Cancer immunotherapy strategies based on transition-metal medical materials: Still a long way to go (Review)

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Abstract. Transition-metal nanoparticles (NPs) have been extensively studied owing to their unique physical and chemical properties, ability to form a variety of nanostructures and targeting properties. After surgery, chemotherapy, radiotherapy and targeted therapy, immunotherapy has emerged as a major strategy for cancer treatment. In particular, immune checkpoint inhibition has attracted much attention in preclinical and clinical applications. The combination of transition-metal NPs with tumor immunotherapy offers great potential. Therefore, the present review focused on four major transition-metal NPs (Au, Ag, Cu and Fe NPs) and their respective categories, presented their characteristics and roles in the biomedical field and discussed their potential toxicities. In addition, the mechanisms of action of different tumor immunotherapies and the applications of transition-metal NPs in tumor immunotherapy are discussed. The current status of, and challenges associated, with the clinical transformation of transition-metal NPs in tumor immunotherapy are described to provide ideas for the subsequent development and clinical application of transition-metal NPs.

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Abbreviations: aAPCs, artificial antigen-presenting cells; ACT, adoptive cell therapy; AgNPs, silver nanoparticles; APCs, antigen-presenting cells; AuNPs, gold nanoparticles; CT, computed tomography; CTLA-4, cytotoxic T lymphocyte antigen-4; Cu, copper; DAP, diaminopimelic acid; DCs, dendritic cells; FDA, United States Food and Drug Administration; ICD, immunogenic cell death; ICIs, immune checkpoint inhibitors; ICOS, inducible T-cell costimulator; IONPs, iron oxide nanoparticles; MOFs, metal-organic frameworks; MRI, magnetic resonance imaging; NPs, nanoparticles; OVA, ovalbumin; PD-1, programmed death receptor-1; PD-L1, programmed cell death ligand 1; PDT, photodynamic therapy; PEG, polyethylene glycol; PTT, photothermal therapy; ROS, reactive oxygen species; siR, small interfering RNA; SPIONs, superparamagnetic iron oxide nanoparticles; STING, stimulator of interferon genes; TLR, Toll-like receptor; TME, tumor microenvironment; TNFR, tumor necrosis factor receptor

Key words: transition metal nanoparticles, cancer immunotherapy, cancer vaccines, immune checkpoint inhibitors, adoptive cell therapy

Contents

1. Introduction

Traditionally, cancer is considered to originate from genomic instability, whereas recent research has indicated that epigenetic changes alone are sufficient to cause cancer (1,2). The main forms of cancer therapy available at present are surgery, radiation therapy, chemotherapy, targeted therapy and immunotherapy. Tumor immunotherapy, which targets tumor escape mechanisms, has both targetability and long-lasting therapeutic effects. The immunotherapeutic modalities that are mainly used at present are lysosomal virus therapy, cancer vaccines, cytokine therapy, chimeric antigen receptor T-cell therapy and immune checkpoint inhibition therapy (3). However, immunotherapy remains expensive, lengthy and associated with off-target effects, posing challenges in improving treatment efficiency (4).

Nanomaterials have emerged as promising therapeutic agents for cancer because of their ability to improve

efficacy, high stability and specificity, capacity to control drug release more precisely and the inherent therapeutic properties of certain nanomaterials in response to stimuli (5-7). Transition-metal NPs, which are derived from transition metals (d-group elements), are particularly notable for their high stability, modifiable properties and ability to participate in multiple therapeutic modalities (8). In comparison with conventional tumor immunotherapy, transition-metal NPs are highly targeted; moreover, they are capable of combining multiple effects of chemistry, optics and thermodynamics for treatment and can improve the bioavailability and *in vivo* residence time of drugs (9,10). Studies have suggested that transition-metal NPs hold great potential in tumor immunotherapy; however, their safety concerns and potential adverse effects require cautious consideration. The present review focused on the properties of transition-metal NPs, their advantages and limitations in immunotherapy and their potential clinical applications. Furthermore, it explored the feasibility of categorizing such materials for future clinical practice.

2. Characteristic and effects of transition-metal NPs

Gold NPs (AuNPs). AuNPs are the most stable transition-metal NPs and show excellent stability, oxidation resistance, biocompatibility and low toxicity, rendering them suitable for biomedical applications (11). Notably, their tunable size and shape allow for diverse functionalization, which is facilitated by negatively charged surfaces that enable conjugation with biologically active groups, such as amines and sulfhydryl groups (11,12).

AuNPs can be classified on the basis of their shapes, such as nanospheres, nanorods, nanoplates, nanocages, nanotriangles, nanostars, nanoflowers and network dendrites, with each shape showing a specific biomedical application (Fig. 1). AuNPs, particularly in nanoplate or nanorod forms, have shown applications in imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) (13). Gold nanorods, nanocages and nanoshells are considered excellent imaging NPs for cancer therapy (14); for example, an AuNP for CT imaging cancer therapy was studied by Wang *et al* (15). AuNPs also exhibit antimicrobial effects, possibly due to the surface charge, with the surface modification between bacteria and AuNPs generating reactive oxygen species (ROS). NPs also affect the cell membrane permeability by disrupting intercellular communication (16). Bankar *et al* (17) have described the antibacterial activity of network-dendritic AuNPs.

AuNPs are excellent drug carriers that can not only carry small molecules but also transport large biomolecules through different interactions, enabling drug release at the target location (18). Additionally, drug-loaded AuNPs can enhance drug accumulation and retention (19). Gold nanospheres have a uniform size, good tissue permeability and relatively simple surface modifications, which are conducive to drug delivery (20,21). Gold nanocages have hollow interiors and porous structures, such that small molecules enter the nanocages through the pores on the surfaces and are encapsulated therein, which can be applied to the targeting area (20).

In photothermal therapy (PTT), AuNPs convert light into heat, thereby inducing high temperatures that cause irreversible damage. Moreover, *in vitro* studies employing tumor cell lines have confirmed that AuNPs can penetrate various tumor cells, including lung, gastric and colorectal cancers, for targeted therapy (22-24).

Despite these advantages, AuNPs should be used with caution. The size, shape and surface properties of AuNPs are also associated with their cytotoxicity. Additionally, modifications such as PEGylation may induce toxicity (14). Exposure time and concentration affect the cellular uptake of NPs and thus their cytotoxicity (25).

Silver NPs (AgNPs). AgNPs have attracted substantial attention because of their nano-sized effects, surface properties and localized surface plasmon resonance, making them valuable in antibiotics, sensors and biomedical applications. Therefore, they have been synthesized in various shapes to meet specific requirements (26).

AgNPs have attracted growing interest in cancer research because of their potential for next-generation diagnosis and treatment, since they show broad anticancer effects by inhibiting cancer cell growth and viability. AgNPs can induce apoptosis and necrosis by generating ROS and damaging DNA (27). *In vitro* studies have shown that AgNPs induce apoptosis by upregulating or downregulating gene expression (28,29). They can also induce apoptosis by altering key signaling pathways (30). Additionally, cancer cells treated with AgNPs may experience cell cycle arrest (31). AgNPs inhibit tumor cell migration and angiogenesis *in vitro*, indicating their possible role in reducing distant metastasis (32). AgNPs can also be used to treat cancer by coating them with polymers or by conjugating them with drugs. Furthermore, because of their targeting ability and biocompatibility, AgNPs show excellent anti-tumor efficacy and few adverse reactions.

AgNPs inhibit tumor cell migration and invasion in a concentration- and dose-dependent manner, which are critical features for cancer development and progression (33,34). Although AgNPs have been shown to inhibit tumor invasion, the underlying mechanism remains unknown. One hypothesis suggests that AgNPs may reduce the production of cytokines and growth factor proteins and inhibit the enzymatic activity of matrix metalloproteinases in cancer cells (35).

Copper (Cu)-based NPs. Cu-based NPs mainly include CuNPs, CuONPs and CuS NPs. CuNPs are of interest owing to their unique physical and chemical properties, high surface-to-volume ratio, low preparation cost, low toxicity and good biocompatibility (36-38). Cu-based NPs exhibit antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis* and *Proteus vulgaris*. This antimicrobial property may be related to cell wall damage, internalization of NPs into bacterial cells, Cu ion release, excess ROS, oxidative stress, mitochondrial damage and DNA damage (Fig. 2) (39). CuNPs act as anti-tumor agents through various cytotoxic mechanisms, including ROS production, cell cycle blockade, DNA damage, apoptosis and autophagy and are effective against a wide range of cancer cell lines (39-41). Woźniak-Budych *et al* (42) demonstrated that sulfobetaine-stabilized Cu(I) oxide NPs promoted the suppression of cancer cell growth in a concentration-dependent manner in tumor cell line models. Due to their large surface area, CuNPs

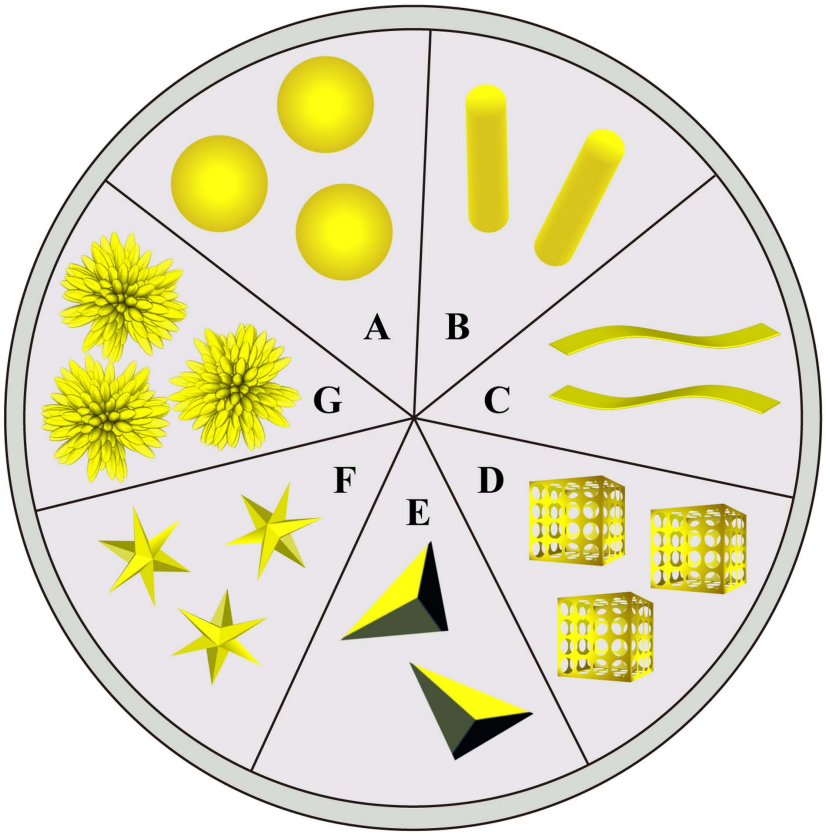

Figure 1. The different shapes of AuNPs. (A) Gold nanospheres. (B) Gold nanorods. (C) Gold nanoplates. (D) Gold nanocages. (E) Gold nanotriangles. (F) Gold nanostars. (G) Gold nanoflowers. AuNPs, gold nanoparticles.

