⁵⁸. Emerging safety assessment models, like organ-on-a-chip systems, offer more accurate predictions of NP behavior in human physiology than traditional models, improving our understanding of their safety profiles before clinical use. Regulatory frameworks

are also adapting to nanomedicine's rapid evolution by incorporating comprehensive toxicity evaluations and safety standards tailored to the unique properties of nanomaterials¹⁵⁹.

In summary, by studying the biological behavior of nanomaterials, developing new biocompatible materials, and establishing comprehensive safety assessment systems, a robust foundation can be laid for the implementation of nanotechnology in medicine¹⁶⁰. These measures will safeguard patient well-being and support the sustainable growth of nanomedicine as a transformative field in healthcare¹⁶¹.

4.4. Achieving active targeted delivery

To tackle the challenges of active targeting for treating tumors, nanomedicine is pioneering innovative strategies to enhance the specificity of NPs' recognition of cancer cells¹⁶². These strategies focus on designing effective targeting ligands, overcoming tumor heterogeneity and the dynamic TME, and developing intelligent NPs capable of responding to tumor-specific signals¹⁶³.

NPs' affinity and specificity for tumor cells can be enhanced by modifying the NP surface with targeting ligands such as antibodies, small molecule ligands, peptides, or nucleic acid aptamers^{164,165}. Careful selection of these ligands is crucial, as they must selectively recognize and bind to specific markers on the surface of tumor cells, thereby facilitating NP accumulation at the tumor site¹⁶⁶. For effective targeted delivery, these ligands must not only possess high affinity and specificity but also maintain the stability and bioactivity of the NPs¹⁶⁷.

Overcoming tumor heterogeneity and the dynamic TME is challenging in cancer treatment. Nanomedicine addresses these challenges by developing multifunctional NPs capable of adapting to the heterogeneous and dynamic nature of tumors¹⁶⁸. These NPs are engineered to deliver therapeutic agents specifically to diverse cancer cell populations and modulate the TME, enhancing treatment efficacy and reducing off-target effects.

Developing intelligent NPs that respond to tumor-specific signals is a major advancement in nanomedicine. These smart NPs are engineered to recognize and react to various stimuli present in the TME, such as pH changes, enzymatic activity, and hypoxia, enabling targeted drug release and minimizing off-target effects¹⁶⁹. This approach not only enhances drug delivery precision but also allows real-time monitoring and adjustments of treatment in response to the evolving characteristics of the tumor, advancing precision oncology.

By integrating these strategies, nanomedicine enhances the precision and efficiency of active targeting in tumor treatment. This requires a profound understanding of tumor biology and the TME, as well as collaborative effort across disciplines, including materials science, chemistry, biology, and medicine, to develop next-generation nanotherapeutic schemes¹⁷⁰.

4.5. Scaling up manufacturing: Balancing cost-effectiveness and repeatability

As nanotechnology expands its application in medicine, particularly in drug delivery, diagnostics, and therapeutics, efficiently and cost-effectively transitioning nanomedical products from the laboratory to the market has become a significant challenge. Addressing this challenge necessitates the development of scalable, cost-effective production processes, rigorous quality control measures, and collaboration with industry partners to ensure product consistency and quality.

Researching and developing efficient NP synthesis techniques is essential for scalable and cost-effective production. Techniques such as microemulsion, nanoprecipitation, and self-assembly should be easily scalable and low-cost while yielding high output¹⁷¹. Adopting automated and integrated production processes can reduce manual operations, enhance efficiency, and lower costs. For instance, using continuous flow reactors instead of traditional batch synthesis methods can ensure more consistent NP production¹⁷². Additionally, developing environmentally friendly production methods can minimize harmful solvents and waste, thereby reducing costs and meeting sustainability goals¹⁷³.

Maintaining product consistency and quality through stringent quality control measures is also paramount. This entails establishing a robust quality management system aligned with international standards, ensuring that every stage, from raw material procurement to product packaging, adheres to rigorous quality criteria. Utilizing advanced analytical techniques and real-time monitoring equipment for NPs guarantees consistency across batches¹⁷⁴.

Also critically important for bridging the gap from laboratory research to commercial production is collaborating with industry partners. This involves forging alliances between universities, research institutions, and leading industry firms to exchange resources, expertise, and technologies, thereby accelerating the development and application of new innovations. Effective technology transfer agreements facilitate the transition of laboratory-developed technologies to industrial-scale production, addressing technical and engineering challenges associated with scale-up. Additionally, close collaboration with regulatory bodies ensures that production processes and products comply with regulatory requirements and standards, facilitating smooth market entry.

