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REVIEW

# Combating cancer immunotherapy resistance: a nano-medicine perspective

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**List of Abbreviations:** AKT, Protein kinase B; APCs, Antigen-presenting cells; CAFs, Cancer-associated fibroblasts; CAR, Chimeric antigen receptor; CAR-T, Chimeric antigen receptor T-cell therapy; cGAS, Cyclic GMP-AMP synthase; CRT, Calreticulin; CSF-1, Colony-stimulating factor-1; CSF-1R, Colony-stimulating factor-1 receptor; CTL, Cytotoxic T lymphocyte; CTLA-4, Cytotoxic T-lymphocyte-associated antigen 4; CXCL, Chemokine ligand; DC, Dendritic cell; DOX, Doxorubicin; ECM, Extracellular matrix; FDA, Food and Drug Administration; F-PLP, Folate personalized liposome; GPX4, Glutathione peroxidase 4; Hb, Hemoglobin; HIF-1, Hypoxia-inducible factor-1; HIF-1$\alpha$, Hypoxia-inducible factor-1$\alpha$; HLA, Human leukocyte antigen; IBR, Ibrutinib; ICB, Immune checkpoint blockade; ICI, Immune checkpoint inhibitors; IDO1, Indoleamine 2,3-dioxygenase 1; IFN, Interferon; IFN-$\gamma$, Interferon-gamma; IL, Interleukin; LNPs, Lipid nanoparticles; MHC, Major histocompatibility complex; MSR, Mesoporous silica microrods; mTOR, mammalian target of rapamycin; NIR, Near infrared; NK, Natural killer; NPs, Nanoparticles; NSCLC, Non-small cell lung cancer; PD-1, Programmed death 1; PD-L1, Programmed death ligand 1; PDT, Photo dynamic therapy; PDX, Patient-derived xenograft; PEI, Polyethyleneimine; PI3K, Phosphatidylinositol 3-kinase; PLGA, Poly lactic-co-glycolic acid; PTT, Photothermal therapy; pBIM, BIM-S plasmid; ROS, Reactive oxygen species; siRNA, small interfering RNA; STING, Stimulator of interferon genes; STING-LNPs, STING agonist loaded lipid nanoparticles; TAM, Tumor-associated macrophage; TCR, T cell receptor; TDE, Tumor-derived exosome; TIME, Tumor immunosuppressive microenvironment; TME, Tumor microenvironment; TNBC, Triple-negative breast cancer; TNF, Tumor necrosis factor; TLR, Toll-like receptor; Treg, Regulatory T cell; VEGF, Vascular endothelial growth factor.

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**Abstract**

Cancer immunotherapy offers renewed hope for treating this disease. However, cancer cells possess inherent mechanisms that enable them to circumvent each stage of the immune cycle, thereby evading anti-cancer immunity and leading to resistance. Various functionalized nanoparticles (NPs), modified with cationic lipids, pH-sensitive compounds, or photosensitizers, exhibit unique physicochemical properties that facilitate the targeted delivery of therapeutic agents to cancer cells or the tumor microenvironment (TME). These NPs are engineered to modify immune activity. The crucial signal transduction pathways and mechanisms by which functionalized NPs counteract immunotherapy resistance are outlined, including enhancing antigen presentation, boosting the activation and infiltration of tumor-specific immune cells, inducing immunogenic cell death, and counteracting immunosuppressive conditions in the TME. Additionally, this review summarizes current clinical trials involving NP-based immunotherapy. Ultimately, it highlights the potential of nanotechnology to advance cancer immunotherapy.

**KEYWORDS**
Cancer immunotherapy, drug delivery system, drug resistance, nanomedicine

## 1 | INTRODUCTION

Cancer immunotherapy offers new hope for treating cancer by leveraging the patient's immune system to target tumor cells. However, possess inherent mechanisms that enable them to evade each stage of the immune cycle, leading to resistance [1]. Despite significant advances, developing resistance to these therapies remains a major challenge [1, 2].

The integration of nanotechnology into cancer treatment has opened new avenues to combat cancer resistance. Nanoparticles (NP), ranging from 1 to 100 nanometers in size, exhibit unique physicochemical properties that enable the targeted delivery of therapeutic agents directly to cancer cells and allow for the modulation of immune activity. In cancer immunotherapy, NP-based nanomedicine is designed to reach target sites, facilitate biomolecule interactions, promote cell-specific internalization, deliver cargo to targeted subcellular compartments, and enhance immune responses [3]. NPs can deliver tumor-associated antigens and adjuvants to antigen-presenting cells (APCs), such as dendritic cells (DCs) [4]. Tumor-targeted nanomedicines can create a subset of tumor-specific immune cells by delivering immunomodulatory cytokines, inducing immunogenic damage to cancer cells, promoting the infiltration of antitumor immune cells, and enhancing interactions with cancer cells [5]. Additionally, the tumor microenvironment (TME) can adversely affect the infiltrating immune cells, and NPs can modulate TME to reverse immunotherapy resistance [6].

In this review, we discuss recent findings in addressing immunotherapy resistance using various functionalized NPs modified with cationic lipids, pH-sensitive compounds, or photosensitizers. The key signal transduction pathways and mechanisms by which functionalized NPs reverse immunotherapy resistance are outlined. Current clinical trials involving NP-based immunotherapy are summarized. Ultimately, this review aims to provide insights into the potential of nanotechnology in enhancing cancer immunotherapy and to inspire further research in this promising field.

## 2 | MECHANISMS OF CANCER IMMUNOTHERAPY RESISTANCE ALONG THE IMMUNITY CYCLE AND POTENTIAL SOLUTIONS

Cancer immunotherapy is a transformative approach in oncology, aimed at restoring and manipulating the immune system to combat cancer. This therapy encompasses various modalities such as non-specific immunotherapies, immune checkpoint inhibitors (ICIs), cellular therapies, and cancer treatment vaccines, each utilizing different mechanisms to induce antitumor activity

[7, 8]. The immune system eliminates tumor cells through a process known as the "tumor immune cycle [9]." This cycle involves the production and release of tumor-associated antigens (TAAs), the capture and processing of neoantigens by APCs, the activation of effector T cells, the infiltration of activated tumor-specific T cells through the TME, and the engagement of T cell receptors (TCR) with MHC complexes presenting the antigen, leading to the recognition and destruction of target cancer cells and initiating a new cycle of immune response [9]. However, any stage of this cycle may be disrupted, contributing to the development of an immunosuppressive TME, tumor immune escape, and ultimately immunotherapy resistance [10]. The immune system and the TME are intricately complex, with various mechanisms interacting to establish a dynamic immunosuppressive state that fosters tumor immunotherapy resistance.

In some cancers, particularly those with a low tumor-mutation burden or low immune-cell infiltration, an adequate immune response may not be triggered initially. This can hinder the maturation of key APCs, such as DCs, leading to an impaired immune response. Research has demonstrated that cancer vaccines can induce APC maturation and T cell activation [11]. Additionally, certain cytokines, including Interferon-$\alpha$, granulocyte-macrophage colony-stimulating factor (GM-CSF), Toll-like receptor (TLR) agonists, and stimulators of interferon genes (STING) agonists, are known to enhance the maturation of DCs and activate antigen-specific T cells [12].

After immune cell priming and activation, any defect affecting immune cell trafficking, migration, and infiltration into the TME can undermine anticancer immunity. Cytokines within the TME influence the migration and recruitment of immune cells to the tumor site. Certain cytokines, such as chemokine ligand (CXCL) 10 and IFN-$\gamma$, initiate chemotactic functions that attract cytotoxic T cells [13]. Delivering cytokines that promote T cell infiltration and blocking immunosuppressive cytokines may reverse immunotherapy resistance.

Cancer cells that evade immune recognition can proliferate as resistant variants. Tumors may modify the expression of immune checkpoint proteins, facilitating immune escape. The inhibition of immune checkpoints, such as programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), Lymphocyte activation gene-3 (LAG-3), and T cell immunoglobulin and mucin domain-containing protein-3 (TIM-3), is a standard approach in immunotherapy [14], given their role in promoting T cell non-responsiveness and immune tolerance [15]. Currently, Food and Drug Administration (FDA)-approved immune checkpoint blockades (ICB) include anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA4), anti-PD-1, and anti-PD-L1 antibodies. Reducing or blocking the expression of these proteins and their pathways can diminish tumor immune escape and potentially reverse immunotherapy resistance.

Immunogenic cell death (ICD) activates the host's adaptive immune response through antigens from dead cells. Essential for inducing ICD are damage-associated molecular patterns (DAMPs) such as calreticulin (CRT) exposure, ATP, type I interferon (IFNs) expression, and the release of the non-histone nuclear protein high mobility group box 1 (HMGB1) [16].

The intricate dynamics of tumor immunity underscore the pivotal role of the TME in the efficacy of cancer immunotherapy [17]. Within the TME, stromal and tumor cells can obstruct immune recognition and surveillance, alter cellular metabolism, and impact angiogenesis, thereby impeding immune cell circulation and contributing to resistance [17]. Thus, a thorough study of these cells is essential to enhance targeting of the TME and counteract immunotherapy resistance.

## 3 | STRATEGIES OF DIFFERENT NPS IN COUNTERACTING IMMUNOTHERAPY RESISTANCE

NPs have become a powerful tool in cancer immunotherapy due to their versatile structure, composition, and functionalization. These properties enable NPs to effectively manipulate and deliver immunological components to specific target locations [3, 4]. Nanomedicine enhances the targeting of immune cells and the release of drugs, adjuvants, and cytokines. It also improves the release and presentation of tumor antigens, thereby augmenting the treatment of cancers with low immunogenicity. The binding of NPs to DCs and the subsequent release of their cargo facilitate the presentation of tumor antigens to T cells, leading to T-cell activation [18, 19]. This process enhances the immune response mediated by cytotoxic T lymphocytes (CTLs), and modifies the immunosuppressive TME. Additionally, due to its increased permeability and retention in target cells, this approach holds significant therapeutic potential [20]. Customized polymeric nanocarriers (such as nanospheres, micelles, and dendrimers), inorganic NPs (including gold NPs and mesoporous silica NPs), and lipid-based NPs (like liposomes and lipid NPs) are extensively used in cancer immunotherapy [20, 21]. Each type of NP presents unique advantages and limitations, influencing the efficacy of immunotherapy differently. A detailed comparison of these NP types is presented in Table 1.