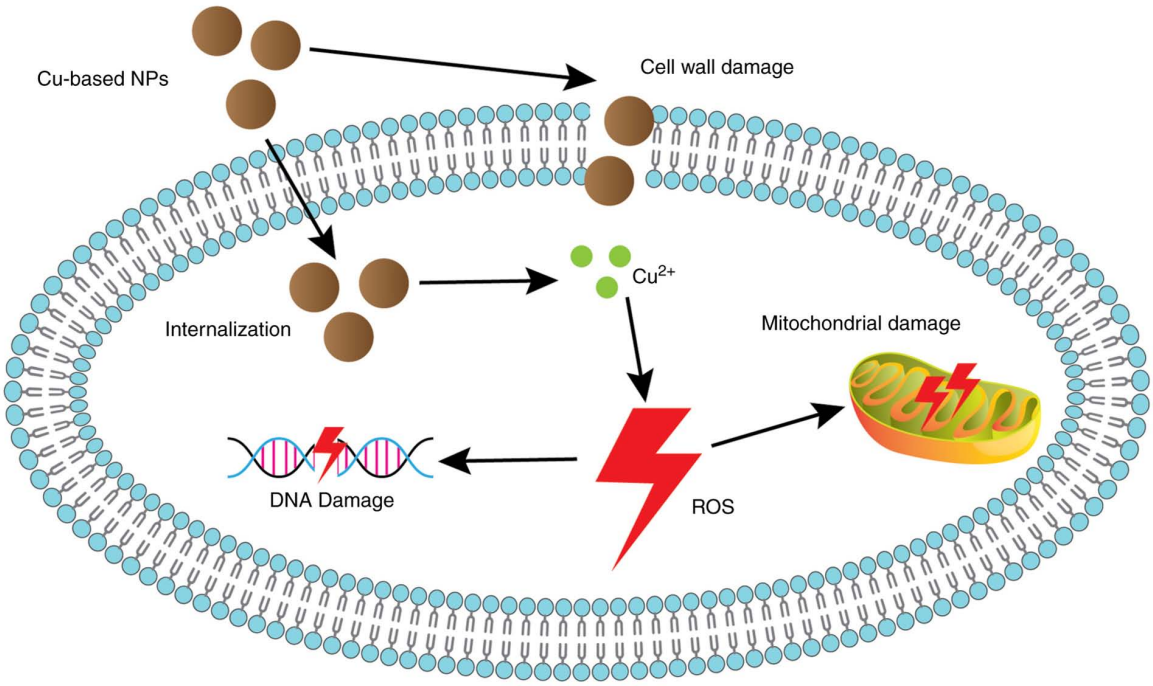

Figure 2. Antibacterial mechanism of Cu-based NPs. Cu-based NPs are capable of damaging the cell walls. At the same time, they are internalized in bacterial cells, releasing Cu^{2+}, leading to ROS accumulation and oxidative stress, which can damage mitochondria and DNA. Cu, copper; NPs, nanoparticles; ROS, reactive oxygen species.

facilitate high-density surface ligand attachment, making them suitable drug carriers for the controlled release of anticancer drugs during tumor treatment (43,44). In tumor therapy, CuS is a potential photothermal agent owing to its good photothermal

effect. Yuan *et al* (45) used CuS NPs as photothermal agents and found that encapsulated CuS NPs can be used for PTT combined with chemotherapy, achieving improved results in late-stage combined anticancer therapy *in vivo*.

However, the stable synthesis of CuNPs still remains challenging at present because Cu is easily oxidized. The rapid dissolution of nanodrugs may also involve the oxidation of CuO, which increases the toxicity of CuONPs.

Iron-based NPs. Owing to their magnetic properties, iron-based NPs have been broadly used in MRI, photodynamic therapy (PDT)/PTT combination therapy and immunotherapy (46). Iron-based NPs include FeNPs, iron oxide nanoparticles (IONPs) and iron-based bimetallic NPs, of which IONPs are the most widely used (47). IONPs are cheap to produce and are biocompatible (47). Their large surface area reduces the amount of drugs required and their toxic effects on cells (48). They are degraded into ferric ions *in vivo* and participate in physiological iron homeostasis. In addition, an *in vitro* study demonstrated the antagonistic effect of Fe_3O_4 NPs on ROS accumulation, indicating their ability to regulate oxidative stress and apoptosis (49,50). As ferromagnetic materials, IONPs can be surface-modified to obtain superparamagnetic iron oxide nanoparticles (SPIONs), ensuring uniform size and stability at the desired pH. In addition, elevated iron levels induce the Fenton reaction, which leads to an increase in ROS (51). When ROS production exceeds the cellular clearance capacity, it leads to lipid peroxidation and DNA damage, resulting in iron death, a mechanism that provides ideas for disease treatment (51). Since the upregulation of the dehydrogenase redox system in tumor cells affects lipid peroxidation, Chen *et al* (52) designed a layered double hydroxide nanoplatform co-loaded with the ferroptosis agent IONPs and the dehydrogenase inhibitor small interfering RNA (siR). Evidence from both *in vitro* and *in vivo* studies has confirmed that this platform synergistically induces cancer cell death by releasing IONPs and siR to enable the mass production of ROS while accelerating the accumulation of lipid peroxidation (52).

IONPs can generate excess ROS and disrupt biofilms, which opens up the possibility of antimicrobial therapy (53). In addition, IONPs can be used for tissue repair (54). SPIONs are capable of targeted drug delivery by binding to drugs and biomolecules, localizing them to target sites and releasing them through the action of a magnetic field.

IONPs can be used in PTT, PDT, hyperthermia therapy and tumor immunotherapy of tumors owing to their magnetic and superparamagnetic properties (55). In PTT, IONPs can act as photo-absorbents (56). IONPs may also be suitable as intensifiers for radiotherapy (57,58). In magnetic hyperthermia therapy, IONPs are exposed to an alternating magnetic field and produce a local heating effect, causing protein denaturation, cancer cell apoptosis and tissue damage through high temperatures >42˚C. IONPs used in hyperthermia therapy must be defined in terms of size and shape to obtain improved therapeutic effects (59). Magnetic hyperthermia therapy can also be used as a stimulating agent in tumor immunotherapy (60,61). IONPs are not only competent in transporting tumor-specific antigens to dendritic cells (DCs) and T cells, but also in treating tumors by inducing a shift in macrophage polarization toward the M1 type and increasing ROS production (62,63).

Nanoscale iron-based metal-organic frameworks (MOFs) play an important role in biomedical engineering because of the extensive porosity, surface area and chemical and thermal stability, as well as their good biocompatibility and biodegradability (64-66). Nanoscale iron-based MOFs are ideal for drug delivery systems because of their unique properties and their catalytic and redox activities make them suitable for use in biosensors and electrochemical sensors. This catalytic activity has been used in nano-catalytic medicine to generate ROS for cancer treatment. Using *in vitro* and *in vivo* studies, Yang *et al* (67) demonstrated that an iron-containing metal-organic framework [MOF(Fe)] nano-catalyst, acting as a peroxidase mimic, catalyzes the generation of highly oxidizing •OH radicals in cancer cells and amplifies oxidative damage in synergy with autophagy-inhibiting drugs. Iron metal-phenolic networks have a specific range of absorption peaks in the ultraviolet range and pH-responsiveness and can be efficiently dissociated to release drugs under acidic conditions (68). They are capable of functional modification and can undergo the Fenton reaction to induce ferroptosis. Luo *et al* (69) designed an integrated nanoplatform called FCS/GCS that takes advantage of the properties of metal-phenolic networks to enhance the anti-tumor effect; thus nanoconjugates are degraded and released in the acidic tumor microenvironment (TME) and the Fenton reaction can occur, which induces ferroptosis *in vitro and in vivo*.

3. Applications in cancer immunotherapy

Cancer vaccines. Cancer vaccines act against cancer by activating the innate cellular or humoral immune systems, with most vaccines triggering the proliferation of $CD8^+$ T cells that specifically identify and eliminate cancer cells (70,71). To date, three cancer vaccines have been approved by the United States Food and Drug Administration (FDA) (72). Cancer nanovaccines, whose antigens can be peptides, RNA, or DNA, are more flexible and may elicit more robust immune responses. The simplest cancer nanovaccine could be an antigen, an adjuvant, or even a heterogeneous antigen in NPs with adjuvant properties (73). Currently, both therapeutic and prophylactic vaccines against tumors are under investigation.

Metal ions are involved in several critical immune processes in organisms; therefore, the application of transition-metal NPs to tumor vaccines may promote effective immunomodulation (74,75). NPs are modified to possess surface properties similar to those of pathogens, thereby modulating the interaction of the vaccine with antigen-presenting cells (APCs) and enhancing antigen immunogenicity (76). In addition, NPs can increase the specificity of tumor vaccines and minimize harm to normal cells in comparison with conventional tumor vaccines. Transition-metal-based nanomaterials are often used as adjuvants and drug carriers in tumor nanovaccines.

A lack of adjuvants in vaccinations often results in weaker immune responses. Currently, Toll-like receptor (TLR) agonists and stimulator of interferon genes (STING) agonists are being studied as vaccine adjuvants (77,78). The human body has 10 different TLRs, which are distributed on the

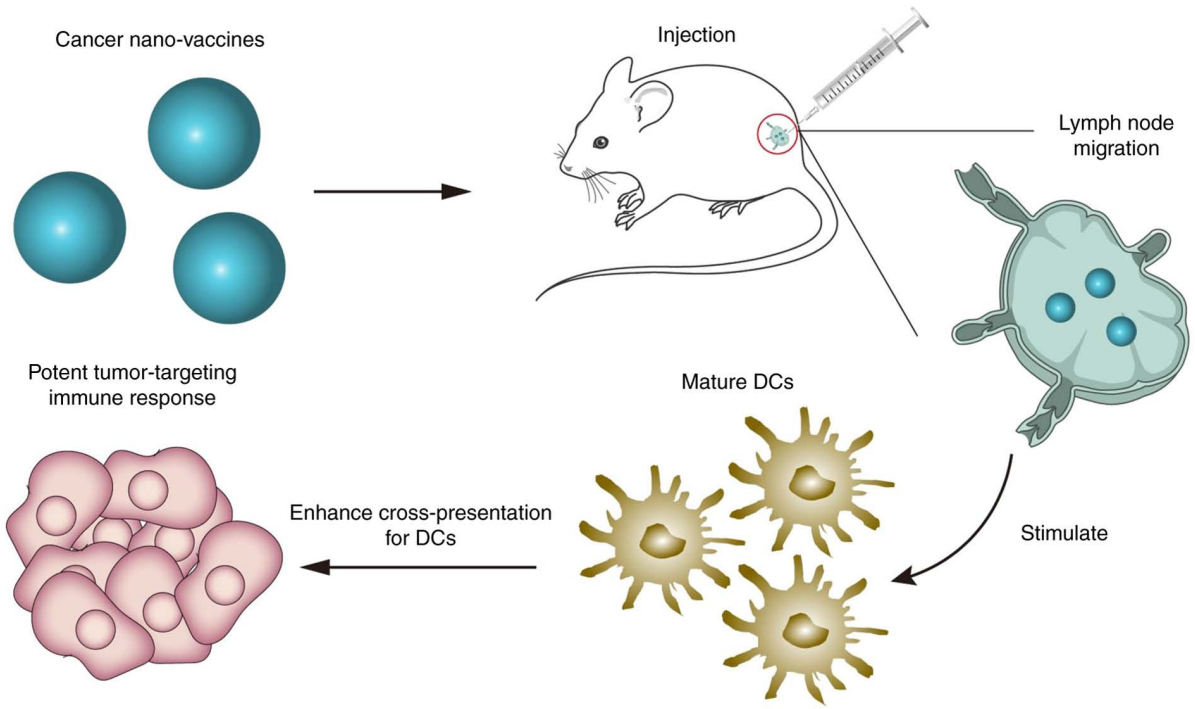

Figure 3. Schematic illustration of the synthesis and function of cancer vaccine formulation encapsulating OVA antigen. Upon administration, the nano-vaccine migrates to lymph nodes, promoting DC maturation and enhancing antigen cross-presentation. This process activates a durable anti-tumor T-cell immune response for protection against melanoma. OVA, ovalbumin; DCs, dendritic cells.

extracellular and endosomal membranes of immune cells and can induce the secretion of cytokines, chemokines and type I interferons, thereby activating the innate immune system and mediating the activation of acquired immune responses (79,80). Shinchi *et al* (80) took into account the high affinity of AuNPs for thiol-functionalized molecules, such as the TLR7 ligand and antigens and combined the small-molecule synthetic TLR7 ligand 2-methoxyethoxy-8-oxo-9-(4-carboxy benzyl)adenine (1V209) and α-mannose co-immobilized on the surface of AuNPs, which served as a potent adjuvant to enhance the activation of TLR7 on endosomal membranes. STING is a transmembrane protein integrated within the endoplasmic reticulum that activates type I interferons (81). The cyclic GMP-AMP synthase-STING pathway may act as an anti-tumor agent by inducing a proinflammatory response dominated by type I interferons, which may be a potential target for immunotherapy (82). Ding *et al* (83) designed a TME-responsive adjuvant called MnO_x nanospikes and prepared a vaccine using ovalbumin (OVA) proteins as antigens to suppress primary and distal tumor growth as well as tumor metastasis *in vitro* and *in vivo*. In addition, a number of other cytokines with immunostimulatory effects, such as IL-2, IL-1 and interferons, can be used as adjuvants. Granulocyte-macrophage colony-stimulating factor facilitates the attraction of DCs to the target site, promotes DC maturation and facilitates antigen presentation (84,85). Inorganic nanoadjuvants, which have been found to enable the sustained release of antigens and specifically increase the immune response, have also gained widespread interest (86). Wang *et al* (87) used human tubercle bacillus-loaded Zn- and Mg-tricalcium phosphates as adjuvants to boost the immune response and stimulate the secretion of granulocyte-macrophage colony-stimulating factor, which markedly inhibited the development of Lewis lung cancer cells *in vivo*.