Implementing these strategies will effectively address the challenges of cost and reproducibility in scaling up nanomedical products. These approaches will accelerate the commercialization process, enabling broader application in clinical therapy. Success hinges on technological advancements, interdisciplinary collaboration, and adept management strategies to ensure seamless technology transfer and widespread market acceptance.

4.6. Navigating clinical translation: regulatory challenges, clinical trials, and adoption pathways

The clinical translation of nanoparticulate nanomedicines (NNMs) from bench to bedside is crucial for advancing drug delivery research but faces significant hurdles, including regulatory challenges, complex clinical trials, and the need for systematic adoption strategies. Regulatory barriers are particularly prominent, as existing frameworks often rely on traditional drug assessment methods that fail to address the unique characteristics of NNMs, such as their nanoscale size and complex pharmacokinetics. The lack of specific guidelines for NNMs complicates the evaluation of their safety, efficacy, and quality, leading to prolonged approval processes and uncertainties for manufacturers and developers¹⁷⁵. Regulatory bodies like the FDA and EMA often evaluate NNMs on a case-by-case basis, highlighting the need for iterative, flexible, and product-specific approaches to keep pace with rapid advancements in nanotechnology¹¹⁹.

The clinical trial landscape for NNMs is diverse, with promising candidates like Doxil and ThermoDox (thermosensitive liposomal doxorubicin) showing potential in treating cancer. However, despite their therapeutic benefits, NNMs face challenges in clinical translation because of inconsistent results among patient populations, variations in TMEs, and difficulties in ensuring

stability and reproducibility during scale-up manufacturing¹⁷⁶. The EPR effect, often cited as a mechanism for passive targeting of NNMs, varies significantly between tumor types and within the same tumor, affecting clinical outcomes¹⁷⁷. Active targeting strategies using ligands to enhance specificity have shown inconsistent clinical benefits due to the significant influence of ligand density, target receptor expression, and the microenvironment on the effectiveness of these formulations²⁸.

Successfully integrating NNMs into clinical practice requires robust validation processes that ensure reproducibility and consistency across preclinical and clinical studies. These involve validating NP stability, therapeutic efficacy, and safety profiles under conditions that closely simulate clinical use¹⁷⁸. Scalable manufacturing is crucial for NNMs, requiring compliance with good manufacturing practice (GMP) standards to ensure batch-to-batch reproducibility and maintain key quality attributes like particle size, surface charge, and drug loading efficiency. Advanced techniques such as microfluidics and automated synthesis can achieve scalability while preserving product quality¹¹⁸.

Developing a regulatory strategy is crucial for clinical adoption, requiring early and ongoing engagement with regulatory authorities to address the specific challenges of NNMs. This includes establishing clear characterization methods and safety thresholds. A proactive approach can streamline the approval process by aligning NNM development with regulatory expectations and incorporating feedback throughout¹⁷⁸. Clinical trial designs must reflect the unique properties of NNMs, utilizing biomarkers for patient stratification, adaptive trial designs to account for variability, and comprehensive assessments of pharmacokinetics and biodistribution. Trials should also compare NNMs directly with standard-of-care treatments to demonstrate their added value. Additionally, post-market surveillance is vital for monitoring the long-term safety and efficacy of NNMs, involving ongoing pharmacovigilance, real-world effectiveness studies, and risk management plans¹⁷⁵. Coordinating these steps will facilitate the successful transition of NNMs from research to clinical practice, ultimately enhancing patient outcomes and expanding therapeutic options in modern medicine.

5. Case studies and practical applications

Nanotechnology in cancer treatment has gained significant attention due to several clinically validated nanomedicines that have enhanced therapeutic efficiency and safety¹⁷⁹. These nanomedicines optimize drug delivery, reduce toxicity to healthy cells, and minimize side effects while improving efficacy¹⁸⁰. This shift to nanomedicines promotes more personalized and precise therapies over traditional one-size-fits-all treatments.

Two prominent examples of clinical application are Doxil and Abraxane. Doxil, the pioneering FDA-approved nanomedicine, uses lipid NPs to deliver doxorubicin, extending drug circulation time and notably reducing side effects like cardiotoxicity, offering new treatment options for ovarian cancer, AIDS-related Kaposi's sarcoma and various solid tumors¹⁸¹. Abraxane combines paclitaxel with albumin, using a nanotechnological approach to enhance drug solubility, bioavailability, and tumor-targeted delivery and offering effective treatment for breast cancer, non-small cell lung cancer, and pancreatic cancer¹⁵³.