Tumor development is accompanied by various protein mutations affecting immune activity. Overcoming

**TABLE 1** Comprehensive overview of bioactive nanoparticle types for cancer immunotherapy.

| Entry | Nanoparticle type | Material | Description | Advantages | Drawbacks | Applications | Related studies | Current research focus |
|---|---|---|---|---|---|---|---|---|
| 1 | Metallic NPs | Gold | NPs that exhibit low cytotoxicity and are easily functionalized for tumor targeting. | Biocompatibility; precise drug release control; photothermal properties | Potential toxicity issues; challenges in large-scale production | Tumor immunotherapy; photothermal therapy | Polyaniline-based glyco-condensation on Au NPs enhancing M1 polarization [22] | Exploring combination therapies with immune checkpoint inhibitors. |
| 2 | Metallic NPs | Iron oxide | NPs used for both imaging and as therapeutic agents in cancer treatment. | Superparamagnetic properties; dual functionality | Concerns about long-term toxicity; possible accumulation in organs | MRI imaging; targeted therapy | Zanganeh *et al.* demonstrating ferumoxytol's effects in breast cancer [23] | Investigating applications in targeted drug delivery. |
| 3 | Metallic NPs | Manganese | Enhances immune activation via innate immune pathways. | Promotes type I IFN production; responsive to TME | Potential for toxicity with prolonged exposure | Immune activation; enhancing cytotoxic responses | Studies on manganese-based NPs enhancing immunotherapy [24] | Research on improving TME modulation techniques. |
| 4 | Non-metallic NPs | Silica | Porous structure allows for drug loading and sustained release. | Excellent biocompatibility; customizable surface | Low solubility in vivo; production challenges | Cancer vaccines; photoimmunother-apy | Yang *et al.* using mesoporous silica for combined therapies [25] | Development of personalized cancer vaccines using silica NPs. |
| 5 | Non-metallic NPs | Carbon nanotubes | High surface area can stimulate immune response and enhance drug delivery. | Feasible surface modifications; rapid cellular uptake | Biocompatibility concerns; potential toxicity | Drug delivery; cancer immunotherapy | Zhou *et al.* developing GO nanosystems for immune modulation [26] | Investigating their role in targeted therapy approaches. |
| 6 | Non-metallic NPs | Quantum dots | NPs with unique optical properties, useful in bioimaging and targeted therapy. | High stability; tunable properties | Limited applications in immunotherapy | Bioimaging; potential use in immunotherapy | BPQDs as immune-photothermal therapy agents [27] | Focusing on their applications in imaging-guided therapy. |

(Continues)

**TABLE 1** (Continued)

| Entry | Nanoparticle type | Material | Description | Advantages | Drawbacks | Applications | Related studies | Current research focus |
|---|---|---|---|---|---|---|---|---|
| 7 | Organic NPs | Polymer-based NPs | Biodegradable polymer widely used for drug delivery and vaccine formulations. | High encapsulation efficiency; FDA-approved | Stability and drug loading limitations | DNA vaccines; targeted therapies | Various clinical trials utilizing PLGA for DNA delivery [28–30] | Enhancing stability and bioavailability of mRNA vaccines. |
| 8 | Organic NPs | Liposomes | Versatile carriers for hydrophobic drugs; excellent biocompatibility. | Non-immunogenic; improves drug stability | Rapid clearance from the bloodstream | Chemotherapy delivery; adjuvant for immunotherapy | Clinical studies on liposomal delivery of immunotherapies [31, 32] | Investigating lipid formulations for mRNA delivery. |
| 9 | Organic NPs | Amphiphilic copolymer-based NPs | Amphiphilic copolymers that improve the solubility of poorly soluble drugs. | High drug-loading capacity; ease of cellular uptake | Toxicity concerns with poorly designed formulations | Targeted delivery; combination therapies | Research on polymeric micelles for enhanced drug delivery [33] | Development of multifunctional micelles for combined therapies. |
| 10 | Biomimetic NPs | Cell membrane-coated NPs | NPs designed to mimic immune cell functions for better targeting. | Improves delivery efficiency; lowers immune evasion | Challenges in large-scale production | Targeted cancer therapy | NExT platform using T-cell coatings for drug delivery [34] | Focus on personalized medicine approaches. |
| 11 | Hybrid NPs | PEGylated reduced GO | Combines lipid and polymer properties for improved drug delivery. | Enhanced stability; multi-functionality | Safety complexities due to combined materials | Cancer vaccination | RGO-PEG for neoantigen delivery and T cell activation [35] | Developing safer formulations for clinical applications. |
| 12 | Nanorobots | Functionalized nanorobots | Devices that navigate the body to deliver drugs and modulate the TME. | Targeted delivery; adaptability to environmental cues | Technical challenges in design and function | Immunotherapy delivery | Ongoing clinical trials on nanorobots [36, 37] | Exploring novel delivery mechanisms to overcome drug resistance. |

Abbreviations: AuNPs, Gold nanoparticles with glyco-condensatio; BPQD, Black phosphorus quantum dots; GO, Graphene oxide; IFN, Interferon; MRI, Magnetic resonance imaging; NPs, Nanoparticle; PEG, Polyethylene glycol; PLGA, Poly lactic-co-glycolic acid; RGO, Reduced graphene oxide; TME, Tumor microenvironment.

immunotherapy resistance with a single functional nanoagent proves challenging due to the immunosuppressive nature of cancer cells. Significant efforts are necessary to induce a robust T cell immune response. Multiantigen delivery targets multiple mutant proteins, promotes antigen endosomal escape, enhances cellular uptake, and stimulates cell-mediated immune responses [19, 38]. Furthermore, incorporating adjuvants and other antigens into the NP delivery system improves immunotherapy outcomes through various mechanisms [39–42]. This research provides valuable insights into the innovative and effective multifunctional nano-platform for addressing key mechanisms of immune drug resistance.

## 4 | NP-BASED DRUG DELIVERY SYSTEMS ENHANCE THE TUMOR IMMUNE CYCLE TO OVERCOME RESISTANCE TO IMMUNOTHERAPY

### 4.1 | Targeted delivery of NPs to promote APC maturation and T cell activation

DC maturation is essential for initiating immunity. In light of this, researchers have focused on antigen-loaded NPs, which can be conjugated with targeted ligands to improve biocompatibility and responsiveness to acidic environments. Targeted NP delivery to DCs enhances mRNA translation efficiency and stimulates signaling pathways that promote DC maturation [3, 38, 43]. Additionally, NPs target critical sites within the immune cycle, such as reducing inhibitory checkpoints on T cells and enhancing T cell activation [44].

Nanoparticulate RNA vaccines precisely target DCs, increasing RNA uptake and inducing a potent type-I-IFN-driven immune response to combat immunotherapy resistance [45]. An mRNA-based cancer vaccine integrates antigen-coded mRNA, CpG oligodeoxynucleotides, an acidic-responsive DNA sequence, and a DC-targeting aptamer. This vaccine forms aggregates in the acidic environment of lysosomes, escaping into the cytoplasm to increase mRNA translation efficiency significantly. Activation of the TLR9 signaling pathway considerably enhances DC maturation and pro-inflammatory cytokine secretion [3] (Figure 1A). $Mn_3O_4$ NPs, combined with lipid NPs (LNPs), form a hybrid delivery vehicle (MnLNPs) for mRNA vaccine fabrication. MnLNPs reduce reactive oxygen species (ROS) production, increase intracellular ATP levels through oxygen release, and enhance mRNA translation efficiency. $Mn^{2+}$ from MnLNPs activates the STING signaling pathway, promoting DC maturation and antigen presentation ability [4] (Figure 1B). A dual-STING-activating micelle system releases small-molecule agonists to rapidly activate STING following endocytosis. Concurrently, a pH-sensitive polymeric agonist from the polymer carrier buffers lysosomal protons, preventing STING protein degradation and continuously providing STING activation signals to enhance DC maturation and tumor antigen presentation [43].

NPs effectively manipulate or deliver immunological components to optimal target sites. Researchers isolated autophagosomes from the pleural and ascitic fluid of cancer patients, integrating autophagosome-derived antigens and two adjuvants (TLR-9 and STING agonists) to form nanovaccines. These nanovaccines significantly enhance APC maturation through effective antigen and adjuvant delivery to lymph nodes [38]. A novel nanomodulator specifically targets DCs in tumor-draining lymph nodes, promotes the maturation of DCs through synergistic activation of TLR4 and TLR7/8 pathways, and prevents T cell exhaustion by reducing the expression of inhibitory immune checkpoints (such as PD-1 and TIM-3) on the surface of T cells by targeting siRNA [44] (Figure 1C).

NPs not only deliver immunological components to DCs more effectively but also enhance $CD8^+$ T cell activation following antigen presentation. An NP co-loaded with tumor antigen and a STING agonist (cdGMP) was integrated into the cavity of OVA epitope self-presenting dendrosomes (ODs) to construct the dendrosome ODs/NP (cG, OVA) nanovaccines. DCs immunized with ODs/NP (cG, OVA) displayed more epitopes and promoted antigen presentation to T cells, inducing heightened levels of antigen-specific T cells. Additionally, cytoplasmic cdGMP interacts with STING on the DC endoplasmic reticulum membrane, stimulating downstream signaling pathways to enhance DC maturation [19] (Figure 1D). Another nanostructure significantly activates the NF-$\kappa$B signaling pathway in DCs through $K^+$ efflux and $Ca^+$ influx, thereby improving DC function. It also significantly reduced the invasion of TAMs, MDSCs and Tregs in the tumor, and increased the number of $CD8^+$ T cells infiltrated by the tumor [18] (Figure 1E).

### 4.2 | NP-enhanced T cell infiltration

NPs counteract immunotherapy resistance by increasing mRNA translation efficiency and promoting T cell infiltration into tumor sites. This is achieved by delivering cytokines favorable for T cell infiltration and by blocking immunosuppressive cytokines [46, 47]. A lipid NP vector system delivers mRNA encoding Interleukin (IL)-2 and IL-7, whose synergistic effects significantly enhance $CD8^+$ T cell infiltration and increase IFN-$\gamma$ and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) secretion. By boosting the