Transition-metal NPs can modulate their size and shape to deliver antigens and adjuvants to specific tissues and have been used as delivery carriers for cancer nanovaccines (88,89). Vaccines that use AuNPs as carriers exhibit high immunostimulatory activity (90). Zhang *et al* (91) studied multilayer polyelectrolytic AuNPs with anionic poly I:C and antigenic peptides as nanocarriers, which could induce more antigen-specific $CD8^+$ T cells. Zhao *et al* (92) prepared a vaccine carrier containing Mn^{2+} ions and *meso*-2,6-diaminopimelic acid (DAP) to encapsulate the OVA antigen to form a cancer vaccine (Fig. 3). This vaccine could effectively co-deliver OVA and DAP to the lymph nodes, stimulate the maturation of DCs, enhance OVA cross-presentation to DCs and serve as a prophylactic vaccine for B16-OVA melanoma tumors *in vivo*.

Nanovaccines can also be integrated with other immunotherapies to enhance their efficacy (73). Jin *et al* (93) developed polyethyleneimine modified gold nanorods called GNRs-PEI. Subsequently, GNR-PEI/cyclic dimeric guanosine monophosphate-adenosine monophosphate-laden macrophages (GPc-RAWs) were injected into the tumor with simultaneous introduction of a programmed cell death ligand 1 (PD-L1) antibody. This strategy inhibits tumor growth and metastasis through a combination of tumor vaccines and checkpoint inhibitors *in vivo*. Chen *et al* (94) assembled an iron nano-adjuvant containing IONPs and STING agonists that activated STING while forming a vaccine with OVA antigens to induce long-lasting anti-tumor immunity and prevent postoperative recurrence and distant metastasis *in vivo* by synergistic treatment with checkpoint inhibitors.

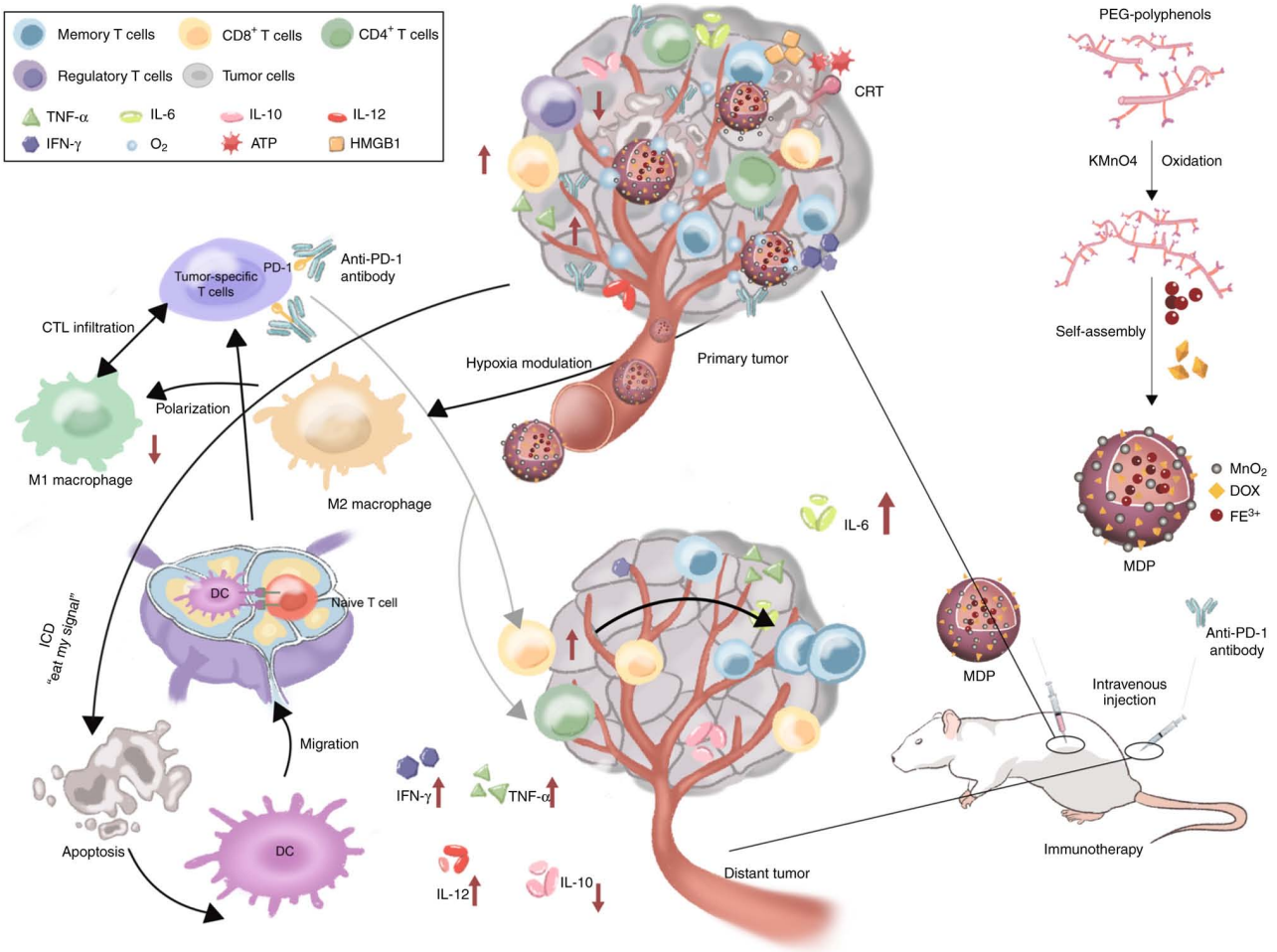

Figure 4. Mechanism of MDP NPs-induced immunogenic cell death synergizing with anti-PD-1 therapy for tumor suppression. This schematic illustration depicts a phenolic immunogenic cell death nano-inducer designed to sensitize tumors to anti-PD-1 checkpoint blockade immunotherapy and its underlying immune mechanisms. It first presents the self-assembly process forming MDP NPs. Subsequently, a mouse bilateral tumor model demonstrates the evaluation of these NPs combined with PD-1 blockade for tumor inhibition and elucidates their immune mechanisms. MDP NPs, metal-doxorubicin-phenolic nanoparticles; PD-L1, programmed cell death ligand 1; NPs, nanoparticles; PEG, polyethylene glycol; DOX, doxorubicin; CTL, cytotoxic T lymphocyte; DC, dendritic cell; ICD, immunogenic cell death.

Immune checkpoint inhibitors. Cancer immunotherapies promote immune system specificity against cancer. The blockade of immune checkpoint programmed death receptor-1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) removes immune suppression, enabling tumor clearance (95).

Nanometallic materials have become a hotspot in research on checkpoint blockade immunotherapy. Hybrid nanometallic frameworks function as immunogenic cell death (ICD) inducers, enhancing tumor sensitivity to immunotherapy. Researchers have developed a phenolic ICD inducer to improve antigen generation, tumor-specific T-cell infiltration and PD-1 checkpoint blockade, stimulating anti-tumor immunity and generating significant abscopal effects on distant tumors *in vivo* (Fig. 4) (96). Moreover, Sang *et al* (97) developed metal-phenolic network nanopumps to overcome resistance to combined radiotherapy/anti-CTLA-4 immunotherapy. Evidence from both *in vitro* and *in vivo* studies confirmed that these NPs enhanced RT efficacy, alleviated hypoxia/induced apoptosis, suppressed therapy-induced PD-L1 upregulation, effectively reversed T-cell exhaustion and enabled immunotherapy for immunologically non-responsive tumors (Fig. 5).

Immune checkpoint agonist antibodies. Immune cells are stimulated by exogenous antigens to avoid autoimmunity and tissue damage through regulation of costimulatory and co-suppressive receptors, that is, the regulation of immune checkpoints (98). Evidence support the important role of the costimulatory pathway in mediating anti-cancer immunity. The targets of immune agonist antibodies are mainly the B7-CD28 and tumor necrosis factor receptor (TNFR) families (98,99).

Typical costimulatory receptors of the B7-CD28 family are CD28 and inducible T-cell costimulator (ICOS). CD28 activates downstream signaling after adhering to the ligands CD80 and CD86, driving T-cell function, proliferation and survival (100). ICOS responds to ICOS ligands to activate T cells and memory T cells. Thus, CD28 and ICOS are potential targets for the development of therapeutic agonists for tumor treatment (101,102). Chiang *et al* (103) reported an inherently therapeutic fucoidan-dextran-based magnetic nanomedicine (IO@FuDex^3) combined with a checkpoint inhibitor and T-cell activators, demonstrating *in vivo* that combining IONPs with anti-PD-L1 and agonist antibodies enhances the efficacy of immunotherapy.