A case study of Doxil showed that patients with recurrent ovarian cancer experienced significantly fewer severe side effects compared to those receiving traditional chemotherapy, highlighting

Doxil's improved safety and efficacy¹⁸². Similarly, compared to solvent-based paclitaxel, Abraxane demonstrated increased PFS in metastatic breast cancer patients, underscoring its clinical value¹⁸³. Another example is Onivyde (liposomal irinotecan), approved in 2023 for treating pancreatic cancer¹⁸⁴. The phase III NAPOLI 3 trial showed that compared to nab-paclitaxel and gemcitabine, combining Onivyde with oxaliplatin, leucovorin, and fluorouracil (NALIRIFOX) significantly improved median OS (11.1 vs. 9.2 months) and overall response rate (41.8% vs. 36.2%). These results, demonstrating its efficacy and tolerability over the current standard regimen, support NALIRIFOX as a potential first-line treatment for metastatic pancreatic ductal adenocarcinoma. Future research will explore Onivyde's use in combination therapies and for earlier cancer stages. Despite its benefits, Onivyde has limitations, including common gastrointestinal side effects like diarrhea and neutropenia, which require close patient monitoring¹⁸⁵. This highlights the need for balanced treatment approaches that weigh efficacy against potential side effects.

Recent advancements highlight nanotechnology's significant role in oncology. For instance, integrating nanomedicines with immunotherapy enhances the immune response against cancer cells and overcomes resistance to treatments¹⁸⁶. Chen et al.¹⁸⁷ showed that PLGA-R837@Cat NPs combined with RT improved immune responses in mice, increasing their survival rate (60% vs. 0% in controls). This treatment eliminated primary tumors, reduced secondary growth, and provided long-term immune memory, highlighting nanomedicine's potential for enhancing cancer immunotherapy. Nanomedicines also increase tumor radiosensitivity in RT, improving outcomes and reducing radiation doses¹⁸⁸. Xu et al.¹⁸⁹ showed that X-ray-responsive, proteolysis-targeting chimera (PROTAC) NPs degraded bromodomain-containing protein 4 (BRD4), enhancing tumor radiosensitivity and achieving a 92.61% tumor volume reduction compared to controls.

In clinical settings, nanomedicines are being assessed for their potential to overcome multi-drug resistance (MDR) in cancer treatment. For instance, a study on polymeric micelles in chemotherapy-resistant ovarian cancer reported increased drug accumulation in tumor tissues, effectively overcoming MDR and improving therapeutic outcomes¹⁹⁰. In surgical oncology, NPs are being explored for intraoperative imaging and targeted therapy, aiding in precise tumor removal and reducing recurrence rate¹⁹¹. In one study, melanin NPs functionalized with RGD improved intraoperative imaging for breast cancer surgery¹⁹². In MDA-MB-231 tumor-bearing mice, these NPs enhanced photoacoustic intensity by 2.1-fold and increased the ratio of photoacoustic intensity at the tumor site to a healthy tissue site (3.2 for targeted NPs vs. 1.7 for non-targeted NPs). This method also reduced the need for re-excision and provided accurate three-dimensional (3D) imaging for effective tumor removal, minimizing recurrence. The clinical application of NPs in surgical oncology is still in its early stages, facing challenges like stability, targeting precision, and potential toxicity that require further research. This highlights the need for ongoing innovation and refinement in nanomedicine technology.

The development of Onpatro, the first FDA-approved siRNA-based nanomedicine, highlights the potential of gene delivery systems in clinical use. By using lipid NPs to target transthyretin (TTR) synthesis, Onpatro treats polyneuropathies in hereditary transthyretin amyloidosis (hATTR). The phase III APOLLO trial showed an over 80% reduction in serum TTR levels with a well-tolerated safety profile, establishing Onpatro as a model for

nucleic acid-based therapies and expanding nanomedicine's role in gene and protein delivery¹⁹³. This integrated approach significantly enhances therapeutic effects, personalizes treatment, minimizes damage to healthy tissues, reduces treatment-related complications, and improves overall treatment efficiency, thereby enhancing patient quality of life.