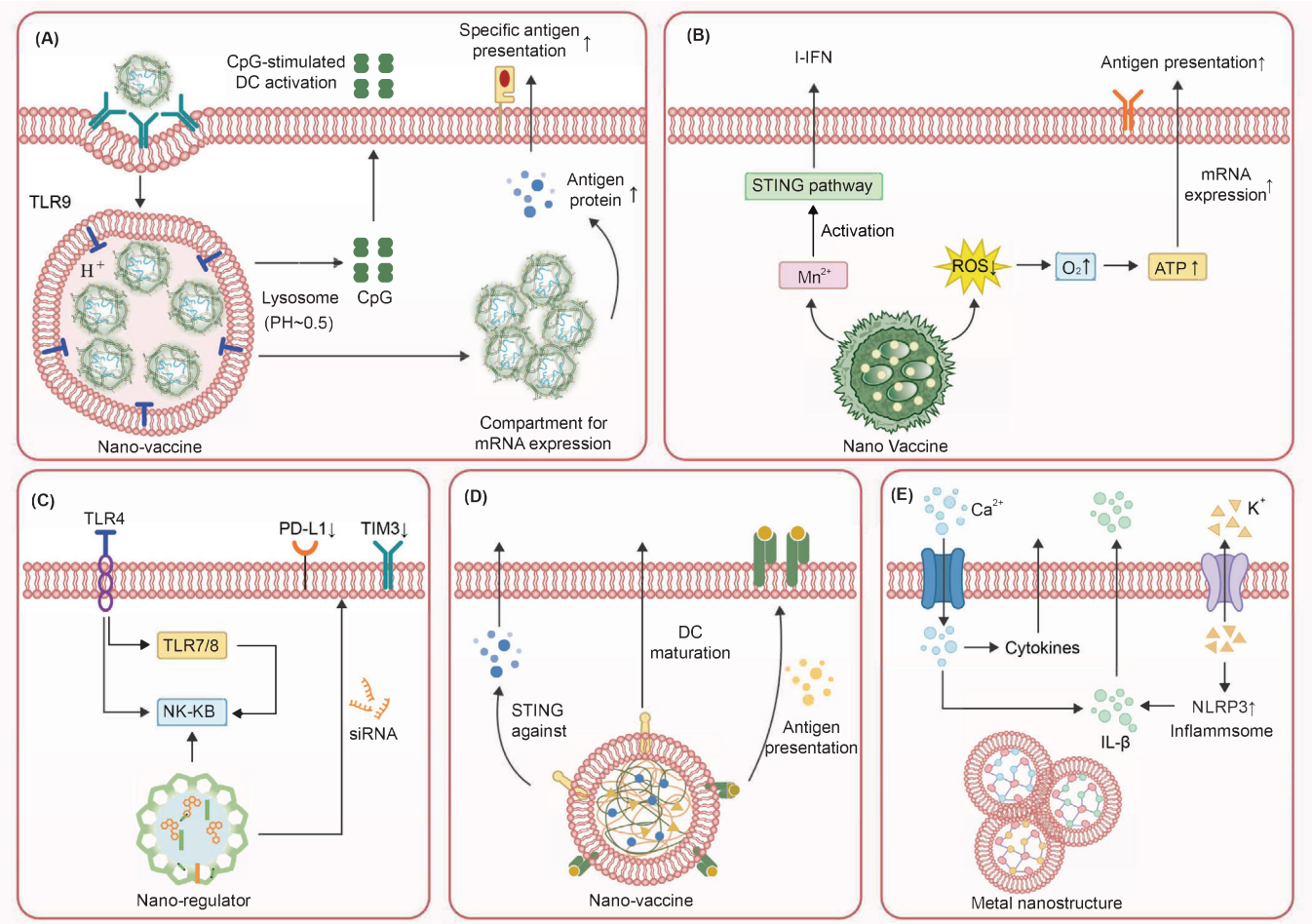


**FIGURE 1** Targeted delivery of NPs to promote DC maturation and T cell activation. (A) A nano-vaccine formed aggregates in the acidic environment of lysosomes to increase mRNA translation and enhance DC maturation. (B) A nano-vaccine (MnLNP) reduced ROS production, increased intracellular ATP levels through oxygen release, and enhanced mRNA translation efficiency. $Mn^{2+}$ from MnLNPs activated the STING signaling pathway and promoted DC maturation. (C) A novel nano-regulator specifically targeting DCs promoted the maturation of DCs through synergistic activation of TLR4 and TLR7/8 pathways, and prevented T cell exhaustion by reducing the expression of inhibitory immune checkpoints (such as PD-1 and TIM-3) on the surface of T cells by targeting siRNA. (D) A nano-vaccine was co-loaded with tumor antigen and a STING agonist. DCs immunized with it displayed more epitopes, promoting antigen presentation to T cells. Additionally, activation of STING pathways enhanced DC maturation. (E) A nanostructure significantly activated IL-$\beta$ secretion in DCs through $K^+$ efflux and $Ca^+$ influx, thereby improving DC maturation. Abbreviations: ATP, Adenosine triphosphate; DC, Dendritic cell; I-IFN, I-Interferon; IL-$\beta$, Interleukin-$\beta$; MnLNP, $Mn_3O_4$ nanoparticle combined with lipid nanoparticle; NPs, Nanoparticles; PD-1, Programmed death 1; ROS, Reactive oxygen species; STING, Stimulator of interferon genes; TIM-3, T cell immunoglobulin domain and mucin domain-3; TLR4, Toll-like receptor 4; TLR7/8, Toll-like receptor 7/8.

activity and function of tumor-infiltrating $CD8^+$ T cells, robust anti-tumor immune responses are induced locally [46]. A calcium carbonate NP, stabilized and modified with anti-PD-1 antibody and 12-myristate 13-acetate, targets delivery and drug synergy. PD-1-mediated endocytosis enters CTLs, significantly raising intracellular calcium levels, activating the NF-$\kappa$B signaling pathway, and inducing T cells to express CD69 and secrete key cytokines like IFN-$\gamma$ and TNF-$\alpha$, thereby enhancing CTL's tumor infiltration and killing capabilities [48]. A low-intensity focused ultrasound-guided immunotherapy strategy, termed "open source and slow down," enhances $CD8^+$ T cell infiltration and activity through sequential delivery of CXCL10, IL-2, and anti-PD-L1, achieving a 3.39-fold increase in $CD8^+$ T cell numbers compared to traditional treatments [49]. Another team mitigated the immunosuppressive microenvironment and boosted $CD8^+$ T cell infiltration by applying a self-assembling peptide that forms hydrogels on tumor cell surfaces, inhibiting exosome dissemination [47]. This nanosystem carries enzymes that relieve tumor hypoxia; the expression in exosomes significantly regulates, particularly in T cell signaling processes, enhancing $CD8^+$ T cell infiltration and ameliorating the immunosuppressive microenvironment [47].

### 4.3 | Reversal of Tumor Immune Escape by NPs

A broad array of nanomedicine-mediated strategies has been employed to counter tumor immune escape. Effective approaches such as the photothermal therapy (PTT) [42, 50] and the photodynamic therapy (PDT) [51] are extensively utilized. Additionally, functional NPs are more effectively conjugated with targeted ligands by co-assembling with biological components like cell membranes [40], bacteriophages [52], and bacteria [41, 42] to enhance biocompatibility. Recent advancements in various functionalized NPs for reversing tumor immunotherapy resistance are explored herein.

Researchers encoded anti-PD-L1 and anti-CD9 nanoantibodies into *E. coli* and encapsulated the photosensitizer within a metal-organic framework. Near-infrared (NIR) light irradiation controlled the release at the tumor site, targeting tumor-derived exosomes (TDE). This significantly reduced TDE uptake in normal cells, promoted TDE clearance by macrophages, decreased immune escape, and enhanced T cell infiltration at tumor sites [50]. Using CRISPR-Cas9 and a photosensitizer as the core nanoplatform, CRISPR-Cas9 substantially reduced PD-L1 expression (inhibition rate of 83.4%) and NIR laser irradiation generated ROS, enhancing T cell activity and impeding tumor immune escape. Potent induction of tumor cell death markedly increased CD8+ T cell infiltration [51].

Functional NPs can be assembled with biological components to more precisely conjugate with targeted ligands and block immune checkpoint receptors or diminish immune checkpoint expression. A tumor-targeting filamentous phage precisely blocks the PD-1/PD-L1 pathway, activating an immune response against tumors. This phage effectively targets tumors in a mouse melanoma model, enhances $CD8^+$ T cell immune infiltration, and significantly curtails tumor growth [52] (Figure 2A). Researchers developed PD-1 transfected macrophage membrane NPs (PMMNPs) by extracting the cell membrane from PD-1 transfected macrophages and co-assembling it with lipids. These NPs boost macrophage phagocytosis and T cell cytotoxic activity by targeting and binding to CD47 and PD-L1 on cancer cell surfaces, thereby obstructing PD-L1 and CD47. The anti-tumor efficacy of this system was validated in vivo in a mouse model [40] (Figure 2B). A thermosensitive engineered bacterium (15&15R@VNP), combined with MWA, locally induces the expression of the IL-15 and IL-15R$\alpha$ complex within the TME, enhancing the anti-tumor immune response. The bacteria were further optimized to co-express IL-15&IL-15R$\alpha$ and soluble PD-1 (sPD-1) for synergistic anti-tumor effects through checkpoint blockade and T-cell reactivation [41] (Figure 2C). Another system combines photothermal NPs and genetically engineered bacteria that attach to the bacterial surface via pH-responsive Schiff base bonds. When accumulated at the tumor site, the NPs detach from the bacteria, enter tumor cells, facilitate gene transfection, induce apoptosis in tumor cells, and reduce PD-L1 expression, thereby alleviating the immunosuppressive TME. NIR-II light illumination further enhances systemic immune responses and promotes sustained IL-2 expression, ultimately significantly boosting anti-tumor effects [42] (Figure 2D).

Beyond PD-1/PD-L1, emerging functionalized NPs also target additional pathways to reverse immune escape strategies. Researchers utilized iron oxide hydroxide (FeOOH) nanocomposites to mask the surface of tumor-derived exosomes, blocking immune escape signals such as CD47. The masked exosomes (mTEVs) are more effectively engulfed by DCs and macrophages both in vitro and in vivo, proving that nanomasking effectively counteracts the suppressive effects of immune escape signals such as CD47 [53]. Researchers have devised a therapeutic platform comprising modified gold nanocups (Au nanocups) and anti-CD24 antibodies. This platform enhances tumor targeting through surface modification with fucoidan and precisely controls drug release via photothermal effects. Blocking CD24 effectively eliminates the CD24-Siglec-10 signaling pathway, enhancing macrophage recognition and phagocytosis of tumor cells to inhibit CD24-mediated tumor immune escape [54].

### 4.4 | NPs-mediated targeted delivery to induce ICD

Increasing evidence supports that NP-mediated drug delivery induces ICD in cancer immunotherapy by enhancing drug accumulation in tumors and improving the targeting of tumor delivery, thus increasing the efficiency of ICD inducers [55, 56]. The effectiveness of ICD, induced by drug-loaded liposomes, is well-established. Innovative functional NPs enhance ICD by optimizing tumor targeting, increasing ROS accumulation, and triggering copper death, among other mechanisms [57–60]. Nanoplatforms integrated with photothermal therapy (PTT) and photodynamic therapy specifically target tumors in acidic environments, achieving efficient accumulation at tumor sites [55, 56]. Functional NPs alter the redox balance of tumor cells by releasing nitric oxide (NO), metal ions, activating enzymes, and catalysts, thus promoting ROS accumulation and boosting the ICD of tumor cells [58, 61–63]. Moreover, nanoplatforms induce ICD in tumor cells through copper death mechanisms and mitochondrial triggers [60, 64]. This section discusses recent studies on NPs used to transport and deliver ICD inducers to tumor cells,