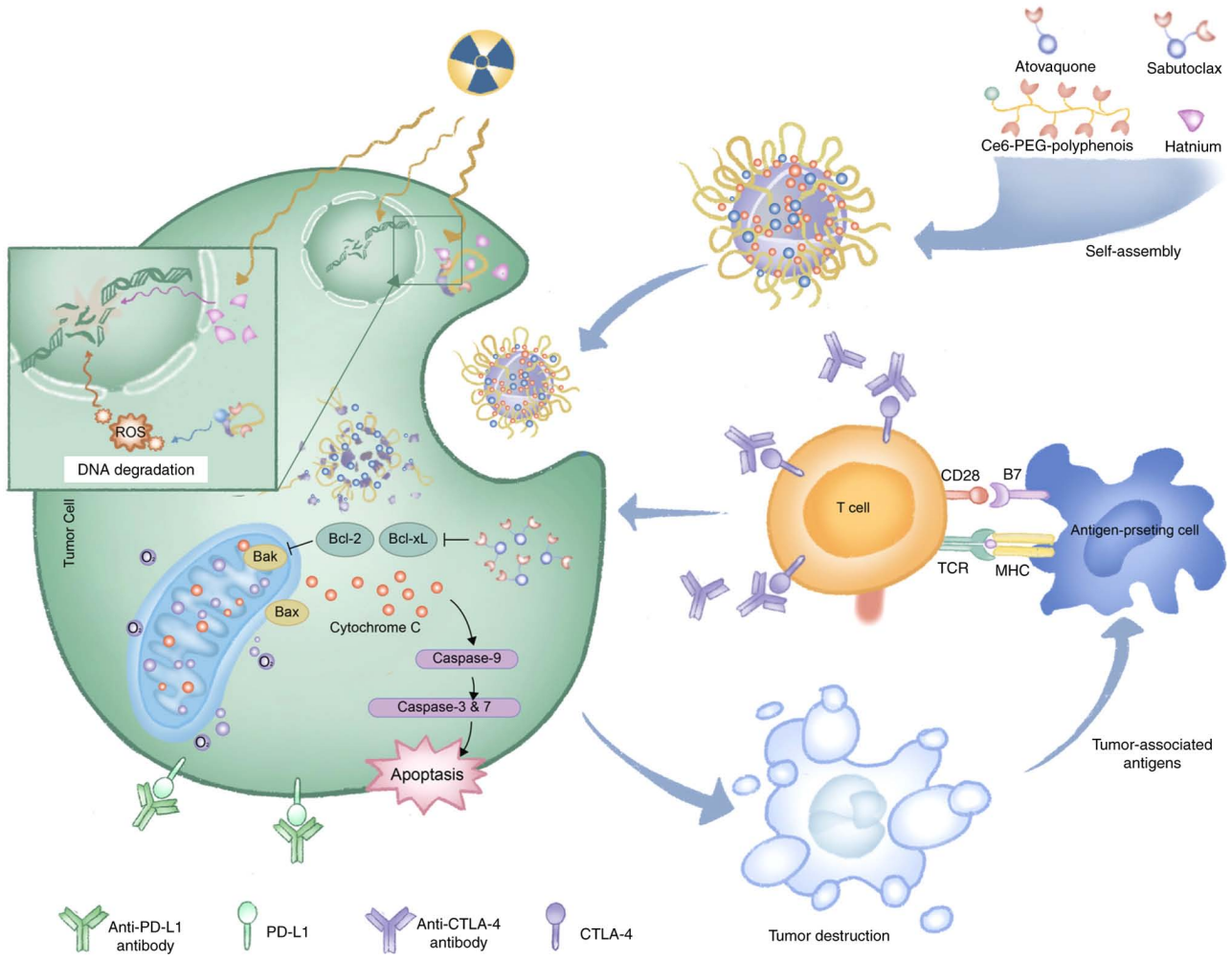

Figure 5. Mechanism of triple-kill tumor eradication synergized with immunotherapy via metal-phenolic network nanopumps (AHSC NPs). This schematic illustrates the preparation of AHSC NPs and their triple therapeutic strategy for tumor eradication. The nanopumps were synthesized via the self-assembly of Hf coordinated with Ce6-PEG-polyphenols, atovaquone and sabutoclax. Within this system, Hf acts as a radiosensitizer to enhance radiation efficacy; the photosensitizer Ce6 conjugated to PEG is activated by the inelastic scattering of photoelectrons generated from X-ray energy transferred by Hf, thereby boosting ROS production; sabutoclax targets the apoptotic signaling pathway to promote the activation of downstream apoptotic proteins, increasing tumor cell death; and atovaquone regulates mitochondrial function to liberate more oxygen within the tumor microenvironment, which is crucial for alleviating radioresistance. Furthermore, the strategy incorporates two antibodies (anti-CTLA-4 and anti-PD-L1) to trigger a potent immune response at the tumor site, enabling immune recognition while suppressing PD-L1 expression on tumor cells, thereby amplifying therapeutic efficacy. Notably, tumor-associated antigens can be internalized by receptors on APCs, invoking a robust immune response. AHSC NPs, atovaquone-hafnium-sabutoclax-Ce6 nanoparticles; Hf, hafnium; PEG, polyethylene glycol; ROS, reactive oxygen species; CTLA-4, cytotoxic T lymphocyte antigen-4; PD-L1, programmed cell death ligand 1; APCs, antigen-presenting cells; TCR, T cell receptor; MHC, major histocompatibility complex.

The TNFR superfamily influences the maturation and differentiation of B and T lymphocytes and is involved in physiological processes such as apoptosis, inflammation and autoimmunity (104). Six receptors have been suggested to play major roles as immune costimulators, namely, CD40, OX40, 4-1BB, CD27, GITR and CD30 (98). Among them, agonistic CD40 monoclonal antibody activates host APCs, especially DCs, thus inducing anti-tumor T-cell responses, which are considered promising for research (105).

Although nanomedicines targeting TNFR have been investigated, nanomedicines based on transition-metal NPs targeting TNFR are still lacking (106). Overall, the use of immune checkpoint agonist antibodies incorporating transition-metal NPs remains an area that requires further exploration.

Adoptive cell therapy (ACT). ACT is a form of treatment in which T cells are isolated from plasma or tumor samples, expanded and activated *in vitro*, conditioned and modified and injected back into the patient to activate the immune system and suppress cancer (107-109). This method is based on the principle of engineering T cells is to create T cells with tumor-targeting structural domains, which enhances the specificity of T-cell recognition in tumors (110,111). Due to the complexity and expense of the natural activation process of T cells, the primary focus of current research is the use of artificial antigen-presenting cells (aAPCs), which mimic the function of APCs, to stimulate T cells to initiate tumor-specific adaptive immunity (112). Nanoscale aAPCs have been developed owing to their small size, low toxicity and low-dose requirements (113,114).

The preservation and expansion of therapeutic cells *in vitro* during ACT often results in low cell viability. Youn *et al* (115) proposed a cell-in-shell strategy using TiO_2 shells to protect Jurkat cells and improve their viability *in vitro*. The authors formulated Jurkat@TiO_2 to allow CD3 and other

antigens on the cell surface to remain accessible to antibodies without impeding IL-2 secretion. Some transition-metal nanomaterials can serve as nanoprobes to track adoptive immune cells and reveal their therapeutic mechanisms. Nie *et al* (116) conjugated magnetic nanoclusters based on superparamagnetic IONPs on the surface of adoptive T cells and tracked them using MRI after infusing them back into mice. The key to ACT anti-tumor activity is tumor tropism; however, the complex barrier of tumor tissue and multiple oncogenic factors in the TME affect the infiltration and action of therapeutic cells (117,118). To address this situation, Lin *et al* (119) developed a nano-immunomodulator AuNSP@αCD16, which partially disrupts the tumor's physical barrier, remodels the TME and modifies the tumor surface with the CD16 antibody through slight photothermal intervention, thus achieving strong natural killer cell activation by CD16-mediated antibody-dependent cellular cytotoxicity *in vitro and in vivo*. This strategy demonstrates the possibility of using nanoimmunomodulators to reconstitute the ACT-favorable TME (119).

4. Combination therapies

PTT. PTT, which induces localized thermotherapy, is one of the few NP-based therapies to enter clinical trials for cancer and is expected to be applied synergistically with immunotherapy in tumor treatment (120,121). Paholak *et al* (122) demonstrated that PTT mediated by highly crystalline IONPs efficiently eliminated breast cancer stem cells in a transformed model of triple-negative breast cancer, thereby improving the long-term survival of patients with metastatic breast cancer by inducing a systemic immune response targeting distal cancer cells.

Nanoenzyme-based catalytic therapy is a novel strategy for treating tumors; however, challenges such as hypoxia, immunosuppression and insufficient endogenous H_2O_2 levels in the TME limit the efficacy of this strategy. Researchers have developed a trimetallic nanoenzyme (Au@Pt@Rh) that exhibits endogenous peroxidase- and catalase-like activities under acidic TME conditions. Au@Pt@Rh-activated photothermal thermotherapy has also been shown to improve peroxidase- and catalase-mimicking activity. By loading the transforming growth factor-β inhibitor LY2157299, this nanocomplex successfully reprogrammed the immunosuppressive TME, alleviated tumor hypoxia and generated highly toxic hydroxyl radicals (•OH) (123).

Although PTT combined with immunotherapy shows potential for tumor treatment, the toxicity of NPs and possible damage to normal tissues from high temperatures and prolonged irradiation remain to be addressed. Furthermore, considering the effects of different temperatures on immune cells, the design of specific strategies to maximize the effects of PTT and immunotherapy requires further exploration.

PDT. PDT can induce an immune response and destroy tumor tissues. PDT-mediated immunotherapy is a promising therapeutic modality used to treat cancer. Duan *et al* developed Zn-pyrophosphate NPs loaded with photosensitizer thermolipids (ZnP@pyro) and found that ZnP@pyro PDT combined with anti-PD-L1 therapy eradicated primary breast tumors and generated systemic tumor-specific cytotoxic T-cell responses to completely suppress distant tumors. These results showed that NP-mediated PDT can enhance immunotherapy by activating the innate and adaptive immune systems in the TME (124). Nevertheless, insufficient light-penetration depth remains an unresolved limitation of PDT, posing a challenge to the clinical translation of PDT and immune combination therapies.

Radiotherapy. Radiotherapy causes ionizing damage to tumor tissue in an X-ray dose-dependent manner, with the maximum radiation dose defined as the dose that causes no damage to adjacent normal tissue (125). High-dose hyperfractionated radiotherapy and radiotherapy sensitizers have been investigated to enhance checkpoint blockade immunotherapy (126). Ni *et al* (127) reported two porous Hf-based nMOFs that act as effective radioenhancers. More importantly, *in vitro* and *in vivo* studies showed that these nMOFs are capable of mediating low-dose radiotherapy in combination with anti-PD-L1 treatment, which simultaneously treats both local and distant tumors through a distant effect. Nevertheless, further studies should explore these nMOFs in relation to their therapeutic efficacy, toxic response and drug design in terms of clinical transformation.

Chemotherapy. Conventional chemotherapy combined with metallic nanomaterials is expected to synergistically inhibit tumor progression, metastasis and recurrence. Xu *et al* (128) reported synergistic immunotherapy for triple-negative breast cancer on the basis of the premise of stimulating and promoting an ICD response using a transformable NP that simultaneously delivered cisplatin, adjudin and WKYMVm. The *in vitro* and *in vivo* results showed that the NP could markedly inhibit primary tumor growth and lung metastasis and enhance innate and adaptive anti-tumor immunity, resulting in significant survival benefits.

Through both *in vitro* and *in vivo* studies, Liu *et al* (129) designed a dual pH-responsive multifunctional nanoparticle system, HA-DOX/PHIS/R848, which enabled the targeting of immune and cancer cells by delivering R848 and DOX to the TME and breast cancer cells, thus enabling the combined treatment of immunotherapy and chemotherapy.

5. Clinical transformation and challenges

To date, among transition-metal NPs, drugs that have received FDA approval are mainly iron-based NPs, including INFed, Dexferrum, Venofer, Feraheme, Injectafer, Monoferric, Feridex and Ferrlecit (130,131). The main applications of these iron-based NPs are in the treatment of iron-deficient anemia and imaging (132). Nanotherm® is an FDA-approved device with a SPION formulation that causes apoptosis in cancer cells heated in a high-frequency magnetic field (133). However, most transition-metal NPs are not used clinically.

Clinical studies employing transition-metal NPs as a therapeutic option for oncology patients have focused on modalities such as chemotherapy and hyperthermia. Khoobchandani *et al* (134) applied AuNP-based Nano Swarna Bhasma to patients with stage IIIA or IIIB breast cancer and found that the treatment group that received the nanomedicine showed 100% clinical benefit in comparison with the group that received standard of care treatment.

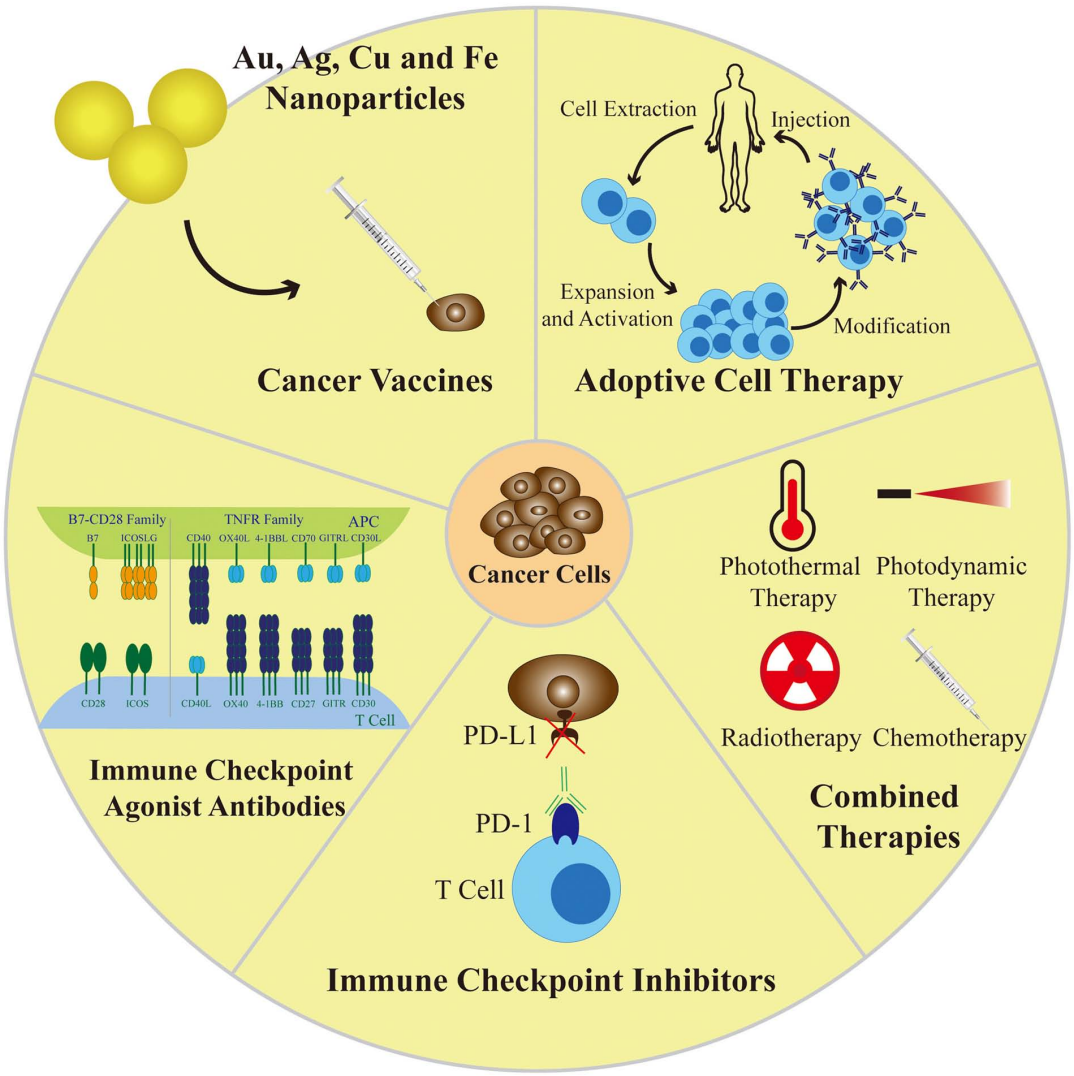

Figure 6. Graphical summary of the present review. Au, gold; Ag, silver; Cu, copper; Fe, iron; PD-L1, programmed cell death ligand 1; PD-1, programmed death receptor-1; TNFR, tumor necrosis factor receptor; APC, antigen-presenting cell; ICOS, inducible T-cell costimulator; ICOSLG, inducible T-cell costimulator ligand.