6. Future opportunities in cancer nanomedicine development

The future of cancer nanomedicine promises significant advancements in treatment. Key challenges include optimizing NP design, ensuring biocompatibility, and collaborating with regulators to streamline approvals. Advancements will involve modifying the TME to enhance immune response and reduce resistance, improving treatment outcomes. Integrating AI and big data will optimize NP design, predict patient responses, and personalize treatments. Addressing metastasis, recurrence, and side effects will expand nanomedicine's applications. A promising direction is the development of multifunctional NPs for imaging, theranostics, and combinational therapies, leading to more effective cancer treatments (Figs. 7 and 8 illustrate the current applications and future prospects of tumor nanomedicine.).

6.1. Enhancing the clinical translation of nanomedicine

The rapid progress of nanotechnology in cancer treatment shows great promise, but clinical translation remains challenging. Key issues include ensuring biocompatibility and safety, addressing targeted delivery, and the TME¹⁹⁴. Moreover, tumor heterogeneity

necessitates personalized nanomedicine approaches, with ongoing research aiming to tailor nanocarriers to individual patient profiles¹⁹⁵.

Overcoming the remaining hurdles requires fostering interdisciplinary collaboration among researchers, clinicians, and regulators. Such collaboration accelerates nanomedicine development through knowledge exchange and resource sharing¹⁹⁶. Conferences and workshops serve as crucial platforms for discussing advancements, optimizing clinical trials, and tackling regulatory obstacles.

Public-private partnerships merge academic innovation with pharmaceutical expertise to expedite nanomedicine commercialization. Streamlining regulatory processes with clear guidelines and fast-track review mechanisms is critical¹⁹⁷. Effective communication between developers and regulators is vital for mutual understanding and ensuring a smooth transition through clinical trials and approval pathways¹⁹⁸.

Identifying and addressing research gaps is crucial for translating nanomedicine effectively. Improving preclinical studies by employing models that mimic human diseases improves the predictability and clinical relevance of research outcomes¹⁹⁹. Promoting data sharing and transparency helps researchers learn from both successes and failures²⁰⁰. Conducting multicenter clinical trials increases sample sizes, enhancing the statistical power, generalizability, and credibility of research findings across diverse patient populations²⁰¹.

Implementing these strategies can expedite the clinical translation of nanomedicine for cancer treatment, improving outcomes and expanding therapeutic options²⁰². This progress relies on ongoing technological innovation, interdisciplinary collaboration,

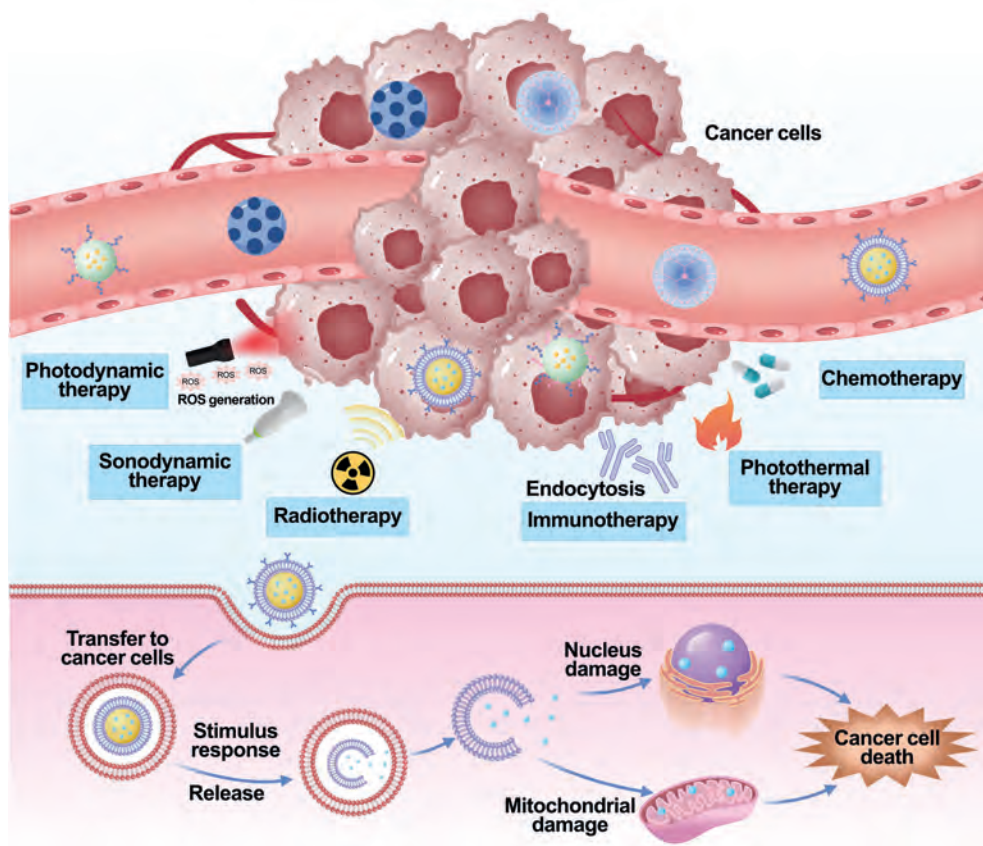


Figure 7 The extensive range of current applications in cancer nanomedicine.