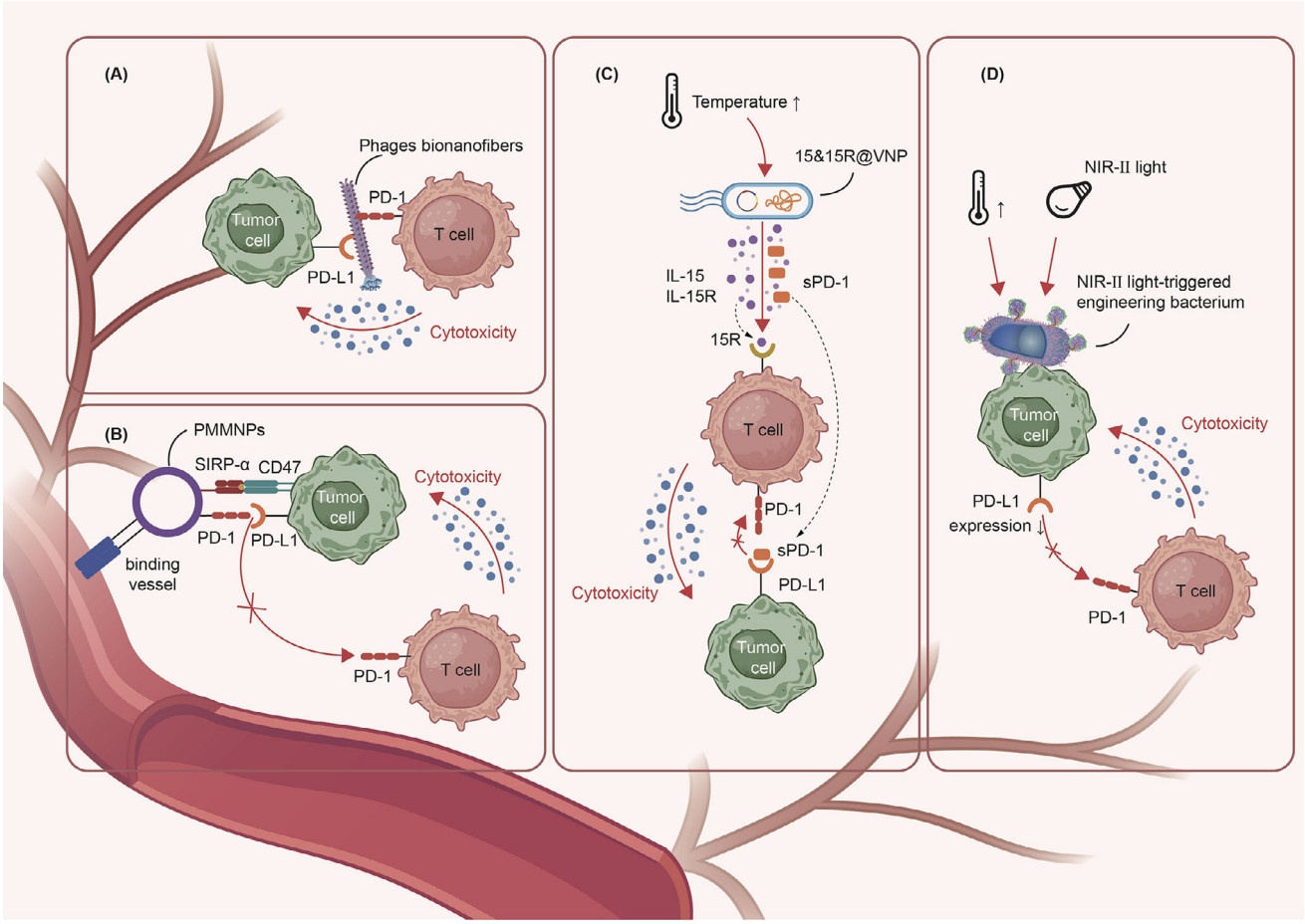


**FIGURE 2** Strategies of the reversal of tumor immune escape by NPs. (A) NPs block the PD-1/PD-L1 pathway. A tumor-targeting filamentous phage precisely blocks the PD-1/PD-L1 pathway, activating an immune response against tumors. PMMNPs boost macrophage phagocytosis and T cell cytotoxic activity by targeting and binding to CD47 and PD-L1 on cancer cell surfaces, thereby obstructing PD-L1 and CD47. (B) NPs express competitors to block immune checkpoints. An engineered bacterium (15&15R@VNP) expresses IL-15&IL-15Rα and sPD-1 for synergistic anti-tumor effects through checkpoint blockade and T-cell reactivation. (C) NPs downgrade PD-L1 expression. (D) NIR-II light-triggered engineered bacterium accumulate at the tumor site, and the NPs detach from the bacteria, enter tumor cells, facilitate gene transfection and reduce PD-L1 expression. Abbreviations: CD, Cluster of differentiation; IL-15, Interleukin-15; IL-15Rα, Interleukin-15α; NPs, Nanoparticles; PD-1, Programmed death 1; PD-L1, Programmed death ligand 1; PMMNPs, Programmed death 1 transfected macrophage membrane nanoparticles; SIRP-α, Signal regulatory protein α; sPD-1, soluble PD-1.

aimed at promoting immunostimulation and combating resistance in cancer immunotherapy.

The ability of chemotherapeutic drug-conjugated liposomes to trigger ICD makes them particularly attractive for immunotherapy applications. Upon drug delivery, these liposomes can induce cellular stress, provoke the release of danger signals, and activate the immune response, leading to enhanced tumor-specific immunity. This process not only enhances the therapeutic effect of the drugs but also helps reprogram the tumor microenvironment (TME) to be more responsive to subsequent immune attacks. Liposomal formulations such as Doxil® and Onivyde® are FDA-approved for treating specific cancers, such as breast cancer and pancreatic cancer. These formulations not only enhance drug accumulation in tumor tissues through the enhanced permeability and retention (EPR) effect but also induce ICD, promoting the recruitment of DCs and enhancing the activation of the immune system [65].

Through the synergistic effects of Fe3O4-mediated magnetic targeting and the cell membrane-bound functional proteins, PD-1 and Lymphocyte Function-associated Antigen 1, the biomimetic nanoplatform selectively accumulates at tumor sites. This platform concurrently administers photothermal therapy, induces calcium overload, obstructs immunosuppressive molecules, and promotes apoptosis via the cell membrane-associated apoptosis-related factor ligand, ultimately triggering ICD. This process releases TAAs, which catalyze the maturation of DCs, thereby suppressing primary tumor growth effectively [55]. Additionally, the PEG2000-SiNcTI-Ph/CpG-ZIF-8@CM

biomimetic nanoplatform, cloaked by CD47 protein on its surface, eludes macrophage phagocytosis, prolongs its circulatory half-life, and targets tumors efficiently via the PD-1 protein, enabling substantial tumor-specific accumulation. Under tumor-specific conditions and laser exposure, this platform activates PDT, causing apoptosis in CT26 tumor cells and fostering an anti-tumor immune response by enhancing DCs' uptake of CpG and blockade of PD-L1 [56]. Furthermore, the Tm@PDA-GA nano-regulator combines photothermal therapy (PTT) with vascular normalization strategies to bolster the infiltration of immune cells into tumors and amplify the immune response against tumors. This nano-regulator precisely delivers therapeutic agents within the TME, complementing PTT with anti-PD-L1 immunotherapy to mitigate tumor growth and metastasis in triple-negative breast cancer (TNBC) [39].

The acidic TME propels a nanomotor system, PCaP-motor, which demonstrates enhanced motility and drug release, significantly increasing drug accumulation and penetration within tumor cells. This system effectively impedes the CDK12 pathway and its downstream signaling, inducing DNA damage, apoptosis, and ICD in tumor cells. Additionally, it supports the maturation of DCs and infiltration of CTLs, thereby potentiating the efficacy of immune checkpoint inhibitor therapy [5]

A dual-ligand, bimetallic framework, Cu(PBA-NO), liberates NO under ultrasound stimulation, fostering ROS buildup by depleting intracellular glutathione. This disrupts the redox equilibrium in tumor cells, enhancing their ICD. The nanomedicine subsequently augments the body's immune defense against tumors by releasing TAAs, promoting DC maturation, and activating T cells [61]. Additionally, Zn-ZIF in the acidic tumor milieu and UCNP under 980 nm light transform NIR light into visible light, activating the VChR1 channel to increase $Zn^{2+}$ influx. The concomitant release of metal ions and ROS production markedly raises oxidative stress in tumor cells, promoting apoptosis, DC activation, enhanced $CD8^+$ T cell infiltration, and secretion of immune cytokines like TNF-$\alpha$ and IFN-$\gamma$ [58]. The Co-TB COF nanosystem, designed to generate substantial ROS through ultrasound activation, successfully induces Gasdermin D-mediated pyroptosis in tumor cells and enhances tumor immunogenicity. ROS release further activates STING agonists, enhancing the STING signaling pathway, improving tumor vasculature, and facilitating effector T cell infiltration, thereby augmenting the impact of the immunotherapy [59]. Additionally, a copper-based nano-inducer, produces extensive ROS in the TME through various enzymatic activities, initiating tumor cell disulfide apoptosis and pyroptosis and thus stimulating a robust immune response [62]. An electron-enriched platinum-based (Pt-based) reactive oxygen catalyst mimics the enzymatic properties to generate copious amounts of ROS. This ROS production triggers endoplasmic reticulum stress, inducing ICD and releasing DAMPs such as CRT and HMGB1, which further bolster DC maturation and antigen presentation, ultimately enhancing anti-PD-L1 immunotherapy [63]. A nanocovalent organic framework-based thermoelectric catalyst, under NIR laser activation, efficiently produces singlet oxygen ($^1O_2$) and superoxide anion ($\bullet O_2^-$), significantly boosting the ICD induction efficiency. This substantially increases the expression of ICD markers such as CRT and HMGB1, fostering DC maturation, elevating cytokine secretion such as IL-6, IL-12, and TNF-$\alpha$, and in murine tumor models, markedly inhibiting the growth of primary and distant tumors, thereby significantly enhancing the anti-tumor immune response [66].

(AuBiCu-PEG NPs) are employed to regulate the hypoxic TME and deliver $Cu^{2+}$, markedly enhancing the induction of ROS stress-induced tumor cell ferroptosis and cuproptosis while alleviating tumor hypoxia. This potentially boosts efficacy by promoting mitochondrial DNA damage. In vivo studies indicate that AuBiCu-PEG NPs enhance ICD, stimulating a strong anti-tumor immune response [57]. Under NIR-II light, Cu2-xS nanoagents heat rapidly, causing local high-temperature ablation in the tumor and inducing the copper death mechanism, which generates a significant amount of ROS and intensifies oxidative stress and cell death in tumor cells [60].Studies have demonstrated that the copper death triggered by Cu2-xS nanoagents not only causes direct tumor cell death but also induces ICD by releasing DAMPs such as ATP, CRT, and HMGB1, significantly enhancing the body's anti-tumor immune response. In mouse and rabbit breast cancer models, Cu2-xS nanoagents, combined with NIR-II phototherapy, not only effectively eliminate primary tumors but also inhibit tumor metastasis [60]. A drug-free small molecule nanoscale assembly platform effectively triggers mitochondrial dysfunction in tumor cells, leading to the production of mitochondrial superoxide and inducing mitochondrial-related apoptosis and paraptosis. This cell death is accompanied by the release of immunogenic molecules such as HMGB1 and ATP, triggering ICD in tumor cells and enhancing the anti-tumor immune response [64].