Kumthekar *et al* (135) employed brain-penetrant RNA interference-based spherical nucleic acid-containing AuNPs; they observed no treatment-related grade 4 or 5 toxicity after administration, while the presence of gold accumulation in tumor-associated endothelial, macrophage and cancer cells represented a potential strategy for the systemic treatment of glioblastoma. In addition, drugs such as AuroLase and Magnablate have been used in clinical trials for thermal ablation of cancer (132).

Cancer immunotherapy has a promising future, in which NPs have been tested in clinical trials related to cancer vaccines and immune checkpoint inhibitors (ICIs). Rojas *et al* (136) developed mRNA neoantigen vaccines in real time from surgically removed pancreatic ductal adenocarcinoma tumors using uridine mRNA-lipoplex NPs. After an 18-month follow-up period, patients who had T cells expanded by the vaccine exhibited a longer median relapse-free survival than those who did not have vaccine-expanded T cells. Alonso *et al* (137) selected non-muscle invasive bladder cancer patients who were unresponsive to *Bacillus Calmette-Guérin* and applied OncoTherad® nanomedicine for treatment and found that it works by binding the TLR4 to activate the innate immune system and reduce immune checkpoint molecules. In addition, Zhang *et al* (138) found that ICIs combined with nanomedicine chemotherapy inhibited the progression of esophageal squamous cell carcinoma.

Overall, most studies on cancer immunotherapy using transition-metal NPs are in the preclinical stage and lack data from clinical trials. The reasons for this worrisome state of clinical transformation warrant further investigation. Immunotherapy is affected by multiple factors such as off-target toxicity, tissue heterogeneity, poor immune response durability and adverse effects; often, only a limited number of patients respond satisfactorily to immunotherapy (74). In addition, transition-metal NPs face a number of challenges in drug delivery, release and biodistribution and these factors directly determine their efficacy in cancer treatment. Different routes of drug delivery are associated with various biological barriers (139). Local delivery is more direct; however, its invasiveness may pose other problems and local delivery is limited by the site and

Table I. Summary of transition metallic nanoparticles: Biomedical applications, preclinical/clinical studies and commercial examples.

Nanoparticle	Biomedical application	Preclinical studies	Clinical studies	Commercial use	(Refs.)
AuNPs	Imaging (MRI, CT); drug delivery; antibacterial; cancer vaccine carrier; PTT	CT imaging cancer therapy; peptide vaccine carriers; induce antigen-specific CD8+ T cells	Nano Swarna Bhasma for stage IIIA or IIIB breast cancer; AuroLase for thermal ablation for cancer	NA	(14,15,17,91,134, 135,154)
AgNPs	Antibiotics; sensors; anticancer applications	Induce apoptosis via ROS and DNA damage; inhibit tumor cell migration and invasion	NA	NA	(28-34)
Copper-based NPs	Antimicrobial; anticancer applications; drug carrier; PTT agent	Sulfobetaine-stabilized Cu(I) oxide NPs for cancer cell growth suppression; CuS NPs for PTT combined with chemotherapy	NA	NA	(14,39-45)
Iron-based NPs	MRI; PTT; PDT; hyperthermia; immunotherapy; drug delivery; antimicrobial; tissue repair	Induce macrophage polarization to M1; enhance STING activation; used in magnetic hyperthermia; synergize with checkpoint inhibitors	Magnablate for thermal ablation for cancer	Nanotherm® for glioblastoma	(60,61,63,94,132, 133,155-158)

Au, gold; NPs, nanoparticles; Ag, silver; MRI, magnetic resonance imaging; CT, computed tomography; PDT, photodynamic therapy; PTT, photothermal therapy; ROS, reactive oxygen species; STING, stimulator of interferon genes; NA, not available.

type of cancer (140). Although systemic drug delivery is more commonly used, it is influenced by a more complex set of factors. During circulation, the NPs may be destabilized by shear stress (141). Another challenge is the absorption of NPs by the phagocytic cells in the reticuloendothelial system (142). Different portals of entry often allow NPs to target different cell populations and factors such as the size, shape, charge and surface coating of transition-metal NPs affect their biodistribution *in vivo* (89). The molecular mechanisms and interactions between transition-metal NPs and biological systems require further study. The heterogeneity of the TME and enhanced permeability and retention in the human body lead to reduced penetration of NPs and inhomogeneous tumor extravasation of NPs, thus reducing their accumulation in the tumor.

The safety of transition-metal NPs in cancer diagnosis and therapy is an important issue. Although previous studies have demonstrated that transition-metal NPs can promote anti-tumor immune responses *in vivo* (63), these materials have potential safety risks. Immune responses to transition-metal NPs can also cause inflammation and tissue damage (143,144). NPs can elicit allergic reactions, limiting the feasibility and safety of repeated administration (145). Oxidative stress due to ROS imbalance is also a problem owing to the unique ability of Cu-based NPs to generate ROS. In addition, long-term accumulation of metal ions may lead to organ damage. Therefore, future research should systematically evaluate both the short-term immune responses and long-term toxicity of these nanomaterials.

6. Conclusions and prospects

The present review critically analyzed the existing applications and future potential of major transition-metal NPs in cancer immunotherapy and a brief graphical summary of the review is provided in Fig. 6. It began with a detailed overview of the classification, properties, biomedical roles and toxicity of major transition-metal NPs. The applications of transition-metal NPs in tumor immunotherapies, including cancer vaccines, ICIs, immune checkpoint agonist antibodies, ACT and combination therapies, were then introduced. Finally, the current status and challenges associated with clinical transformation were discussed to provide ideas for subsequent clinical studies. To provide a consolidated overview of biomedical applications, current cancer research status and clinical transformation progress, Table I presents a comparative summary of transition metal NPs.

Transition-metal NPs can provide new insights into cancer immunotherapy (76). However, the relationship between these NPs and the biological effects of immunotherapy

requires exploration. The adoption of less toxic biosynthesis methods for NPs and selection of different metal elements are undoubtedly important (146). In addition, the toxicity of NPs, the resulting immune response, stability and biodistribution are all influenced by their physicochemical properties (140). Therefore, the size, shape, charge, mode of administration, dose and surface modification of NPs must be carefully selected. For example, small-sized nanomedicines are more suitable for cell-targeted drug delivery; low-concentration administration can prevent agglomeration; and rod-shaped NPs are more likely to penetrate tumors (147-149). Since positively charged NPs tend to be more readily cleared, the surface charge of nanomedicines should also be considered during formulation design (150). In addition, surface modifications, such as coating with polyethylene glycol and cell membranes, can reduce interactions with phagocytes. Modulation of temperature, pH and biodegradability of NPs can control the release of nanodrugs. This range of modifiable properties of transition-metal NPs may provide a direction for their development in specific cancer immunotherapies. To further translate tunable physicochemical properties into reliable immunotherapeutic strategies, the molecular mechanisms of NPs must be investigated in depth. Current evidence indicates that metal NPs can induce ICD in immunogenic cells, enhancing DC-mediated cross-presentation and potentiating synergistic anti-tumor effects with ICIs (151). IONPs can polarize macrophages toward the M1 phenotype by reprogramming the TME (152). These established molecular mechanisms provide a theoretical rationale for the application and clinical transformation of transition metallic materials in cancer immunotherapy.

In conclusion, the efficacy and safety of transition-metal NPs remain obstacles to clinical research (153). Further research regarding the design of NPs and their interactions *in vivo* is required to improve specificity. Personalization of therapy for different patient groups remains a challenge for clinical transformation. In the future, systematic immunogenicity testing combined with long-term clinical follow-up is recommended to comprehensively evaluate the safety of metal-based materials. Emerging technologies, such as single-cell transcriptomics and spatial omics, may provide critical insights outlining how nanoparticles reshape immune cell lineages and functions within the TME, yielding a deeper mechanistic understanding. In addition, the development of scalable manufacturing processes, demonstration of batch-to-batch consistency and establishment of standardized clinical-grade production workflows are essential steps toward successful clinical translation. Transition-metal immunotherapy is still in its infancy and much work remains to be conducted to make the application of transition NPs in tumor immunotherapy a reality.

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Availability of data and materials

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Authors' contributions

CS and YH were responsible for conceptualization. ZD, ZC and CF were responsible for investigation. CF and YH were responsible for project administration. CS and YH were responsible for supervision. ZD and ZC were responsible for visualization. ZD and ZC were responsible for writing the original draft. ZD, ZC, DX, LX, CF, CS and YH were responsible for writing, reviewing and editing. CS made a significant contribution to the manuscript revision. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zhang Y and Zhang Z: The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol 17: 807-821, 2020.
2. Parreno V, Loubiere V, Schuettengruber B, Fritsch L, Rawal CC, Erokhin M, Győrffy B, Normanno D, Di Stefano M, Moreaux J, *et al*: Transient loss of Polycomb components induces an epigenetic cancer fate. Nature 629: 688-696, 2024.
3. Chong G, Zang J, Han Y, Su R, Weeranoppanant N, Dong H and Li Y: Bioengineering of nano metal-organic frameworks for cancer immunotherapy. Nano Res 14: 1244-1259, 2021.
4. Surendran SP, Moon MJ, Park R and Jeong YY: Bioactive Nanoparticles for cancer immunotherapy. Int J Mol Sci 19: 3877, 2018.
5. Bertrand N, Wu J, Xu X, Kamaly N and Farokhzad OC: Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology. Adv Drug Deliv Rev 66: 2-25, 2014.
6. Shi J, Kantoff PW, Wooster R and Farokhzad OC: Cancer nanomedicine: Progress, challenges and opportunities. Nat Rev Cancer 17: 20-37, 2017.
7. Zheng X, Wu Y, Zuo H, Chen W and Wang K: Metal nanoparticles as novel agents for lung cancer diagnosis and therapy. Small 19: e2206624, 2023.