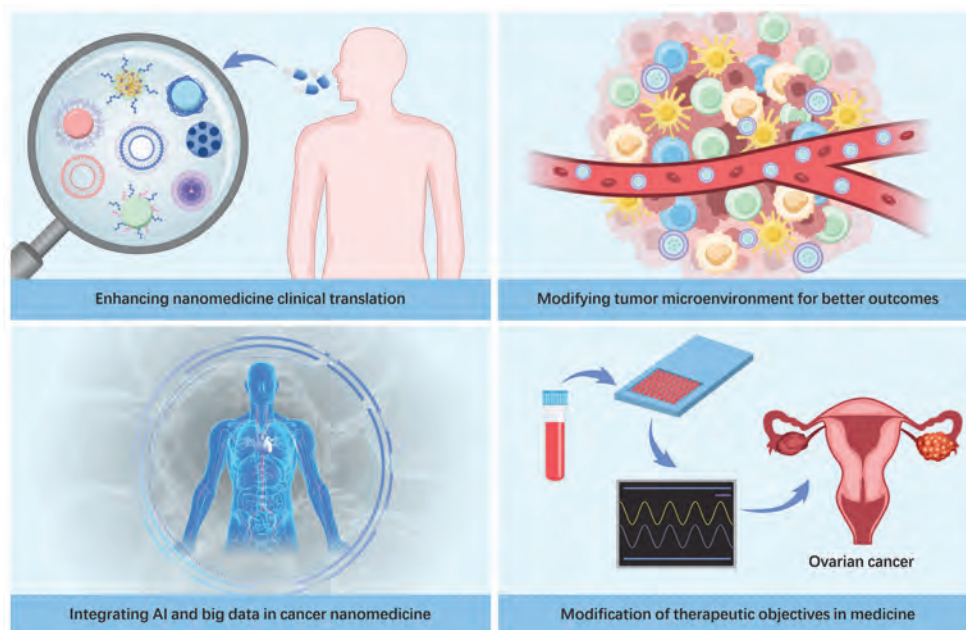


Figure 8 Prospective applications of cancer nanomedicine.

and effective management and regulatory strategies to ensure safe and effective clinical integration²⁰³. Taken together, these strategies will drive advancements in nanomedicine development and application.

6.2. Modifying the TME for improved therapeutic outcomes

Optimizing the TME for better NP delivery is a key focus in future cancer research. The complex TME, including factors like hypoxia, acidic pH, and high interstitial pressure, challenges drug delivery²⁰⁴. Researchers are exploring ways to modulate these factors to enhance the effectiveness of nanomedicines.

One strategy is to enhance hemodynamics and reduce interstitial pressure for better NP permeability. Vascular normalization agents (*e.g.*, anti-angiogenic drugs) improve tumor blood vessel function, while matrix metalloproteinase (MMP) inhibitors are often used to degrade the ECM or inhibit its production, lowering interstitial pressure²⁰⁵. Another strategy is to leverage the interaction between immune cells and the TME to boost the efficacy of nanomedicines. Recent studies have highlighted several mechanisms and therapeutic strategies in this area. For instance, Chen et al.²⁰⁶ demonstrated that bio-responsive immunotherapeutic gels sprayed *in situ* significantly enhanced post-surgical cancer treatment by effectively stimulating local immune responses and reducing tumor recurrence. The researchers found that fibrin gel, loaded with calcium carbonate NPs pre-loaded with anti-CD47 antibodies, created a bio-responsive environment that modulated the TME. Specifically, the calcium carbonate NPs dissolved in the acidic TME, releasing the anti-CD47 antibodies to block the “don’t eat me” signal on cancer cells. This blockade promoted the phagocytosis of cancer cells by macrophages and subsequently enhanced antigen presentation to T cells, thus activating a robust anti-tumor immune response²⁰⁷.