## 5 | NPs IN REMODELING IMMUNOSUPPRESSIVE TME

NP-based drug delivery system has been applied to improve immunotherapy via multiple strategies to reverse immunotherapy resistance

## 5.1 | NP-based strategies for counteracting tumor hypoxia

Oxygen deprivation, or hypoxia, within the TME results from rapid cellular proliferation and aberrant vascular formation, fueling processes such as angiogenesis, metastasis, and drug resistance [67]. Hypoxia may also promote immunotherapy resistance by eliciting specific immunological responses, thus representing a crucial target in oncology [68]. In response, recent advances in nanotechnology have developed NP strategies for delivering oxygen to hypoxic tumor zones, targeting hypoxia directly, and producing oxygen within the TME [69].

One approach involves using NP vehicles to transport oxygen to hypoxic tumor sites. In pancreatic ductal adenocarcinoma (PDAC), hypoxia in the TME can enhance immune checkpoint expression or fibrosis, thereby complicating immunotherapy. Reversal of hypoxic conditions in the TME is a potential strategy to overcome ICB resistance. Researchers have developed oxygen microcapsules stabilized by polydopamine nanoparticles (polydopamine-NP) that demonstrate excellent stability, bioavailability, and biocompatibility. These microcapsules can directly deliver oxygen to tumor sites via interfacial polymerization. It was observed that these microcapsules could sustain oxygen concentration over extended periods both in vitro and in vivo, significantly reducing ICB resistance and enhancing the effectiveness of ICB against PDAC. Regarding the mechanism, the combination of oxygen microcapsules with ICB was shown to inhibit the invasion of tumor-associated macrophages (TAMs) and encourage the transformation of M2 macrophages to anti-tumor M1 macrophages. Additionally, this therapy increased the number of Th1 cells and CTLs, facilitating the anti-tumor immune response within the TME [70]. These findings indicate that oxygen-delivering NPs could be used to counteract hypoxia and address immunotherapy resistance, although their clinical efficacy requires further investigation.

Instead of direct oxygen delivery, NPs may be equipped with agents that generate oxygen to address the immunotherapy resistance [6, 71].

Os@Au-TPA, a multifunctional sonosensitizer, possesses catalase-like catalytic activity that converts $H_2O_2$ into $O_2$, reducing tumor hypoxia, promoting the transformation of M2 macrophages into M1 macrophages, and achieving significant outcomes in tumor sonoimmunotherapy [6]. To tackle the generally hypoxic tumor environment that complicates immunotherapy, Yuan and colleagues designed cancer cell membrane-camouflaged gelatin NPs that deliver the $O_2$-generating agent catalase and CD73 small interfering RNA (siRNA) simultaneously. This enhances tumor oxygenation by producing endogenous $O_2$ and alleviating CD73- adenosine pathway-mediated T cell immunosuppression, thus enhancing T-cell-specific immunity. The nanosystem proved effective in treating hypoxia, offering insights into potential strategies to overcome the PD-1/PD-L1 immune checkpoint resistance [71]. Zhang *et al.* designed a PD-1-expressing mimetic nanoemulsion where perfluorinated carbons supply oxygen to combat hypoxic tumors and also serve as a source for PDT. This nanoemulsion delivers PD-1 proteins and photosensitizers together, contributing to a synergistic effect of PDT and immunotherapy, potentially reversing immunotherapy resistance by stimulating DC maturation and increasing the infiltration of cytotoxic T lymphocytes [72].

In conclusion, NP-based strategies for targeting hypoxia within the TME present a promising pathway for enhancing the efficacy of existing cancer therapies. By improving oxygen availability and reducing the tumorigenic and immunosuppressive effects of hypoxia, these nanoformulations may revolutionize the fight against cancer.

## 5.2 | NP strategies for targeting TAMs

Macrophages perform indispensable roles in wound healing and immunity [67]. In response to specific stimuli, they may differentiate into M1 or M2 types. For instance, exposure to IFN-$\gamma$ and lipopolysaccharide promotes classical M1 subtype polarization, which inhibits tumor cell proliferation through IL-12 secretion. Conversely, macrophages may transform into M2 types, fostering cancer cell progression and tissue repair [67]. Given their dual role, macrophages act as a double-edged sword in tumor progression. Initially, TAMs may enhance tumor immunotherapy, but as the disease progresses, they promote angiogenesis and become centers of immunodepression, reflecting dynamic changes within the TME [73]. Therefore, developing strategies specifically targeting TAMs could represent a valuable approach to combating cancer immunotherapy resistance.

### 5.2.1 | Targeting TAM and modulation of TAM polarization

The novel Photo-STING agonist employs red blood cells to mimic the phagocytic delivery mode and accurately targets tumor tissues and TAMs to activate the cGAS-STING pathway, inducing a transformation of TAMs from an immunosuppressive M2 phenotype to a proinflammatory M1 phenotype. Through photodynamic activation, NPs not only produce ROS but also initiate mitochondrial DNA fragmentation, enhancing STING pathway activation, promoting ICD, DCs maturation, and T cell infiltration [74]. Macrophages were engineered with Glypican-3

targeting peptide and were loaded with exosomes carrying TLR7/TLR8 agonist and indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor. These modified macrophages effectively targeted tumor cells expressing high levels of Glypican-3 and significantly increased tumor cell phagocytosis. Exosomes efficiently released TLR7/TLR8 agonists and IDO1 inhibitors, modulated TAM polarization, curbed tumor immune escape mechanisms, and activated T cell anti-tumor activity [75].

Iron-oxide NPs, such as ferumoxytol, approved for treating iron deficiency symptoms, have been shown to catalyze the reorientation of macrophages from M2 to M1 types, thereby inhibiting tumor growth [76]. Another iron-based NP modifies TAM-binding molecules on S dots, which possess abundant $O_2$-containing groups on their surface [77]. Once internalized by lysosomes, these NPs release iron, eliciting ROS and inducing a shift in macrophages from M2 to M1. Moreover, ultra-tiny NPs have been shown to enable deeper penetration into cancer tissue [77]. These findings suggest that leveraging endogenous components might enhance the efficacy of immunotherapy.

Others have developed a biomimetic formulation targeting tumors that reprograms M2 subtypes and enhances cancer immunotherapy, incorporating resiquimod (R848) coated with PLGA and B16-OVA membrane [78]. This innovative approach targets Toll-like receptors and reorients M2 subtype TAMs.

Tumor vaccines based on Tumor-derived antigenic microparticles, mimicking their parental cells' cytosolic components and biological properties, are promising due to their highly immunogenic antigens [79]. These NP strategies have been found to effectively stimulate an anti-cancer response in various solid tumors.

The Os@Au-TPA sonosensitizer is capable of producing more than 40-fold more singlet oxygen ($^1O_2$) than a conventional sonosensitizer under ultrasound activation, markedly enhancing ROS generation efficiency. With catalase-like catalytic activity, it converts $H_2O_2$ to $O_2$, diminishes tumor hypoxia, and facilitates the transformation of M2 macrophages into M1 macrophages. Similarly, a novel Os-doped Au-tri (pyridin-4-yl) amine coordination structure-based sonosensitizer achieves the same level of singlet oxygen production and ROS generation efficiency improvement under ultrasound. This activity also leads to the conversion of $H_2O_2$ to $O_2$, reduction of tumor hypoxia, and promotion of M2 to M1 macrophage transformation [6].

### 5.2.2 | Suppression of TAM survival and function

In an innovative study, NPs were shown to enhance the uptake of Ibrutinib (IBR), a Bruton tyrosine kinase inhibitor, by TAMs, thus contributing to immune restoration and tumor suppression [80]. These NPs could efficiently deliver IBR into macrophages, resulting in a decrease in tumor volume and angiogenesis [80]. The colony-stimulating factor-1 (CSF-1) - colony-stimulating factor-1 receptor (CSF-1R) axis is known to induce TIME formation, and blocking the binding of CSF-1 to CSF-1R has been identified as an effective strategy to inhibit TAM transport and reduce tumor immunotherapy resistance. Chen *et al.* developed TAM-like up-conversion nano-photosensitizers (NPR@TAMM) by coating TAM membranes on photosensitizer-loaded up-conversion NPs [81]. These TAM mimics NPR@TAMMs can selectively accumulate at tumor sites and bind to the immunomodulatory molecule CSF-1. This interaction reduced the binding of CSF-1 to endogenous TAM, thereby mitigating the immunosuppression of the TME and reversing immunotherapy resistance [81].

Wei *et al.* created a lipoplex (F-PLP/pBIM) consisting of a folate-personalized liposome (F-PLP) and a BIM-S plasmid (pBIM) aimed at simultaneously targeting cancer cells and folate receptor $\beta$-positive macrophages TAMs. F-PLP/pBIM was found to significantly affect M2 macrophage apoptosis, modifying TIME, and preventing tumor angiogenesis and progression in LL/2 and A549 tumor models [82].

In essence, NP strategies aimed at targeting TAMs promise to overcome traditional drawbacks, such as subpar solubility, poor circulation, and non-specific delivery, leading to improved immunotherapeutic outcomes. However, due to the complex dynamics of TAM polarization, these NP strategies require extensive validation in clinical trials to assess their therapeutic efficacy. A polymeric nanolysosome targeting chimera (nano-LYTAC), targeting the interleukin-4 receptor (IL-4R) in M2 macrophages, significantly enhanced the degradation of IL-4R. Nano-LYTAC inhibited the expression of CD206 and IL-10 in M2 macrophages at low concentrations, induced apoptosis, and promoted the infiltration of M1 macrophages and effector T cells at high concentrations [83], thus remodeling the tumor immune microenvironment and addressing resistance to immunotherapy.

## 5.3 | Exploiting nanomedicine to precisely target cancer-associated fibroblasts (CAFs)

CAFs significantly influence the TME. These fibroblasts engage in a reciprocal interaction with tumor cells, which is crucial for maintaining the tumor matrix [69]. Recent research has intriguingly implicated CAFs in promoting drug resistance and impeding drug delivery [84].

Consequently, CAF-oriented NP approaches have emerged to combat resistance.

#### 5.3.1 | Disruption of CAF-related barriers: a potential pathway to subvert resistance

The first approach focuses on the targeted disruption of key CAF components. For instance, myofibroblasts, a significant fraction of CAFs, are formed through the action of transforming growth factor-beta 1, which increases ROS and $\alpha$-SMA levels, effects that antioxidants can mitigate [85]. Alili *et al.* have demonstrated that nanoceria NPs can effectively modulate myofibroblast formation, reduce $\alpha$-SMA in these cells, and inhibit tumor cell invasion [86].

#### 5.3.2 | Targeting CAFs: amplifying the efficacy of tumor treatment

The second strategy establishes barriers to hinder drug absorption and penetration [69]. It has been shown that Wnt16, a molecule upregulated in CAFs following treatment with cisplatinum, promotes therapy resistance [87]. Nevertheless, NPs carrying Wnt16-siRNAs have been shown to enhance the cytotoxicity of cisplatinum in stroma-rich environments [87].