8. Zhao W, Li A, Zhang A, Zheng Y and Liu J: Recent advances in functional-polymer-decorated transition-metal nanomaterials for bioimaging and cancer therapy. ChemMedChem 13: 2134-2149, 2018.
9. Yang J and Zhang C: Regulation of cancer-immunity cycle and tumor microenvironment by nanobiomaterials to enhance tumor immunotherapy. Wiley Interdiscip Rev Nanomed Nanobiotechnol 12: e1612, 2020.
10. Liu W, Song X, Jiang Q, Guo W, Liu J, Chu X and Lei Z: Transition metal oxide nanomaterials: New weapons to boost anti-tumor immunity cycle. Nanomaterials (Basel) 14: 1064, 2024.
11. Daniel MC and Astruc D: Gold nanoparticles: Assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology. Chem Rev 104: 293-346, 2004.
12. Lee KX, Shameli K, Yew YP, Teow SY, Jahangirian H, Rafiee-Moghaddam R and Webster TJ: Recent developments in the facile bio-synthesis of gold nanoparticles (AuNPs) and their biomedical applications. Int J Nanomed 15: 275-300, 2020.
13. Hemalatha T, Prabu P, Gunadharini DN and Gowthaman MK: Fabrication and characterization of dual acting oleyl chitosan functionalised iron oxide/gold hybrid nanoparticles for MRI and CT imaging. Int J Biol Macromol 112: 250-257, 2018.
14. Singh P, Pandit S, Mokkapati VRSS, Garg A, Ravikumar V and Mijakovic I: Gold nanoparticles in diagnostics and therapeutics for human cancer. Int J Mol Sci 19: 1979, 2018.
15. Wang R, Deng J, He D, Yang E, Yang W, Shi D, Jiang Y, Qiu Z, Webster TJ and Shen Y: PEGylated hollow gold nanoparticles for combined X-ray radiation and photothermal therapy in vitro and enhanced CT imaging in vivo. Nanomedicine 16: 195-205, 2019.
16. Karthika V, Arumugam A, Gopinath K, Kaleeswarran P, Govindarajan M, Alharbi NS, Kadaikunnan S, Khaled JM and Benelli G: Guazuma ulmifolia bark-synthesized Ag, Au and Ag/Au alloy nanoparticles: Photocatalytic potential, DNA/protein interactions, anticancer activity and toxicity against 14 species of microbial pathogens. J Photochem Photobiol, B 167: 189-199, 2017.
17. Bankar A, Joshi B, Kumar AR and Zinjarde S: Banana peel extract mediated synthesis of gold nanoparticles. Colloids Surf, B Biointerfaces 80: 45-50, 2010.
18. Kumar CG, Poornachandra Y and Mamidyala SK: Green synthesis of bacterial gold nanoparticles conjugated to resveratrol as delivery vehicles. Colloids Surf, B Biointerfaces 123: 311-317, 2014.
19. Cheng J, Gu YJ, Cheng SH and Wong WT: Surface functionalized gold nanoparticles for drug delivery. J Biomed Nanotechnol 9: 1362-1369, 2013.
20. Li W, Cao Z, Liu R, Liu L, Li H, Li X, Chen Y, Lu C and Liu Y: AuNPs as an important inorganic nanoparticle applied in drug carrier systems. Artif Cells Nanomed Biotechnol 47: 4222-4233, 2019.
21. Kim DY, Kim M, Shinde S, Sung JS and Ghodake G: Cytotoxicity and antibacterial assessment of gallic acid capped gold nanoparticles. Colloids Surf, B Biointerfaces 149: 162-167, 2017.
22. Lee KD, Nagajyothi PC, Sreekanth TVM and Park S: Eco-friendly synthesis of gold nanoparticles (AuNPs) using *Inonotus obliquus* and their antibacterial, antioxidant and cytotoxic activities. J Ind Eng Chem 26: 67-72, 2015.
23. Naraginti S and Li Y: Preliminary investigation of catalytic, antioxidant, anticancer and bactericidal activity of green synthesized silver and gold nanoparticles using Actinidia deliciosa. J Photochem Photobiol, B 170: 225-234, 2017.
24. Vijayakumar S, Vaseeharan B, Malaikozhundan B, Gopi N, Ekambaram P, Pachaiappan R, Velusamy P, Murugan K, Benelli G, Suresh Kumar R and Suriyanarayanamoorthy M: Therapeutic effects of gold nanoparticles synthesized using Musa paradisiaca peel extract against multiple antibiotic resistant Enterococcus faecalis biofilms and human lung cancer cells (A549). Microb Pathogen 102: 173-183, 2017.
25. Mironava T, Hadjiargyrou M, Simon M, Jurukovski V and Rafailovich MH: Gold nanoparticles cellular toxicity and recovery: Effect of size, concentration and exposure time. Nanotoxicology 4: 120-137, 2010.
26. Ziyu P and Haodong J: Controlled synthesis of silver nanomaterials and their environmental applications. Prog Chem 35: 1229-1257, 2023.
27. Huy TQ, Huyen PTM, Le AT and Tonezzer M: Recent advances of silver nanoparticles in cancer diagnosis and treatment. Anticancer Agents Med Chem 20: 1276-1287, 2020.
28. Mohamed AF, Nasr M, Amer ME, Abuamara TMM, Abd-Elhay WM, Kaabo HF, Matar EER, El Moselhy LE, Gomah TA, Deban MAE and Shebl RI: Anticancer and antibacterial potentials induced post short-term exposure to electromagnetic field and silver nanoparticles and related pathological and genetic alterations: In vitro study. Infect Agent Cancer 17: 4, 2022.
29. Yuan YG, Zhang S, Hwang JY and Kong IK: Silver Nanoparticles potentiates cytotoxicity and apoptotic potential of camptothecin in human cervical cancer cells. Oxid Med Cell Longev 2018: 6121328, 2018.
30. Jeong JK, Gurunathan S, Kang MH, Han JW, Das J, Choi YJ, Kwon DN, Cho SG, Park C, Seo HG, *et al*: Hypoxia-mediated autophagic flux inhibits silver nanoparticle-triggered apoptosis in human lung cancer cells. Sci Rep 6: 21688, 2016.
31. Yin M, Xu X, Han H, Dai J, Sun R, Yang L, Xie J and Wang Y: Preparation of triangular silver nanoparticles and their biological effects in the treatment of ovarian cancer. J Ovarian Res 15: 121, 2022.
32. Noorbazargan H, Amintehrani S, Dolatabadi A, Mashayekhi A, Khayam N, Moulavi P, Naghizadeh M, Mirzaie A, Mirzaei Rad F and Kavousi M: Anti-cancer & anti-metastasis properties of bioorganic-capped silver nanoparticles fabricated from Juniperus chinensis extract against lung cancer cells. AMB Express 11: 61, 2021.
33. Lu W and Kang Y: Epithelial-mesenchymal plasticity in cancer progression and metastasis. Dev Cell 49: 361-374, 2019.
34. Meenakshisundaram S, Krishnamoorthy V, Jagadeesan Y, Vilwanathan R and Balaiah A: Annona muricata assisted biogenic synthesis of silver nanoparticles regulates cell cycle arrest in NSCLC cell lines. Bioorg Chem 95: 103451, 2020.
35. Miranda RR, Sampaio I and Zucolotto V: Exploring silver nanoparticles for cancer therapy and diagnosis. Colloids Surf B Biointerfaces 210: 112254, 2022.
36. Jia B, Mei Y, Cheng L, Zhou J and Zhang L: Preparation of copper nanoparticles coated cellulose films with antibacterial properties through one-step reduction. ACS Appl Mater Interfaces 4: 2897-2902, 2012.
37. Luque-Jacobo CM, Cespedes-Loayza AL, Echegaray-Ugarte TS, Cruz-Loayza JL, Cruz I, de Carvalho JC and Goyzueta-Mamani LD: Biogenic synthesis of copper nanoparticles: A systematic review of their features and main applications. Molecules 28: 4838, 2023.
38. Smith AM, Duan H, Rhyner MN, Ruan G and Nie S: A systematic examination of surface coatings on the optical and chemical properties of semiconductor quantum dots. Phys Chem Chem Phys 8: 3895-3903, 2006.
39. Letchumanan D, Sok SPM, Ibrahim S, Nagoor NH and Arshad NM: Plant-based biosynthesis of copper/copper oxide nanoparticles: An update on their applications in biomedicine, mechanisms, and toxicity. Biomolecules 11: 564, 2021.
40. Rehana D, Mahendiran D, Kumar RS and Rahiman AK: Evaluation of antioxidant and anticancer activity of copper oxide nanoparticles synthesized using medicinally important plant extracts. Biomed Pharmacother 89: 1067-1077, 2017.
41. Mahmood RI, Kadhim AA, Ibraheem S, Albukhaty S, Mohammed-Salih HS, Abbas RH, Jabir MS, Mohammed MKA, Nayef UM, AlMalki FA, *et al*: Biosynthesis of copper oxide nanoparticles mediated Annona muricata as cytotoxic and apoptosis inducer factor in breast cancer cell lines. Sci Rep 12: 16165, 2022.
42. Woźniak-Budych MJ, Przysiecka Ł, Maciejewska BM, Wieczorek D, Staszak K, Jarek M, Jesionowski T and Jurga S: Facile synthesis of sulfobetaine-stabilized Cu2O nanoparticles and their biomedical potential. ACS Biomater Sci Eng 3: 3183-3194, 2017.
43. Wozniak-Budych MJ, Langer K, Peplinska B, Przysiecka L, Jarek M, Jarzebski M and Jurga S: Copper-gold nanoparticles: Fabrication, characteristic and application as drug carriers. Mater Chem Phys 179: 242-253, 2016.
44. Tortella GR, Pieretti JC, Rubilar O, Fernández-Baldo M, Benavides-Mendoza A, Diez MC and Seabra AB: Silver, copper and copper oxide nanoparticles in the fight against human viruses: progress and perspectives. Crit Rev Biotechnol 42: 431-449, 2022.
45. Yuan Z, Qu S, He Y, Xu Y, Liang L, Zhou X, Gui L, Gu Y and Chen H: Thermosensitive drug-loading system based on copper sulfide nanoparticles for combined photothermal therapy and chemotherapy in vivo. Biomater Sci 6: 3219-3230, 2018.
46. Zhang M, Wang W, Cui Y, Chu X, Sun B, Zhou N and Shen J: Magnetofluorescent Fe3O4/carbon quantum dots coated single-walled carbon nanotubes as dual-modal targeted imaging and chemo/photodynamic/photothermal triple-modal therapeutic agents. Chem Eng J 338: 526-538, 2018.