Recent advances have introduced multifunctional nanodrugs that actively remodel the TME. These strategies involve targeting ECM components, modulating tumor-associated fibroblasts (TAFs), and addressing hypoxic regions within tumors. Physical

methods like high-intensity focused ultrasound (HIFU) and PTT can disrupt ECM barriers, enhancing nanodrug penetration. Additionally, biochemical agents such as hyaluronidase degrade ECM components, improving the distribution and efficacy of nanotherapeutics in ECM-rich tumors. Emerging strategies also focus on normalizing abnormal tumor vasculature, which enhances NP perfusion and alleviates hypoxia—an obstacle to effective treatment. This normalization can be achieved with anti-angiogenic agents that improve blood supply and facilitate nanotherapeutic penetration, but timing is crucial, as prolonged normalization may reduce NP uptake by stabilizing blood vessel walls²⁰⁸.

Implementing these types of strategies requires a deep understanding of the complexity of the TME as well as innovative nanotechnologies and combination therapies²⁰⁹. With their diverse cell populations and varying vascularization, tumors are heterogeneous, which complicates targeted drug delivery and promotes drug resistance¹⁷⁶. Additionally, the immunosuppressive tumor environment, with components like tumor-associated macrophages (TAMs) and regulatory T cells, hinders immunotherapy effectiveness²¹⁰. Addressing these issues requires combination strategies that modulate the immune system and overcome physical barriers like dense extracellular matrices and abnormal vasculature²¹¹. Recent advancements in multifunctional nanodrugs enhance targeting and controlled release in cancer therapy. These NPs can modulate the TME, boost immune activation, and enable targeted drug delivery. However, clinical translation requires further optimization to balance TME disruption with normalization, address tumor heterogeneity, and minimize potential toxicities from nanocarrier materials.

6.3. Integrating artificial intelligence (AI) and big data into cancer nanomedicine

Integrating AI and big data into cancer nanomedicine will transform cancer treatment. These technologies have revolutionized drug discovery, optimized personalized treatment strategies, and predicted therapeutic outcomes and toxic reactions, greatly

improving treatment safety and effectiveness. AI-driven drug discovery uses bioinformatics and genetic data to identify novel therapeutic targets and design effective nanomedicines²¹². Machine learning models, especially neural networks, analyze complex relationships between drug properties and biological systems, improving the identification of new drug candidates for NP loading²¹³. AI models also predict how NP structures affect drug delivery efficiency, guiding the design of targeted therapies²¹⁴. Using AI algorithms like artificial neural networks (ANNs), researchers can model how particle size, zeta potential, and encapsulation efficiency affect drug distribution and therapeutic impact, optimizing NPs for specific cancer treatments. Big data technologies enable personalized treatment plans by analyzing genetic information, tumor characteristics, and treatment responses, maximizing efficacy and minimizing side effects²¹⁵. These systems integrate extensive patient data, including clinical history and genetic profiles, to create tailored nanomedicine regimens for individual needs. Additionally, big data analytics help optimize treatment combinations for better outcomes, enhancing precision and decision-making in clinical practice. AI-driven data analysis can dynamically update treatment protocols based on real-time patient response data, ensuring the selection of the most effective therapeutic combinations for each individual²¹⁶.

Developing predictive models for treatment response is a pivotal application of AI and big data in cancer nanomedicine. These models use medical records and biomarkers to forecast nanomedicine treatment outcomes, helping clinicians evaluate treatment plans and recommend optimal nanomedicines on the basis of historical treatment data and real-time patient monitoring²¹⁷. For instance, predictive algorithms can be trained to evaluate the success of various NP formulations in different tumor environments, offering critical insights into which therapies are most likely to succeed in clinical settings. This approach enhances treatment efficacy and patient outcomes. However, challenges such as data quality, privacy, and algorithm interpretability must be addressed through interdisciplinary collaboration and legal and ethical discussions²¹⁸. Many AI models, particularly complex ones like ANNs, act as “black boxes”, complicating the interpretation of their decision-making processes. This lack of transparency hinders clinical adoption, where understanding AI-driven decisions is essential. Developing explainable AI techniques is necessary to help clinicians trust these predictions. Additionally, protecting sensitive patient data during AI processing requires robust encryption and strict compliance with privacy regulations²¹⁶. As technology advances, AI and big data will play an increasingly important role in providing precise, effective, and personalized cancer treatments²¹⁹. The future of cancer nanomedicine depends on improving AI models to better handle diverse datasets, enhancing their applicability across various patient populations and cancer types. Collaboration among data scientists, clinicians, and regulatory experts will be essential to address the technical and ethical challenges of these technologies.