Additionally, the modification of CAFs using NPs forms another aspect of this strategy. Huang *et al.* engineered nanomaterials that, upon administration to mouse xenograft models, induced apoptosis in CAFs and transformed them into a quiescent state. This led to an effective remodeling of the TME, enhancing the effectiveness of subsequent therapeutic interventions [88]. A notable example of biomimetic NPs is the NExT platform, which wraps NPs with membranes from exhausted patient-derived T-cells and has demonstrated significant potential in targeting CAFs. NExT NPs have enhanced the efficacy of chemotherapy in the TME by targeting both tumor PD-L1 and CAFs, leading to stromal remodeling and reduced therapy resistance. In a patient-derived xenograft model of triple-negative breast cancer, NExT facilitated chemotherapy penetration and improved tumor suppression, offering a promising avenue for personalized chemoimmunotherapy approaches [34].

In summary, NP-based drug delivery systems represent an innovative and potentially transformative approach for targeting CAFs, with the potential to reverse drug resistance, enhance T cell infiltration, and reshape the TME to reactivate anti-cancer pathways. This method promises a new direction for personalized therapies and, when combined with concurrent therapeutic strategies, may significantly improve clinical outcomes.

### 5.4 | Employing nanomedicine to modulate tumor extracellular matrix (ECM)

The ECM provides structural support and orchestrates cellular activities, including proliferation, communication, and adhesion [89]. Its characteristics vary based on the resident cells, the specific tumor tissue, and the disease staging [90, 91].

Generally, the ECM contributes to tumor therapy resistance by facilitating evasion of immune surveillance and impeding drug delivery [92]. Typically, small molecular therapeutics are transported from interstitial spaces to tumor cells, driven by blood pressure. However, the ECM's structural organization increases fluid pressure, thereby obstructing drug penetration into interstitial spaces [91]. Additionally, the high density of ECM components in three-dimensional cultured spheroids significantly hinders drug delivery compared to two-dimensional monolayer cultures [93]. Notably, cancer cells within collagen I matrices exhibit increased resistance to 5-fluorouracil/oxaliplatin [93, 94]. Furthermore, proteoglycans in the ECM can enhance inflammatory cytokine production, thus promoting immune evasion [95–97]. Thus, the ECM plays a crucial role in tumorigenesis and offers a target for innovative therapeutic strategies.

Recent research has focused on targeting the ECM. One approach utilizes an ECM-degrading nanoagonist with NIR-II light to control activation of the intracellular STING pathway for mild photothermal-augmented chemodynamic-immunotherapy of breast cancer. This mild photothermal activation combined with ICD enhances anti-tumor immune responses and improves effector T cell infiltration into tumor tissues following ECM degradation [98]. Moreover, the dense ECM is a major barrier to tumor infiltration by CTLs, contributing to hepatocellular carcinoma immunotherapy resistance. Hyaluronidase, IL-12, and anti-PD-L1 antibody were co-delivered using a pH and matrix metalloproteinase -2 dual-sensitive polymer/calcium phosphate hybrid nanocarrier. The dissolution of calcium phosphate facilitated ECM digestion, enhancing CTL infiltration and proliferation, thus promoting anti-tumor effects. This dual-sensitive nanodrug demonstrates an effective approach to reverse immunotherapy resistance [99].

Moreover, NPs designed to deplete collagen have been developed, given that excessive collagen can induce therapy resistance and inhibit drug absorption [100]. TGF-$\beta$ receptor inhibitors (LY2157299) were delivered by using an acidic tumor extracellular pH-responsive clustered NP (LYiClustersiPD-L1). LY2157299 encapsulated in the hydrophobic core of the NP can effectively reduce type I collagen. This NP significantly increases tumor-infiltrating

CD8+ T cells and provokes antitumor immunity, synergistically suppressing tumor growth [101].

### 5.5 | NP-based drug delivery systems for targeting the tumor vasculature

The tumor vasculature is crucial for cancer recurrence, metastasis, and resistance, providing nutrients, oxygen, growth factors, and serving as a channel for waste disposal [102]. Its unique features, such as intricate, branched morphology, irregular blood flow, and leaky vessel walls, substantially impede drug delivery, fostering an environment conducive to tumor growth and therapeutic resistance [103]. Additionally, the scarcity or absence of lymph vessels in many solid tumors creates high interstitial pressure, which severely limits the transport of large biomolecules away from the tumor tissue [104, 105]. This pressure also hinders the penetration of antibodies and large therapeutic molecules. The aberrant tumor vasculature further complicates the efficient delivery of nutrients and oxygen to cancer cells, leading to metabolic waste accumulation and creating a hypoxic and acidic environment that contributes to drug resistance [106]. It has been shown that drug distribution is strongly associated with the distance from the vasculature to the tumor tissues [107], significantly impacting treatment outcomes in lung, breast, and liver cancers [2].

This understanding has led to the development of NP-based strategies specifically targeting these aberrant blood vessels [67]. However, acquired endothelial resistance has been a formidable obstacle to these approaches [67, 71]. Recent advancements suggest promising avenues in NP drug delivery systems loaded with anti-angiogenic drugs capable of circumventing the endothelial resistance [67]. For instance, Du *et al.* proposed a lipid-nanomaterial strategy combining angiogenesis-inhibiting drugs, antineoplastic drugs, and low-molecular-weight heparin to normalize the tumor vasculature and enhance therapeutic responses [108]. Additionally, gold NPs carrying recombinant endostatin to inhibit vascular endothelial growth factor (VEGF) resulted in reduced hypoxia, normalized vessels, enhanced endostatin accumulation, and improved therapeutic outcomes in xenograft models [109]. A notable innovative approach involves the use of NIR-laser-induced NPs. This non-invasive strategy aims to rapidly and precisely destruct abnormal vasculature by generating high local temperatures, leading to the formation of disruptive bubbles and inducing tumor cell necrosis [110]. Furthermore, the efficiency of nano-based vasculature-disrupting strategies has been shown to be amplified when combined with immunotherapy. In one study, an NP system was used to induce apoptotic death in tumors, simultaneously promoting NP absorption and enhancing radiotoxicity [111]. This approach demonstrated a considerable reduction in tumor volume and tumor vasculature activity. Further efforts to combine anti-angiogenic drugs and immunotherapy have included the development of antiangiogenic copper chelating polymers to create NPs loaded with resiquimod. This combined strategy effectively inhibited tumor cell growth and metastasis in breast cancer through the dual action of copper-deficiency-induced antiangiogenesis and resiquimod-elicited immune activation [112]. Additionally, stable tumor vascular normalization could be a significant strategy for long-term change to remodel the TME and potentially reverse immunotherapy resistance. V@LDL NPs is a nano-delivery system sustainedly releasing Vandetanib to control the dose of the drug to the normalizing level, and prove its stable tumor vascular normalizing effect in four T1 breast cancer models, successfully inhibiting tumor progression [113].

## 6 | DESIGNS, PRECLINICAL PRACTICE AND CLINICAL TRIALS

### 6.1 | Designs and preclinical practice

Several specific nanomedicines have been developed to enhance immunotherapy and address resistance (Table 2). For example, a nanomedicine containing the p53 plasmid has been shown to improve the efficacy of anti-PD1 antibody treatment in mouse models of glioblastoma, NSCLC, and breast cancer [114]. Additionally, the NP AZD1080 has enhanced drug delivery to cancer sites, reduced PD1 expression, and activated $CD8^+$ T cells [115]. Zero-valent-iron NPs have also demonstrated anticancer immunity and cancer-specific cytotoxicity in lung cancer models [116]. Other innovations include nanomedicines designed to improve immunotherapy in lung cancer [117], augment anti-PD1 therapy [118], and target the TME for immunotherapy [119]. Notably, NBTXR3, a first-in-class hafnium oxide radioenhancer NP, has been evaluated in a Phase 2/3 trial for safety and efficacy as a preoperative treatment in soft tissue sarcoma patients [120]. This NP has also been used to combat anti-PD1 resistance in lung cancer [121]. Further advancements include nanodiamond-doxorubicin conjugates (Nano-DOX), which enhance tumor suppression synergistically when combined with anti-PD-L1 agents [122, 123]. Another example is NExT (NPs wrapped in membranes from exhausted patient-derived T cells). These NPs improve tumor suppression in a PDX model of TNBC by combining anti-PD-L1 effects with chemotherapy. NExT exploits tumor immune evasion mechanisms, enhancing chemotherapy penetration and tumor control [34]. These developments highlight the

**TABLE 2** The nano-medicines designed to overcome cancer immunotherapy resistance.

| Entry | Nanomedicine design | Mechanism of action | Cancer models used | Key outcomes and benefits | Possible side effects | Future directions | References |
|---|---|---|---|---|---|---|---|
| 1 | SGT-53 | SGT-53 is a complex formed by a cationic liposome and a p53 plasmid. The p53 gene enhances immune responses in the body. It's primarily used to augment the efficacy of immunotherapy, especially the anti-PD1 antibodies, by promoting tumor immunogenicity. | Brain cancer, lung cancer, breast cancer | In animal models, SGT-53 enhanced the effect of anti-PD1 antibody treatment, suppressed tumor growth and metastasis, and blocked fatal xenogeneic hypersensitivity after anti-PD1 therapy. | NRSEs | Further studies are needed to evaluate SGT-53's effect in human subjects and its possible side effects. | [114] |
| 2 | AZD1080 NPs | This NP design involves remote loading of the GSK3 inhibitor AZD1080 into NPs coated with a lipid bilayer. This setup improves the biodistribution of the drug, delivering it more effectively to cancer sites and reducing the expression of PD1, a protein that suppresses immune response. | Colorectal cancer, pancreatic cancer, lung cancer | In various animal models, AZD1080 NPs reduced tumor growth without showing treatment toxicity. It has the potential to be used in combination with other cancer therapies. | NRSEs. | Further research is required to understand the drug's mechanism and its potential use with other therapies. | [115] |
| 3 | ZVI-NP (Nanomodulator NRF2) | ZVI-NP promote anticancer immunity and induce ferroptotic death in lung tumor cells by regulating lipid peroxidation, causing mitochondria dysfunction and increasing ROS. | Lung cancer | ZVI-NP enhances anti-tumor immunity, suppresses angiogenesis-associated genes, reduces self-renewal capacity of cancer cells, and inhibits tumor metastasis and growth. | NRSEs. | Further studies are required to explore the full potential of ZVI-NP, especially in human trials. | [116] |
| 4 | Au@PG NPs | The design involves glyco-condensation on gold NPs, contributing to tumor suppression and promotion of cytotoxic T cell response in lung cancer. | Lung cancer | These NPs show potential for enhancing tumor suppression and immunosuppression, improving cytokine secretion. In the study, smaller Au@PG NPs displayed better functions than larger ones. | NRSEs | The effect of different NP sizes on the therapy's effectiveness and potential side effects should be studied further. | [124] |

(Continues)