47. Frtús A, Smolková B, Uzhytchak M, Lunova M, Jirsa M, Kubinová Š, Dejneka A and Lunov O: Analyzing the mechanisms of iron oxide nanoparticles interactions with cells: A road from failure to success in clinical applications. J Control Release 328: 59-77, 2020.
48. Xuan S, Wang F, Lai JM, Sham KW, Wang YX, Lee SF, Yu JC, Cheng CH and Leung KC: Synthesis of biocompatible, mesoporous Fe(3)O(4) nano/microspheres with large surface area for magnetic resonance imaging and therapeutic applications. ACS Appl Mater Interfaces 3: 237-244, 2011.
49. Wang L, Wang Z, Li X, Zhang Y, Yin M, Li J, Song H, Shi J, Ling D, Wang L, *et al*: Deciphering active biocompatibility of iron oxide nanoparticles from their intrinsic antagonism. Nano Res 11: 2746-2755, 2018.
50. Jin R, Lin B, Li D and Ai H: Superparamagnetic iron oxide nanoparticles for MR imaging and therapy: Design considerations and clinical applications. Curr Opin Pharmacol 18: 18-27, 2014.
51. Latunde-Dada GO: Ferroptosis: Role of lipid peroxidation, iron and ferritinophagy. Biochim Biophys Acta-Gen Subj 1861: 1893-1900, 2017.
52. Chen S, Yang J, Liang Z, Li Z, Xiong W, Fan Q, Shen Z, Liu J and Xu Y: Synergistic functional nanomedicine enhances ferroptosis therapy for breast tumors by a blocking defensive redox system. ACS Appl Mater Interfaces 15: 2705-2713, 2023.
53. Cormode DP, Gao L and Koo H: Emerging biomedical applications of enzyme-like catalytic nanomaterials. Trends Biotechnol 36: 15-29, 2018.
54. Zhou C, Wang C, Xu K, Niu Z, Zou S, Zhang D, Qian Z, Liao J and Xie J: Hydrogel platform with tunable stiffness based on magnetic nanoparticles cross-linked GelMA for cartilage regeneration and its intrinsic biomechanism. Bioact Mater 25: 615-628, 2023.
55. Ashraf N, Ahmad F, Da-Wei L, Zhou RB, Feng-Li H and Yin DC: Iron/iron oxide nanoparticles: Advances in microbial fabrication, mechanism study, biomedical, and environmental applications. Crit Rev Microbiol 45: 278-300, 2019.
56. Zhou Z, Sun Y, Shen J, Wei J, Yu C, Kong B, Liu W, Yang H, Yang S and Wang W: Iron/iron oxide core/shell nanoparticles for magnetic targeting MRI and near-infrared photothermal therapy. Biomaterials 35: 7470-7478, 2014.
57. Zhang X, Liu Z, Lou Z, Chen F, Chang S, Miao Y, Zhou Z, Hu X, Feng J, Ding Q, *et al*: Radiosensitivity enhancement of Fe3O4@Ag nanoparticles on human glioblastoma cells. Artif Cell Nanomed Biotechnol 46 (Suppl): 975-984, 2018.
58. Zhong D, Zhao J, Li Y, Qiao Y, Wei Q, He J, Xie T, Li W and Zhou M: Laser-triggered aggregated cubic α-Fe2O3@Au nanocomposites for magnetic resonance imaging and photothermal/enhanced radiation synergistic therapy. Biomaterials 219: 119369, 2019.
59. Dennis CL and Ivkov R: Physics of heat generation using magnetic nanoparticles for hyperthermia. Int J Hyperthermia 29: 715-729, 2013.
60. Grauer O, Jaber M, Hess K, Weckesser M, Schwindt W, Maring S, Wölfer J and Stummer W: Combined intracavitary thermotherapy with iron oxide nanoparticles and radiotherapy as local treatment modality in recurrent glioblastoma patients. J Neurooncol 141: 83-94, 2019.
61. Toraya-Brown S and Fiering S: Local tumour hyperthermia as immunotherapy for metastatic cancer. Int J Hyperthermia 30: 531-539, 2014.
62. Goldberg MS: Immunoengineering: How nanotechnology can enhance cancer immunotherapy. Cell 161: 201-204, 2015.
63. Zanganeh S, Hutter G, Spitler R, Lenkov O, Mahmoudi M, Shaw A, Pajarinen JS, Nejadnik H, Goodman S, Moseley M, *et al*: Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues. Nat Nanotechnol 11: 986-994, 2016.
64. Ge X, Wong R, Anisa A and Ma S: Recent development of metal-organic framework nanocomposites for biomedical applications. Biomaterials 281: 121322, 2022.
65. Auer B, Telfer SG and Gross AJ: Metal organic frameworks for bioelectrochemical applications. Electroanalysis 35: e202200145, 2023.
66. Kim SN, Park CG, Huh BK, Lee SH, Min CH, Lee YY, Kim YK, Park KH and Choy YB: Metal-organic frameworks, NH(2)-MIL-88(Fe), as carriers for ophthalmic delivery of brimonidine. Acta Biomater 79: 344-353, 2018.
67. Yang B, Ding L, Yao H, Chen Y and Shi J: A metal-organic framework (MOF) fenton nanoagent-enabled nanocatalytic cancer therapy in synergy with autophagy inhibition. Adv Mater 32: e1907152, 2020.
68. Liu P, Shi X, Zhong S, Peng Y, Qi Y, Ding J and Zhou W: Metal-phenolic networks for cancer theranostics. Biomater Sci 9: 2825-2849, 2021.
69. Luo S, Ma D, Wei R, Yao W, Pang X, Wang Y, Xu X, Wei X, Guo Y, Jiang X, *et al*: A tumor microenvironment responsive nanoplatform with oxidative stress amplification for effective MRI-based visual tumor ferroptosis. Acta Biomater 138: 518-527, 2022.
70. Farhood B, Najafi M and Mortezaee K: CD8+ cytotoxic T lymphocytes in cancer immunotherapy: A review. J Cell Physiol 234: 8509-8521, 2019.
71. Lin MJ, Svensson-Arvelund J, Lubitz GS, Marabelle A, Melero I, Brown BD and Brody JD: Cancer vaccines: the next immunotherapy frontier. Nat Cancer 3: 911-926, 2022.
72. Gupta M, Wahi A, Sharma P, Nagpal R, Raina N, Kaurav M, Bhattacharya J, Rodrigues Oliveira SM, Dolma KG, Paul AK, *et al*: Recent advances in cancer vaccines: Challenges, achievements, and futuristic prospects. Vaccines (Basel) 10: 2011, 2022.
73. Musetti S and Huang L: Nanoparticle-mediated remodeling of the tumor microenvironment to enhance immunotherapy. ACS Nano 12: 11740-11755, 2018.
74. Li J, Ren H and Zhang Y: Metal-based nano-vaccines for cancer immunotherapy. Coord Chem Rev 454: 214345, 2022.
75. Pradeu T and Vivier E: The discontinuity theory of immunity. Sci Immunol 1: AAG0479, 2016.
76. Duan X, Chan C and Lin W: Nanoparticle-mediated immunogenic cell death enables and potentiates cancer immunotherapy. Angew Chem Int Ed Engl 58: 670-680, 2019.
77. Yang Y, Huang CT, Huang X and Pardoll DM: Persistent Toll-like receptor signals are required for reversal of regulatory T cell-mediated CD8 tolerance. Nat Immunol 5: 508-515, 2004.
78. Hanson MC, Crespo MP, Abraham W, Moynihan KD, Szeto GL, Chen SH, Melo MB, Mueller S and Irvine DJ: Nanoparticulate STING agonists are potent lymph node-targeted vaccine adjuvants. J Clin Invest 125: 2532-2546, 2015.
79. Kaur A, Baldwin J, Brar D, Salunke DB and Petrovsky N: Toll-like receptor (TLR) agonists as a driving force behind next-generation vaccine adjuvants and cancer therapeutics. Curr Opin Chem Biol 70: 102172, 2022.
80. Shinchi H, Yamaguchi T, Moroishi T, Yuki M, Wakao M, Cottam HB, Hayashi T, Carson DA and Suda Y: Gold nanoparticles coimmobilized with small molecule toll-like receptor 7 ligand and α-mannose as adjuvants. Bioconjugate Chem 30: 2811-2821, 2019.
81. Ishikawa H and Barber GN: STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. Nature 455: 674-678, 2008.
82. Motedayen Aval L, Pease JE, Sharma R and Pinato DJ: Challenges and opportunities in the clinical development of STING agonists for cancer immunotherapy. J Clin Med 9: 3323, 2020.
83. Ding B, Zheng P, Jiang F, Zhao Y, Wang M, Chang M, Ma P and Lin J: MnOx nanospikes as nanoadjuvants and immunogenic cell death drugs with enhanced antitumor immunity and antimetastatic effect. Angew Chem Int Ed Engl 59: 16381-16384, 2020.
84. Slingluff CL Jr, Petroni GR, Olson WC, Smolkin ME, Ross MI, Haas NB, Grosh WW, Boisvert ME, Kirkwood JM and Chianese-Bullock KA: Effect of granulocyte/macrophage colony-stimulating factor on circulating CD8+ and CD4+ T-cell responses to a multipeptide melanoma vaccine: Outcome of a multicenter randomized trial. Clin Cancer Res 15: 7036-7044, 2009.
85. Serafini P, Carbley R, Noonan KA, Tan G, Bronte V and Borrello I: High-dose granulocyte-macrophage colony-stimulating factor-producing vaccines impair the immune response through the recruitment of myeloid suppressor cells. Cancer Res 64: 6337-6343, 2004.
86. Behzadi M, Vakili B, Ebrahiminezhad A and Nezafat N: Iron nanoparticles as novel vaccine adjuvants. Eur J Pharm Sci 159: 105718, 2021.
87. Wang X, Li X, Onuma K, Sogo Y, Ohno T and Ito A: Zn- and Mg- containing tricalcium phosphates-based adjuvants for cancer immunotherapy. Sci Rep 3: 2203, 2013.
88. Shukla R, Bansal V, Chaudhary M, Basu A, Bhonde RR and Sastry M: Biocompatibility of gold nanoparticles and their endocytotic fate inside the cellular compartment: A microscopic overview. Langmuir 21: 10644-10654, 2005.
89. Dobrovolskaia MA and McNeil SE: Immunological properties of engineered nanomaterials. Nat Nanotechnol 2: 469-478, 2007.
90. Tao Y, Ju E, Li Z, Ren J and Qu X: Engineered CpG- antigen conjugates protected gold nanoclusters as smart self- vaccines for enhanced immune response and cell imaging. Adv Funct Mater 24: 1004-1010, 2014.