6.4. Modification of therapeutic objectives in medicine

Nanotechnology has contributed to current trends in cancer management. Cancer treatment now emphasizes prevention, early detection, and long-term management, underscoring a proactive stance in health management philosophy²²⁰. This approach aligns with the current trend in personalized medicine, which leverages

advanced technologies for tailored interventions²²¹. Nanotechnology introduces noninvasive diagnostic tools for cancer screening and diagnosis, such as imaging technologies and liquid biopsies²²². For example, Zhang et al.²²³ demonstrated that a graphene oxide–polydopamine coated exosome chip could effectively capture ovarian cancer exosomes from plasma samples, providing a high-sensitivity diagnostic method. These advancements enhance detection sensitivity and accuracy, leading to earlier cancer identification and improved treatment outcomes through timely intervention²²⁴. In terms of cancer survivorship and long-term management, the application of nanotechnology reduces treatment frequency, improves patient compliance, mitigates side effects, and improves overall quality of life²²⁵. The integration of nanotechnology into the prevention, early detection, and long-term management of cancer amplifies a proactive shift toward comprehensive health management philosophies and helps manage recurrence risks, tailor personalized rehabilitation plans, and optimize health management during post-treatment stages. As nanotechnology advances, further breakthroughs are anticipated in cancer prevention, diagnosis, and management, offering patients more effective, safe, and personalized treatment options²²⁶.

Early detection, critical for improving prognosis and survival rates, is being facilitated by breakthroughs in biomarker research and noninvasive diagnostic tools. For instance, the use of extracellular vesicles (EVs) for biomarker detection has shown promise in identifying disease-specific signatures in various cancers. Furthermore, the integration of nanotechnology and microfluidics into tools for EV isolation and analysis has significantly improved their sensitivity and specificity, making these tools more viable for clinical applications^{227–229}. As research progresses, these innovative approaches are expected to streamline cancer diagnostics and therapeutics, ultimately contributing to a more proactive and effective health management strategy^{227,230,231}.

6.5. Future directions and research gaps: Emerging NP technologies and novel therapeutic targets

Despite advancements in theragnostic NP technologies, several research gaps persist. A key challenge is the limited clinical translation of optical imaging modalities like fluorescence and bioluminescence, which struggle with poor tissue penetration and signal interference, confining their use to superficial or small animal models. Future research should aim to enhance imaging depth and resolution, potentially through hybrid modalities that integrate optical techniques with MRI or CT for improved anatomical localization and sensitivity²³². While theragnostic NPs have effectively delivered chemotherapeutic agents and siRNAs, the co-delivery of multifunctional agents remains complex and requires further design optimization to balance diagnostic and therapeutic doses. A promising direction is the development of activable NPs that respond to tumor-specific stimuli, such as pH changes or enzyme activity, enabling selective release of therapeutic agents and reducing off-target effects²³³.

Current research primarily emphasizes traditional metal-based NPs and PNPs, leaving a gap in exploring newer 2D nanomaterials like graphene and transition metal dichalcogenides. Despite their high surface area, tunable electronic properties, and potential for dual imaging and therapeutic functions, these materials remain underexplored in theragnostic applications. They could provide superior drug loading, controlled release, and enhanced photothermal

and photodynamic effects compared to conventional NPs²²⁹. However, further research is needed to validate their biocompatibility, physiological stability, and targeted clinical delivery capabilities.

Another significant gap is the precise targeting of the TME. While most NPs focus on directly targeting cancer cells, the TME—including stromal and immune cells, ECM, and signaling molecules—critically influences tumor progression and therapy resistance. Targeting elements like TAMs and cancer-associated fibroblasts (CAFs) are underexplored. For instance, NPs designed to deplete or reprogram TAMs from a pro-tumoral to an anti-tumoral phenotype could enhance treatment efficacy. Additionally, targeting the ECM may improve drug penetration and distribution within solid tumors, addressing a major challenge in nanomedicine²³³.

Future research should focus on hybrid NP systems that integrate organic and inorganic materials to combine their strengths. For example, combining liposomal systems with metallic cores like gold or iron oxide can enhance drug delivery, imaging contrast, and therapeutic efficacy while ensuring biocompatibility. These hybrid systems could respond to multiple stimuli such as pH, redox conditions, and enzymatic activity, allowing precise control over drug release in the TME²³⁴. Additionally, developing smart NPs that self-report their location, drug release status, or therapeutic efficacy through real-time imaging could revolutionize personalized treatment protocols. Another promising avenue is targeting novel therapeutic pathways like cancer metabolism and hypoxia. NPs that deliver metabolic inhibitors directly to cancer cells could disrupt vital energy production pathways, while hypoxia-targeting NPs activated in low-oxygen environments could enhance treatment selectivity and efficacy, minimizing damage to healthy tissues²³⁵.