**TABLE 2** (Continued)

| Entry | Nanomedicine design | Mechanism of action | Cancer models used | Key outcomes and benefits | Possible side effects | Future directions | References |
|---|---|---|---|---|---|---|---|
| 5 | NBTXR3 NPs | NBTXR3 NPs are activated by radiotherapy and cause direct damage to tumor cells. This aids in modulating the tumor microenvironment and increasing cancer sensitivity to anti-PD1 therapy. | Head and neck cancer | These NPs induce tumor cell death and facilitate the effect of anti-PD1 therapy, resulting in tumor regression and long-term disease control. | NRSEs | More comprehensive studies are needed to explore the effects of NBTXR3 NPs on other types of cancer. | [120] |
| 6 | STING-LNP | STING-LNPs are designed to efficiently induce antitumor activity via the activation of NK cells. After intravenous injection, these NPs stimulate the production of type 1 interferons via the STING pathway in liver macrophages, which then activates NK cells in the lung and spleen. This leads to an increase in the expression of PD-L1 in cancer cells, inducing a synergistic antitumor effect when combined with anti-PD-1. | Melanoma | Combination of STING-LNP and anti-PD-1 resulted in a synergistic antitumor effect, overcoming the anti-PD-1 resistance in B16-F10 lung metastasis model. | Liver toxicity could be a potential side effect, but further studies are needed to confirm. | Future studies should evaluate the possible liver toxicity of this treatment and explore the use of different signaling molecules. | [125] |
| 7 | NExT | Combines anti-PD-L1 immune checkpoint inhibition and chemotherapy to enhance tumor suppression by targeting CAFs and tumor cells | Breast cancer | NExT nanoparticles significantly enhance chemotherapy penetration, improve tumor control by targeting both CAFs and tumor cells, and demonstrate synergistic antitumor effects with reduced resistance to treatment. | Potential liver toxicity due to uptake by liver macrophages | Further evaluation of liver toxicity and testing in other cancer models | [34] |

Abbreviations: Au@PG NPs, Gold nanoparticles with glyco-condensation; AZD1080, GSK3 inhibitor-loaded nanoparticles; BMS-1, Bristol-myers squibb PD-L1 inhibitor; CAFs, Cancer-associated fibroblasts; DPA-713-Mn, Manganese-containing nanomedicine for theranostic use; $HfO_2$, Hafnium Oxide; IFN-1, Type I interferons; IFN-$\gamma$, Interferon Gamma; NK cells, Natural killer cells; NBTXR3, Hafnium Oxide nanoparticles; NPs, Nanoparticles; NRF2, Nuclear factor erythroid 2-related factor 2; NRSEs, No reported side effects; NExT, Nanoparticles coated with exhausted patient-derived T-cells; LLC, Lewis lung carcinoma; PD1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; ROS, Reactive oxygen species; SGT-53, p53 gene-carrying liposome complex; STING-LNP, Stimulator of interferon gene-loaded lipid nanoparticles; sTRAIL, Soluble TNF-related apoptosis-inducing ligand; TME, Tumor microenvironment; ZVI-NP, Zero-valent-iron NPs.

potential of nanomedicines to create more effective therapeutic approaches in cancer treatment, addressing existing challenges in immunotherapy.

Significant progress has also been achieved through the work of Takashi Nakamura and his team [125]. They developed lipid NPs loaded with STING agonists (STING-LNPs) to overcome anti-PD1 resistance in melanoma lung metastases. This strategy primarily works by activating NK cells. While anti-PD1 monotherapy showed minimal effect, combining STING-LNPs with anti-PD-1 produced a synergistic antitumor response. Upon intravenous injection, STING-LNPs were efficiently absorbed by liver macrophages, stimulating IFN-1 production and leading to systemic NK cell activation. This enhanced the expression of molecules like CD3, CD4, NK1.1, PD-1, and IFN-$\gamma$ within lung metastases. Activated NK cells produced IFN-$\gamma$, increasing PD-L1 expression in cancer cells. Consequently, combining STING-LNPs with anti-PD1 resulted in a robust antitumor effect [125]. This innovative approach using STING-LNPs presents a promising candidate for combination therapy against anti-PD1-resistant tumors. However, further studies are needed to assess liver toxicity and explore the use of alternative signaling molecules in this therapeutic strategy.

### 6.2 | NPs for combating cancer immunotherapy resistance in clinical trials

Nanoplatforms have demonstrated significant potential in overcoming immunotherapy resistance. Their high loading capacity, adjustable porosity, and targeted delivery capabilities enhance immunotherapy efficacy while reducing adverse effects. Despite substantial progress in preclinical studies, the clinical application of NPs remains in its early stages. Over the past decade, several clinical trials have been initiated to assess NP-based immunotherapy, either as standalone treatments or in combination with conventional immunotherapy, to address cancer and resistance to treatment. A Phase 1 clinical trial is evaluating immune-stimulating crystalline Hafnium oxide NPs with radio-enhancing properties in combination with anti-PD1 therapy for patients with primary cancer and lung or liver metastases [126]. Another Phase 1 trial employed nanoliposomes to deliver the microRNA-34a mimic, which suppresses immunosuppressive tumor genes in patients with solid tumors. Preliminary findings from this study were encouraging but require further verification [127]. Further, a lipid-coated mRNA-4157 encoding multiple tumor antigens was tested in a Phase 1 trial, both independently and with the humanized anti-PD1 antibody pembrolizumab. Early results indicated good dose tolerance, and subsequent Phase 2 trials may provide deeper insights into the resistance suppression [128]. Another Phase 1 trial explored the anticancer potential of an RNA-lipoplex designed to induce DC maturation and activate T-cell responses in patients with advanced melanoma. The trial showed robust T-cell responses in all participants, signaling potential for combating immunotherapy resistance, though further clinical validation is necessary [129].

These trials underscore the promising role of NPs in overcoming cancer immunotherapy resistance. This innovative approach could revolutionize cancer treatment and resistance management. Table 3 summarizes key clinical trials focused on nano-medicine in this area.

The successful transformation of nanomedicines from preclinical development to clinical trials marks a critical step in addressing cancer immunotherapy resistance. To achieve this, several key factors must be carefully considered. Firstly, rigorous, evidence-based research is essential. Preclinical studies must not only confirm the safety and efficacy of nanomedicines but also provide a detailed understanding of their mechanisms of action. These insights are crucial for designing effective clinical trial protocols.

Furthermore, well-designed clinical trials are pivotal. Attention should be given to patient selection criteria, dosing regimens, and endpoints. The unique properties of nanomedicines, such as high drug-loading capacity and precise targeting capabilities, should be leveraged to improve therapeutic outcomes. Combining nanomedicines with established immunotherapies, such as anti-PD1 antibodies, is another promising approach to overcoming immunotherapy resistance.

Safety assessment is critical. Comprehensive evaluation of potential adverse effects, including liver toxicity, immune-related events, and off-target effects, must be conducted during clinical trials. Early identification and mitigation of these safety concerns are essential to ensure patient safety and secure regulatory approval.

Collaboration among researchers, clinicians, and pharmaceutical companies is vital for success. Such partnerships can streamline processes, from optimizing NP formulations to conducting large-scale, multicenter trials.

Ultimately, transparency and robust data collection are indispensable. Reporting both positive and negative findings, along with long-term follow-up data, contributes to the collective knowledge base and guides future research. By addressing these considerations, the successful integration of nanomedicines into clinical trials has the potential to revolutionize cancer immunotherapy, effectively combat resistance, and improve patient outcomes.

## 7 | CONCLUSION AND PERSPECTIVE

The introduction of cancer immunotherapy has marked a significant shift in oncology, introducing a potent approach that utilizes the body's natural defense mechanisms to

**TABLE 3** The important clinical trials about nanomedicine on combating cancer immunotherapy resistance.

| Study | NCT number | Title | Type of NP | Status | Indication(s) | Interventions | Outcome measures | Phase | Number of enrollments | Country of study |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | NCT03003546 | Nab-paclitaxel/ Rituximab-coated NP AR160 in treating patients with relapsed or refractory B-Cell non-hodgkin lymphoma, LS1681 trial | Not mentioned | Suspended | Various types of non-hodgkin lymphoma | Drug: Nab-paclitaxel/ Rituximab-coated NP AR160 | Tumor response, progression-free survival, overall survival | 1 | 18 | United States |
| 2 | NCT04751786 | Dose escalation study of immunomodulatory NPs (PRECIOUS-01) | PLGA NP | Recruiting | Advanced solid tumor | Drug: PRECIOUS-01 | Safety of PRECIOUS-01, multiplex immunohistochemistry assay, recommended phase 2 dose | 1 | 15 | Netherlands |
| 3 | NCT05264974 | Novel RNA-NP vaccine for the treatment of early melanoma recurrence following adjuvant anti-PD-1 antibody therapy | Liposome | Not yet recruiting | Melanoma | Biological: autologous total tumor mRNA loaded DOTAP liposome vaccine | Overall response rate, progression-free survival | 1 | 18 | United States |
| 4 | NCT05280379 | Trained immunity in thyroid carcinoma and colon carcinoma | Lipoprotein NP | Recruiting | Thyroid cancer, colon carcinoma | No intervention will take place | Levels of pro-inflammatory cytokines and chemokines | NA | 60 | Netherlands |
| 5 | NCT03323398 | Dose escalation and efficacy study of mRNA-2416 for intratumoral injection alone and in combination with Durvalumab for participants with advanced malignancies | Lipid NP | Terminated | Various types of malignancies | Biological: mRNA-2416 biological: Durvalumab | Dose limiting toxicities, adverse events, objective response rate | 1/2 | 79 | United States |
| 6 | NCT03739931 | Dose escalation study of mRNA-2752 for intratumoral injection to participants in advanced malignancies | Lipid NP | Recruiting | Various types of malignancies | Biological: mRNA-2752 biological: Durvalumab | Dose limiting toxicities, adverse events, overall response rate | 1 | 264 | United States |
| 7 | NCT03120832 | Phase 1 trial of PAN-301-1 (SNS-301) in cancer patients | Biomimetic NP | Completed | Prostate cancer | Biological: PAN-301-1 | Safety assessed by development of adverse events and dose-limiting toxicity | 1 | 12 | United States |

(Continues)

**TABLE 3** (Continued)

| Study | NCT number | Title | Type of NP | Status | Indication(s) | Interventions | Outcome measures | Phase | Number of enrollments | Country of study |
|---|---|---|---|---|---|---|---|---|---|---|
| 8 | NCT02740985 | A phase 1 clinical study of AZD4635 in patients with advanced solid malignancies | Not mentioned | Active, not recruiting | Various types of malignancies | Drug: AZD4635, Durvalumab, Abiraterone Acetate, Enzalutamide, Oleclumab, Docetaxel | Dose-limiting toxicities, adverse events | 1 | 313 | United States |
| 9 | NCT03719326 | A study to evaluate/tolerability of immune-therapy combinations in participation with TNBC or gynaecologic malignancies | Liposome/ Albumin-bound NP | Completed | TNBC and ovarian cancer | Drug: Etrumadenant, IPI-549, pegylated liposomal doxorubicin, NP albumin-bound paclitaxel | Dose-limiting toxicities, adverse events | 1 | 35 | United States |
| 10 | NCT05157542 | Neoadjuvant LDRT combined with Durvalumab in potentially resectable stage III NSCLC | Albumin-bound NP | Recruiting | Stage III NSCLC | Drug: Durvalumab, NP albumin bound paclitaxel Radiation: low dose radiation therapy | Adverse events, objective response rate, event-free survival, major pathological response rate, pathological complete response rate | 1 | 9 | P. R. China |
| 11 | NCT05101616 | A pilot study of neoadjuvant chemotherapy with or without Camrelizumab for locally advanced gastric cancer | Albumin-bound NP | Recruiting | Gastric cancer | Drug: Camrelizumab + chemotherapy, chemotherapy | Major pathologic response rate, complete pathologic response rate, R0 resection rate, overall survival, disease-free survival, perioperative complications | 1/2 | 100 | P. R. China |
| 12 | NCT04862455 | NBTXR3, radiation therapy, and Pembrolizumab for the treatment of recurrent or metastatic head and neck squamous cell cancer | Hafnium oxide-containing NP | Recruiting | Metastatic head and neck squamous cell carcinoma and recurrent head and neck squamous cell carcinoma | Other: Hafnium oxide-containing NPs NBTXR3 Radiation: hypofractionated radiation therapy Biological: Pembrolizumab Radiation: stereotactic body radiation therapy | Progression free survival, local failure, regional failure, distant failure, objective response rate | 2 | 60 | United States |