91. Zhang P, Chiu YC, Tostanoski LH and Jewell CM: Polyelectrolyte multilayers assembled entirely from immune signals on gold nanoparticle templates promote antigen-specific T cell response. ACS Nano 9: 6465-6477, 2015.
92. Zhao H, Xu J, Li Y, Guan X, Han X, Xu Y, Zhou H, Peng R, Wang J and Liu Z: Nanoscale coordination polymer based nanovaccine for tumor immunotherapy. ACS Nano 13: 13127-13135, 2019.
93. Jin C, Zhang Y, Zhang G, Wang B and Hua P: Combination of GNRs-PEI/cGAMP-laden macrophages-based photothermal induced in situ tumor vaccines and immune checkpoint blockade for synergistic anti-tumor immunotherapy. Biomater Adv 133: 112603, 2022.
94. Chen F, Li T, Zhang H, Saeed M, Liu X, Huang L, Wang X, Gao J, Hou B, Lai Y, *et al*: Acid-ionizable iron nanoadjuvant augments STING activation for personalized vaccination immunotherapy of cancer. Adv Mater 35: e2209910, 2023.
95. Ljunggren HG, Jonsson R and Höglund P: Seminal immunologic discoveries with direct clinical implications: The 2018 Nobel Prize in Physiology or Medicine honours discoveries in cancer immunotherapy. Scand J Immunol 88: e12731, 2018.
96. Xie L, Wang G, Sang W, Li J, Zhang Z, Li W, Yan J, Zhao Q and Dai Y: Phenolic immunogenic cell death nanoinducer for sensitizing tumor to PD-1 checkpoint blockade immunotherapy. Biomaterials 269: 120638, 2021.
97. Sang W, Zhang Z, Wang G, Xie L, Li J, Li W, Tian H and Dai L: A triple-kill strategy for tumor eradication reinforced by metal-phenolic network nanopumps. Adv Funct Mater 32: 2113168, 2022.
98. Mayes PA, Hance KW and Hoos A: The promise and challenges of immune agonist antibody development in cancer. Nat Rev Drug Discov 17: 509-527, 2018.
99. Lim SH, Beers SA, Al-Shamkhani A and Cragg MS: Agonist antibodies for cancer immunotherapy: History, hopes and challenges. Clin Cancer Res 30: 1712-1723, 2023.
100. Boomer JS and Green JM: An enigmatic tail of CD28 signaling. Cold Spring Harb Perspect Biol 2: a002436, 2010.
101. Zhang Q and Vignali DA: Co-stimulatory and co-inhibitory pathways in autoimmunity. Immunity 44: 1034-1051, 2016.
102. Yoshinaga SK, Whoriskey JS, Khare SD, Sarmiento U, Guo J, Horan T, Shih G, Zhang M, Coccia MA, Kohno T, *et al*: T-cell co-stimulation through B7RP-1 and ICOS. Nature 402: 827-832, 1999.
103. Chiang CS, Lin YJ, Lee R, Lai YH, Cheng HW, Hsieh CH, Shyu WC and Chen SY: Combination of fucoidan-based magnetic nanoparticles and immunomodulators enhances tumour-localized immunotherapy. Nat Nanotechnol 13: 746-754, 2018.
104. Locksley RM, Killeen N and Lenardo MJ: The TNF and TNF receptor superfamilies: Integrating mammalian biology. Cell 104: 487-501, 2001.
105. Vonderheide RH and Glennie MJ: Agonistic CD40 antibodies and cancer therapy. Clin Cancer Res 19: 1035-1043, 2013.
106. Zhang Y, Zhao G, Chen YF, Zhou SK, Wang Y, Sun YQ, Shen S, Xu CF and Wang J: Engineering nano-clustered multivalent agonists to cross-link TNF receptors for cancer therapy. Aggregate 4: e393, 2023.
107. Gupta J, Safdari HA and Hoque M: Nanoparticle mediated cancer immunotherapy. Semin Cancer Biol 69: 307-324, 2021.
108. June CH, Riddell SR and Schumacher TN: Adoptive cellular therapy: A race to the finish line. Sci Transl Med 7: 280ps7, 2015.
109. Krishna S, Lowery FJ, Copeland AR, Bahadiroglu E, Mukherjee R, Jia L, Anibal JT, Sachs A, Adebola SO, Gurusamy D, *et al*: Stem-like CD8 T cells mediate response of adoptive cell immunotherapy against human cancer. Science 370: 1328-1334, 2020.
110. June CH, O'Connor RS, Kawalekar OU, Ghassemi S and Milone MC: CAR T cell immunotherapy for human cancer. Science 359: 1361-1365, 2018.
111. Met Ö, Jensen KM, Chamberlain CA, Donia M and Svane IM: Principles of adoptive T cell therapy in cancer. Semin Immunopathol 41: 49-58, 2019.
112. Wang C, Sun W, Ye Y, Bomba HN and Gu Z: Bioengineering of artificial antigen presenting cells and lymphoid organs. Theranostics 7: 3504-3516, 2017.
113. Ichikawa J, Yoshida T, Isser A, Laino AS, Vassallo M, Woods D, Kim S, Oelke M, Jones K, Schneck JP and Weber JS: Rapid expansion of highly functional antigen-specific T cells from patients with melanoma by nanoscale artificial antigen-presenting cells. Clin Cancer Res 26: 3384-3396, 2020.
114. Zheng C, Zhang J, Chan HF, Hu H, Lv S, Na N, Tao Y and Li M: Engineering nano-therapeutics to boost adoptive cell therapy for cancer treatment. Small Methods 5: e2001191, 2021.
115. Youn W, Ko EH, Kim MH, Park M, Hong D, Seisenbaeva GA, Kessler VG and Choi IS: Cytoprotective encapsulation of individual jurkat T cells within durable TiO2 Shells for T-cell therapy. Angew Chem Int Ed Engl 56: 10702-10706, 2017.
116. Nie W, Wei W, Zuo L, Lv C, Zhang F, Lu GH, Li F, Wu G, Huang LL, Xi X and Xie HY: Magnetic nanoclusters armed with responsive PD-1 antibody synergistically improved adoptive T-cell therapy for solid tumors. ACS Nano 13: 1469-1478, 2019.
117. Parkhurst MR, Riley JP, Dudley ME and Rosenberg SA: Adoptive transfer of autologous natural killer cells leads to high levels of circulating natural killer cells but does not mediate tumor regression. Clin Cancer Res 17: 6287-6297, 2011.
118. Baruch EN, Berg AL, Besser MJ, Schachter J and Markel G: Adoptive T cell therapy: An overview of obstacles and opportunities. Cancer 123: 2154-2162, 2017.
119. Lin X, Li F, Gu Q, Wang X, Zheng Y, Li J, Guan J, Yao C and Liu X: Gold-seaurchin based immunomodulator enabling photothermal intervention and αCD16 transfection to boost NK cell adoptive immunotherapy. Acta Biomater 146: 406-420, 2022.
120. Kong C and Chen X: Combined photodynamic and photothermal therapy and immunotherapy for cancer treatment: A review. Int J Nanomedicine 17: 6427-6446, 2022.
121. Xiong Y, Rao Y, Hu J, Luo Z and Chen C: Nanoparticle-based photothermal therapy for breast cancer noninvasive treatment. Adv Mater 37: e2305140, 2025.
122. Paholak HJ, Stevers NO, Chen H, Burnett JP, He M, Korkaya H, McDermott SP, Deol Y, Clouthier SG, Luther T, *et al*: Elimination of epithelial-like and mesenchymal-like breast cancer stem cells to inhibit metastasis following nanoparticle-mediated photothermal therapy. Biomaterials 104: 145-157, 2016.
123. Song G, Shao X, Qu C, Shi D, Jia R, Chen Y, Wang J and An H: A large-pore mesoporous Au@Pt@Rh trimetallic nanostructure with hyperthermia-enhanced enzyme-mimic activities for immunomodulation-improved tumor catalytic therapy. Chem Eng J 477: 147161, 2023.
124. Duan X, Chan C, Guo N, Han W, Weichselbaum RR and Lin W: Photodynamic therapy mediated by nontoxic core-shell nanoparticles synergizes with immune checkpoint blockade to elicit antitumor immunity and antimetastatic effect on breast cancer. J Am Chem Soc 138: 16686-16695, 2016.
125. Thariat J, Hannoun-Levi JM, Sun Myint A, Vuong T and Gérard JP: Past, present, and future of radiotherapy for the benefit of patients. Nat Rev Clin Oncol 10: 52-60, 2013.
126. Wardman P: Chemical radiosensitizers for use in radiotherapy. Clin Oncol (R Coll Radiol) 19: 397-417, 2007.
127. Ni K, Lan G, Chan C, Quigley B, Lu K, Aung T, Guo N, La Riviere P, Weichselbaum RR and Lin W: Nanoscale metal-organic frameworks enhance radiotherapy to potentiate checkpoint blockade immunotherapy. Nat Commun 9: 2351, 2018.
128. Xu CF, Yu YL, Sun Y, Kong L, Yang CL, Hu M, Yang T, Zhang J, Hu Q and Zhang Z: Transformable nanoparticle-enabled synergistic elicitation and promotion of immunogenic cell death for triple-negative breast cancer immunotherapy. Adv Funct Mater 29: 1905213, 2019.
129. Liu Y, Qiao L, Zhang S, Wan G, Chen B, Zhou P, Zhang N and Wang Y: Dual pH-responsive multifunctional nanoparticles for targeted treatment of breast cancer by combining immunotherapy and chemotherapy. Acta Biomater 66: 310-324, 2018.
130. Bobo D, Robinson KJ, Islam J, Thurecht KJ and Corrie SR: Nanoparticle-based medicines: A Review of FDA-approved materials and clinical trials to date. Pharm Res 33: 2373-2387, 2016.
131. Fenton OS, Olafson KN, Pillai PS, Mitchell MJ and Langer R: Advances in biomaterials for drug delivery. Adv Mater: May 7, 2018 (Epub ahead of print).
132. Anselmo AC and Mitragotri S: Nanoparticles in the clinic: An update. Bioeng Transl Med 4: e10143, 2019.
133. Huang Y, Hsu JC, Koo H and Cormode DP: Repurposing ferumoxytol: Diagnostic and therapeutic applications of an FDA-approved nanoparticle. Theranostics 12: 796-816, 2022.
134. Khoobchandani M, Katti KK, Karikachery AR, Thipe VC, Srisrimal D, Dhurvas Mohandoss DK, Darshakumar RD, Joshi CM and Katti KV: New approaches in breast cancer therapy through green nanotechnology and nano-ayurvedic medicine - pre-clinical and pilot human clinical investigations. Int J Nanomedicine 15: 181-197, 2020.

135. Kumthekar P, Ko CH, Paunesku T, Dixit K, Sonabend AM, Bloch O, Tate M, Schwartz M, Zuckerman L, Lezon R, *et al*: A first-in-human phase 0 clinical study of RNA interference-based spherical nucleic acids in patients with recurrent glioblastoma. Sci Transl Med 13: eabb3945, 2021.
136. Rojas LA, Sethna Z, Soares KC, Olcese C, Pang N, Patterson E, Lihm J, Ceglia N, Guasp P, Chu A, *et al*: Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer. Nature 618: 144-150, 2023.
137. Alonso JCC, de Souza BR, Reis IB, de Arruda Camargo GC, de Oliveira G, de Barros Frazão Salmazo MI, Gonçalves JM, de Castro Roston JR, Caria PHF, da Silva Santos A, *et al*: OncoTherad() (MRB-CFI-1) Nanoimmunotherapy: A promising strategy to treat bacillus calmette-guérin-unresponsive non-muscle-invasive bladder cancer: Crosstalk among T-Cell CX3CR1, immune checkpoints, and the toll-like receptor 4 signaling pathway. Int J Mol Sci 24: 17535, 2023.
138. Zhang G, Yuan J, Pan C, Xu Q, Cui X, Zhang J, Liu M, Song Z, Wu L, Wu D, *et al*: Multi-omics analysis uncovers tumor ecosystem dynamics during neoadjuvant toripalimab plus nab-paclitaxel and S-1 for esophageal squamous cell carcinoma: A single-center, open-label, single-arm phase 2 trial. EBioMedicine 90: 104515, 2023.
139. Blanco E, Shen H and Ferrari M: Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotechnol 33: 941-951, 2015.
140. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA and Langer R: Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov 20: 101-124, 2021.
141. Hosta-Rigau L and Städler B: Shear stress and its effect on the interaction of myoblast cells with nanosized drug delivery vehicles. Mol Pharmaceut 10: 2707-2712, 2013.
142. Moghimi SM and Szebeni J: Stealth liposomes and long circulating nanoparticles: Critical issues in pharmacokinetics, opsonization and protein-binding properties. Prog Lipid Res 42: 463-478, 2003.
143. Nizzero S, Ziemys A and Ferrari M: Transport barriers and oncophysics in cancer treatment. Trends Cancer 4: 277-280, 2018.
144. Wagner AM, Gran MP and Peppas NA: Designing the new generation of intelligent biocompatible carriers for protein and peptide delivery. Acta Pharm Sin B 8: 147-164, 2018.
145. Hirai T, Yoshioka Y, Izumi N, Ichihashi K, Handa T, Nishijima N, Uemura E, Sagami K, Takahashi H, Yamaguchi M, *et al*: Metal nanoparticles in the presence of lipopolysaccharides trigger the onset of metal allergy in mice. Nat Nanotechnol 11: 808-816, 2016.
146. Radulescu DM, Surdu VA, Ficai A, Ficai D, Grumezescu AM and Andronescu E: Green synthesis of metal and metal oxide nanoparticles: A review of the principles and biomedical applications. Int J Mol Sci 24: 15397, 2023.
147. Chithrani BD, Ghazani AA and Chan WC: Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells. Nano Lett 6: 662-668, 2006.
148. Wills JW, Summers HD, Hondow N, Sooresh A, Meissner KE, White PA, Rees P, Brown A and Doak SH: Characterizing nanoparticles in biological matrices: Tipping points in agglomeration state and cellular delivery in vitro. ACS Nano 11: 11986-12000, 2017.
149. Agarwal R, Jurney P, Raythatha M, Singh V, Sreenivasan SV, Shi L and Roy K: Effect of shape, size, and aspect ratio on nanoparticle penetration and distribution inside solid tissues using 3D spheroid models. Adv Healthc Mater 4: 2269-2280, 2015.
150. Kou L, Bhutia YD, Yao Q, He Z, Sun J and Ganapathy V: Transporter-guided delivery of nanoparticles to improve drug permeation across cellular barriers and drug exposure to selective cell types. Front Pharmacol 9: 27, 2018.
151. Li W, Jiang Y and Lu J: Nanotechnology-enabled immunogenic cell death for improved cancer immunotherapy. Int J Pharm 634: 122655, 2023.
152. Mulens-Arias V, Rojas JM and Barber DF: The use of iron oxide nanoparticles to reprogram macrophage responses and the immunological tumor microenvironment. Front Immunol 12: 693709, 2021.
153. Younis MA, Tawfeek HM, Abdellatif AAH, Abdel-Aleem JA and Harashima H: Clinical translation of nanomedicines: Challenges, opportunities, and keys. Adv Drug Deliv Rev 181: 114083, 2022.
154. Almeida JPM, Lin AY, Figueroa ER, Foster AE and Drezek RA: In vivo gold nanoparticle delivery of peptide vaccine induces anti-tumor immune response in prophylactic and therapeutic tumor models. Small 11: 1453-1459, 2015.
155. Johannsen M, Gneveckow U, Thiesen B, Taymoorian K, Cho CH, Waldöfner N, Scholz R, Jordan A, Loening SA and Wust P: Thermotherapy of prostate cancer using magnetic nanoparticles: Feasibility, imaging, and three-dimensional temperature distribution. Eur Urol 52: 1653-1661, 2007.
156. Maier-Hauff K, Ulrich F, Nestler D, Niehoff H, Wust P, Thiesen B, Orawa H, Budach V and Jordan A: Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme. J Neurooncol 103: 317-324, 2011.
157. Coyne DW: Ferumoxytol for treatment of iron deficiency anemia in patients with chronic kidney disease. Expert Opin Pharmacother 10: 2563-2568, 2009.
158. Shah A and Dobrovolskaia MA: Immunological effects of iron oxide nanoparticles and iron-based complex drug formulations: Therapeutic benefits, toxicity, mechanistic insights, and translational considerations. Nanomedicine 14: 977-990, 2018.