Advancements in AI and machine learning present new opportunities for NP research. AI can design and optimize NP formulations by predicting how variations in size, shape, and surface modifications affect their behavior in biological systems. Machine learning models can also tailor therapies to individual patient profiles, optimizing NP design for specific cancer subtypes or resistance mechanisms²³⁶. Furthermore, AI-driven data analysis can enhance imaging interpretation, enabling accurate treatment efficacy assessments and real-time therapeutic adjustments.

The emergence of CRISPR/Cas9 technology offers a novel therapeutic target for NPs, enabling precise gene editing within tumors. NPs can be engineered to deliver CRISPR components directly to cancer cells, allowing targeted genetic modifications that disrupt oncogenes or restore tumor suppressor functions²³⁷. This approach marks a significant advancement over traditional gene therapy methods, paving the way for highly specific and personalized cancer treatments²³⁸. Additionally, NP-mediated immunotherapy, such as targeted delivery of immune modulators or checkpoint inhibitors to tumors, could enhance anti-tumor immune responses while minimizing systemic side effects. NPs that modulate the immune microenvironment to boost T-cell activation or reduce immune suppression represent a promising adjunct to existing cancer immunotherapies^{233,239}.

Finally, enhancing real-time monitoring capabilities through advanced optical techniques like Förster resonance energy transfer (FRET) and intravital microscopy could provide deeper insights into drug release kinetics and cellular interactions, leading to more personalized treatment regimens. Addressing these gaps could improve the efficacy and safety of NP-based therapies and highlight the need for interdisciplinary research to overcome current limitations in theragnostic nanomedicine²³³.

7. Concluding remarks

In recent years, cancer nanomedicine has made remarkable strides in transitioning from the lab to the clinic, particularly in drug delivery, targeted therapy, and early disease diagnosis. These advancements demonstrate the profound impact of nanotechnology on enhancing treatment efficacy, reducing toxic side effects, and enabling earlier detection of cancers—pivotal for improving patient outcomes. With customizable size, surface properties, and the ability to carry therapeutic agents, NPs offer unparalleled opportunities for precision medicine by selectively targeting tumors while sparing healthy cells²⁴⁰. Nanomedicines are reshaping cancer treatment, expanding therapy options, and improving outcomes by increasing therapeutic success rates and minimizing adverse effects, driving more efficient and targeted healthcare interventions²⁴¹.

Despite significant progress, several challenges still hinder the widespread clinical use of cancer nanomedicines. Scaling up NP production while maintaining consistency in size, surface properties, and drug loading is crucial for therapeutic safety and efficacy. Additionally, thorough preclinical and clinical evaluations are needed to assess long-term safety, including biodistribution, potential immunogenicity, and clearance. Integrating nanomedicines with conventional treatments like chemotherapy, RT, and immunotherapy also requires a deep understanding of the TME to design precise, combinatory nanotherapeutic strategies that can overcome current treatment limitations, such as drug resistance and tumor heterogeneity²⁴².

Interdisciplinary collaboration is essential for overcoming these challenges and advancing the clinical translation of cancer nanomedicines. A concerted effort from fields such as material science, oncology, pharmacology, and bioengineering is necessary to foster innovation and facilitate the transfer of novel technologies into clinical practice²⁴³. Regulatory frameworks must evolve alongside technological advancements to ensure the safe and effective use of nanomedicines. This includes creating comprehensive guidelines that address the unique properties of NPs, such as their interactions with biological systems and behavior in various physiological environments. Streamlining the regulatory approval process while maintaining rigorous safety standards will be key to accelerating nanomedicine adoption in cancer care²⁴⁴.

In conclusion, cancer nanomedicines have transformative potential to improve treatment outcomes. By prioritizing interdisciplinary research, regulatory innovation, and public awareness, nanomedicines can fulfill their promise, leading to more effective, personalized, and safer therapies. With nanotechnology at the forefront, the future of cancer treatment is set for significant advancements, offering better survival rates and enhanced quality of life for patients globally.

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Conflicts of interest

The authors declare no conflicts of interest.

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