(Continues)

**TABLE 3** (Continued)

| Study | NCT number | Title | Type of NP | Status | Indication(s) | Interventions | Outcome measures | Phase | Number of enrollments | Country of study |
|---|---|---|---|---|---|---|---|---|---|---|
| 13 | NCT04940286 | Gemcitabine, Nab-paclitaxel, Durvalumab, and Oleclumab before surgery for the treatment of in resectable/borderline resectable primary pancreatic cancer | Albumin-bound NP | Recruiting | Borderline resectable pancreatic adeno-carcinoma, resectable pancreatic adeno-carcinoma pancreatic cancer | Biological: Durvalumab, Oleclumab Drug: Gemcitabine, Nab-paclitaxel | Major pathological response rate, adverse events | 2 | 30 | United States |
| 14 | NCT05092373 | Combination with chemotherapy for the treatment of advanced solid tumours involving the abdomen or thorax | Albumin-bound NP | Recruiting | Advanced breast carcinoma, advanced endometrial carcinoma, advanced fallopian tube carcinoma, advanced hepatocellular carcinoma, advanced malignant abdominal neoplasm, advanced malignant female reproductive system neoplasm, advanced malignant thoracic neoplasm, advanced ovarian carcinoma, advanced primary peritoneal carcinoma, advanced renal cell carcinoma | Biological: Atezolizumab Drug: Cabozantinib S-malate, Nab-paclitaxel Procedure: tumor treating fields therapy | Safety and tolerability of tumor treating fields | 1 | 36 | United States |
| 15 | NCT03907475 | Durvalumab in combination with chemotherapy in treating patients with advanced solid tumours | Liposome/ Albumin-bound NP | Recruiting | Locally advanced malignant solid neoplasm, metastatic malignant solid neoplasm, unresectable malignant solid neoplasm | Drug: Capecitabine, Carboplatin, Gemcitabine Hydrochloride, Nab-paclitaxel, Paclitaxel, pegylated liposomal DOXorubicin hydrochloride Biological: Durvalumab | Adverse events | 2 | 115 | United States |

(Continues)

**TABLE 3** (Continued)

| Study | NCT number | Title | Type of NP | Status | Indication(s) | Interventions | Outcome measures | Phase | Number of enrollments | Country of study |
|---|---|---|---|---|---|---|---|---|---|---|
| 16 | NCT05422794 | Testing the addition of anticancer drug, ZEN003694 (ZEN-3694) and PD-1 inhibitor (Pembrolizumab) to standard chemo-therapy (Nab-Paclitaxel) treatment in patients with advanced TNBC | Albumin-bound NP | Recruiting | Anatomic stage III/IV breast cancer locally advanced TNBC, metastatic TNBC, unresectable TNBC | Drug: BET Bromodomain Inhibitor ZEN-3694, Nab-paclitaxel Procedure: biopsy, biospecimen collection, computed tomography, magnetic resonance imaging Biological: Pembrolizumab | Maximum tolerated dose, recommended phase 2 dose, adverse events | 1 | 57 | United States |
| 17 | NCT04964960 | Pembro + Chemo in brain metastasis | Albumin-bound NP | Recruiting | Lung cancer, brain cancer | Drug: Pembrolizumab, Nab paclitaxel, Paclitaxel, Pemetrexed, Carboplatin | Disease control rate | 2 | 45 | United States |
| 18 | NCT03181100 | Atezolizumab with chemotherapy in treating patients with anaplastic or poorly differentiated thyroid cancer | Albumin-bound NP | Active, not recruiting | Metastatic thyroid gland carcinoma, poorly differentiated thyroid gland carcinoma, stage IVA/IVB/IVC thyroid gland anaplastic carcinoma, gland anaplastic carcinoma, unresectable thyroid gland carcinoma | Drug: Atezolizumab, Cobimetinib, Nab-paclitaxel, Paclitaxel, Vemurafenib Biological: Bevacizumab | Overall survival | 2 | 50 | United States |

(Continues)

**TABLE 3** (Continued)

| Study | NCT number | Title | Type of NP | Status | Indication(s) | Interventions | Outcome measures | Phase | Number of enrollments | Country of study |
|---|---|---|---|---|---|---|---|---|---|---|
| 19 | NCT04892953 | Local consolidative therapy and Durvalumab for oligoprogressive and polyprogressive stage III NSCLC after chemoradiation and anti-PD-L1 therapy | Albumin-bound NP | Recruiting | Stage III/IIIA/IIIB lung cancer, stage III/IIIA/IIIB non-small cell lung cancer | Drug: Carboplatin, Gemcitabine, Nab-paclitaxel, Paclitaxel, Pemetrexed Biological: Durvalumab Procedure: local consolidation therapy Other: quality of-life assessment, questionnaire administration | Progression free survival | 2 | 51 | United States |
| 20 | NCT05039632 | Phase I/II randomized study of NBTXR3, radiation therapy, Ipilimumab, and Nivolumab for the treatment of lung and/or liver metastases from solid malignancy | Hafnium oxide-containing NP | Recruiting | Advanced malignant solid neoplasm, metastatic malignant neoplasm in the liver, metastatic malignant neoplasm in the lung, metastatic malignant solid neoplasm | Other: Hafnium Oxide-containing NPs NBTXR3 Radiation: radiation therapy | Dose limiting toxicities, objective response rate | 1/2 | 40 | United States |
| 21 | NCT05451043 | Durvalumab and Tremelimumab in combination with propranolol and chemotherapy for treatment of advanced hepatopancreabiliary tumors | Albumin-bound NP | Not yet recruiting | Pancreatic cancer, hepatocellular cancer, biliary tract cancer, cholangiocarcinoma | Biological: Durvalumab, Tremelimumab Drug: Gemcitabine, Nab paclitaxel, Propranolol, Cisplatin | Efficacy of propranolol in boosting the effects of immunotherapy | 2 | 62 | Canada |

(Continues)

**TABLE 3** (Continued)

| Study | NCT number | Title | Type of NP | Status | Indication(s) | Interventions | Outcome measures | Phase | Number of enrollments | Country of study |
|---|---|---|---|---|---|---|---|---|---|---|
| 22 | NCT05501665 | Split course adaptive radiation therapy with Pembrolizumab with/without chemotherapy for treating stage IV lung cancer (Ongoing) | Albumin-bound NP | Recruiting | Non-small cell lung carcinoma, stage IV lung cancer | Procedure: biospecimen collection, computed tomography, positron emission<br>Drug: Carboplatin, Nab-paclitaxel, Pemetrexed<br>Biological: Pembrolizumab<br>Radiation: radiation therapy | Adverse events, overall response rate | 1/2 | 25 | United States |

*Note*: All clinical trial data in this table were retrieved from The My Cancer Genome clinical trial database (https://www.mycancergenome.org/content/clinical_trials/). This publicly available database provides comprehensive information on ongoing and completed clinical trials related to cancer treatments, including trials involving nanomedicines and immunotherapies. Abbreviations: AJCC: American joint committee on cancer; LDRT: Low dose radiation therapy; NA: Not available data; NBTXR3: Hafnium Oxide nanoparticles; NPs: Nanoparticles; NSCLC: Non-small cell lung cancer; PD-L1, Programmed death-ligand 1PLGA: Poly lactic-co-glycolic acid; TNBC: Triple negative breast cancer.

fight cancer. This review thoroughly explores the principles of cancer immunotherapy, the complex resistance mechanisms, strategies to circumvent these challenges, and the potential role of NPs in enhancing immunotherapy effectiveness.

Despite its transformative effects, cancer immunotherapy faces substantial challenges, notably the development of resistance. Understanding the intricate dynamics between various resistance factors is crucial to improving the effectiveness of these therapies.

Through my extensive work with nanotechnology and cancer immunotherapy, I have identified that NPs offer promising solutions for overcoming immunotherapy resistance. Their unique characteristics enable the manipulation of the TME, improve drug solubility and delivery, and adjust the overall condition of the patient. Specifically, incorporating NPs in drug delivery systems shows potential in improving tumor oxygenation, targeting cell death pathways, and altering the behavior and capabilities of tumor-associated macrophages.

However, several limitations merit careful consideration. The heterogeneity of tumors and variability in enhanced permeability and retention (EPR) effects across different patients introduce uncertainty regarding the enrichment capabilities of NPs, which can impact therapeutic efficacy. Interactions between NPs and biological components—such as proteins, cells, and tissues—can influence their behavior and safety, raising concerns about potential autoimmune side effects resulting from enhanced immune responses. Furthermore, discrepancies between preclinical and clinical outcomes, stemming from differences between animal models and human tumors, pose significant challenges for the clinical translation of NP-based strategies.

The complexity of the safety profiles of nano-immunotherapy, coupled with challenges in scalability, cost-effectiveness, and regulatory compliance in manufacturing and commercializing these treatments, presents significant challenges.

These issues highlight the need for continuous research, refinement, and collaboration to overcome the hurdles associated with nanomedicine in cancer immunotherapy. It is critical to pursue robust, evidence-driven research and detailed clinical trials, along with careful design of NP systems, to effectively tackle these challenges.

In conclusion, as our understanding of the intricate relationships among cancer, the immune system, and nanotechnology expands, further advancements in cancer treatment are expected. The synergy of these elements offers promising prospects for enhancing patient outcomes and broadening our understanding of the body's capacity to combat disease. Continued exploration in these areas is likely to lead to more personalized and effective treatment

strategies for cancer patients, ultimately enhancing their prognosis and quality of life.

## AUTHOR CONTRIBUTIONS

Xiangyi Kong: Investigation, Data curation, Visualization, Methodology, Writing - original draft, Writing - review & editing. Xintong Xie: Investigation, Data curation, Visualization, Methodology, Software, Writing - original draft, Writing - review & editing. Juan Wu: Visualization, Software, Writing - review & editing.

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## CONFLICTS OF INTEREST STATEMENT

The authors declare no competing interests. Figures were created with biorender.com.

## DATA AVAILABILITY STATEMENT

Not applicable.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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