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REVIEW

The progress and perspective of nanomedicine in modulating the tumor immune microenvironment

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Abstract The widespread application of nanomedicine in oncology is reshaping cancer treatment paradigms. Using the precise targeting mechanisms and the rapid advancements in nanoscale materials, nanomedicine is driving progress in cancer therapy, particularly within the complex landscape of the tumor immune microenvironment (TIM). This review provides a comprehensive overview of recent studies elucidating the critical role of nanomedicine in modulating the TIM, augmenting the efficacy of immunotherapies, and overcoming therapeutic resistance. Emphasis is placed on the significance of targeted drug delivery systems, innovative nanoscale vaccines, and strategies for reprogramming immunosuppressive cells. Furthermore, the review explores the clinical applicability and prospects of personalized nanomedicine, highlighting its increasingly prominent role in tailored cancer therapeutics.

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1. Introduction

The tumor immune microenvironment (TIM) is a multifaceted and dynamic ecosystem in which neoplastic cells interact with immune cells, the extracellular matrix (ECM), and various signaling molecules. In contrast to the normal immune microenvironment, which is tasked with maintaining immune surveillance and eliminating abnormal cells, the TIM is characterized by its immunosuppressive properties, chronic inflammatory nature, and distinctive tumor metabolic features. This complex environment significantly influences cancer progression, metastasis, and response to therapy. The TIM acts as both a physical barrier to immune cell infiltration and as an active contributor to the suppression of anti-tumor immunity through the secretion of immunosuppressive cytokines and the recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs)[1,2]. A profound understanding of the TIM's intricacies is essential for developing effective cancer combat strategies.

Nanomedicine is a broad field that leverages nanotechnology to prevent, monitor, and intervene in diseases through new modes of imaging, diagnosing, treating, repairing, and regenerating biological systems. The scope of nanomedicine is not limited to nanoparticles; it also encompasses nanorobots and a variety of nanoscale tools, such as liposomes, polymer micelles, and other targeted delivery systems. Engineered nanomedicine can penetrate the dense extracellular matrix (ECM) of tumors, deliver immunomodulatory agents directly to the tumor site, and counteract the immunosuppressive characteristics of the TIM[3]. The ability of nanomedicine to enhance the efficacy of immunotherapies by normalizing vasculature and improving immune cell penetration into the tumor is a subject of intense research[4]. The advantages of nanomedicine in TIM therapy are multifaceted. For instance, nanosized particles are more effectively uptaken by antigen-presenting cells (APCs), which is crucial for activating the immune response[5]. Additionally, the targeted delivery of chemotherapeutic agents using nanocarriers can reduce systemic toxicity while increasing local drug concentration, thus enhancing the therapeutic index of cancer treatment. Moreover, the use of multifunctional bio-nanostructures in cancer therapy has been a focus of extensive research, with these structures showing promise in drug targeting, controllable drug release, and efficient transport within the complex tumor microenvironment[6].

This review aims to comprehensively outline the current progress and prospects of nanomedicine in modulating the TIM. We will discuss various nanomedicine-based strategies being explored to enhance the effectiveness of cancer immunotherapy. Additionally, we will highlight the challenges associated with nanomedicine development, such as the need for improved targeting, reduced off-target effects, and the optimization of nanomedicine design for enhanced biocompatibility and biodegradability. Furthermore, we will explore the clinical implications of these strategies and the potential for personalized nanomedicine in light of the heterogeneous nature of the TIM. By contrasting the frontiers and differences between basic scientific research and clinical applications, we hope to provide insights into the next steps in the development of nanomaterials for the tumor immune microenvironment.

2. Overview of the tumor immune microenvironment

The TIM is a complex and enigmatic arena where immune cells, cancer cells, and non-hematopoietic stromal cells engage in a continuous interplay that influences tumor progression and response to therapy[7,8]. The TIM encompasses immune cells including T cells, B cells, macrophages, and dendritic cells, along with non-immunological components such as fibroblasts, endothelial cells, and the ECM[9]. Tumor-infiltrating lymphocytes (TILs) are immune cells that have migrated from the bloodstream into the tumor microenvironment (TME) (Fig. 1). TILs play a crucial role in the immune response against tumors and can exert both beneficial and detrimental effects on tumor growth and progression. The presence and composition of TILs within tumors have been associated with clinical outcomes in cancer patients. Elevated levels of TILs, especially cytotoxic $CD8^+$ T cells, have been linked to improved prognosis and enhanced response to immunotherapy in specific cancer types. Conversely, tumors with low TIL levels or an immunosuppressive microenvironment may evade immune surveillance and develop resistance to treatment.

2.1. T cells in the TIM

T cells play a crucial role in mounting immune responses against tumors. T cells can be broadly classified based on their T cell receptor (TCR) subunits and the expression of core lineage markers such as CD8 and CD4[10]. The $\alpha\beta$ TCR complex, present in CD8 and CD4 T cells, allows recognition of peptides presented on the cell surface in the context of major histocompatibility complex (MHC) class I or class II, respectively. On the other hand, $\gamma\delta$ T cells, characterized by the $\gamma\delta$ TCR subunit, function independently of MHC classes I and II. In tumor tissues, $CD8^+$ and $CD4^+$ TCR$\alpha\beta$ T cells are the most abundant T cell subsets.

$CD8^+$ T cells, also known as cytotoxic T lymphocytes (CTL), are primarily responsible for recognizing and destroying tumor cells[11]. They recognize specific antigens presented on major histocompatibility complex class I (MHC-I) molecules expressed on the surface of cancer cells. Upon activation, $CD8^+$ T cells undergo clonal expansion, generating a large population of effector $CD8^+$ T cells capable of directly eliminating tumor cells[12]. They achieve this through the release of cytotoxic molecules, such as perforin and granzymes, which induce apoptosis (programmed cell death) in the target cells. $CD8^+$ T cells also produce and release cytokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α)[13,14]. IFN-γ activates other immune cells and enhances immune surveillance, contributing to the antitumor immune response, while TNF-α induces tumor cell apoptosis and stimulates immune cell activity to clear tumor cells. However, in the TIM, $CD8^+$ T cells can also encounter immune inhibitory signals that dampen their function. Tumor cells often exploit immune checkpoint pathways, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), to evade immune destruction[15]. Interaction of these inhibitory receptors with their ligands on tumor cells leads to T cell exhaustion, a state of functional impairment characterized by reduced cytokine production and cytotoxic activity. Immunotherapies targeting immune checkpoint molecules, known as immune checkpoint blockade (ICB), have been developed to block the inhibitory signals and restore the activity of $CD8^+$ T cells, leading to enhanced tumor cell killing[16].

$CD4^+$ T cells, or helper T cells, express the CD4 co-receptor on their cell surface and play crucial roles in coordinating and regulating immune responses[17]. They differentiate into various subsets based on their cytokine profiles and transcription factors, including Th1, Th2, Th17, Tregs, and follicular helper T cells (Tfh)[18]. Th1 cells produce cytokines such as IFN-γ and TNF-α, which promote cellular immune responses and enhance the

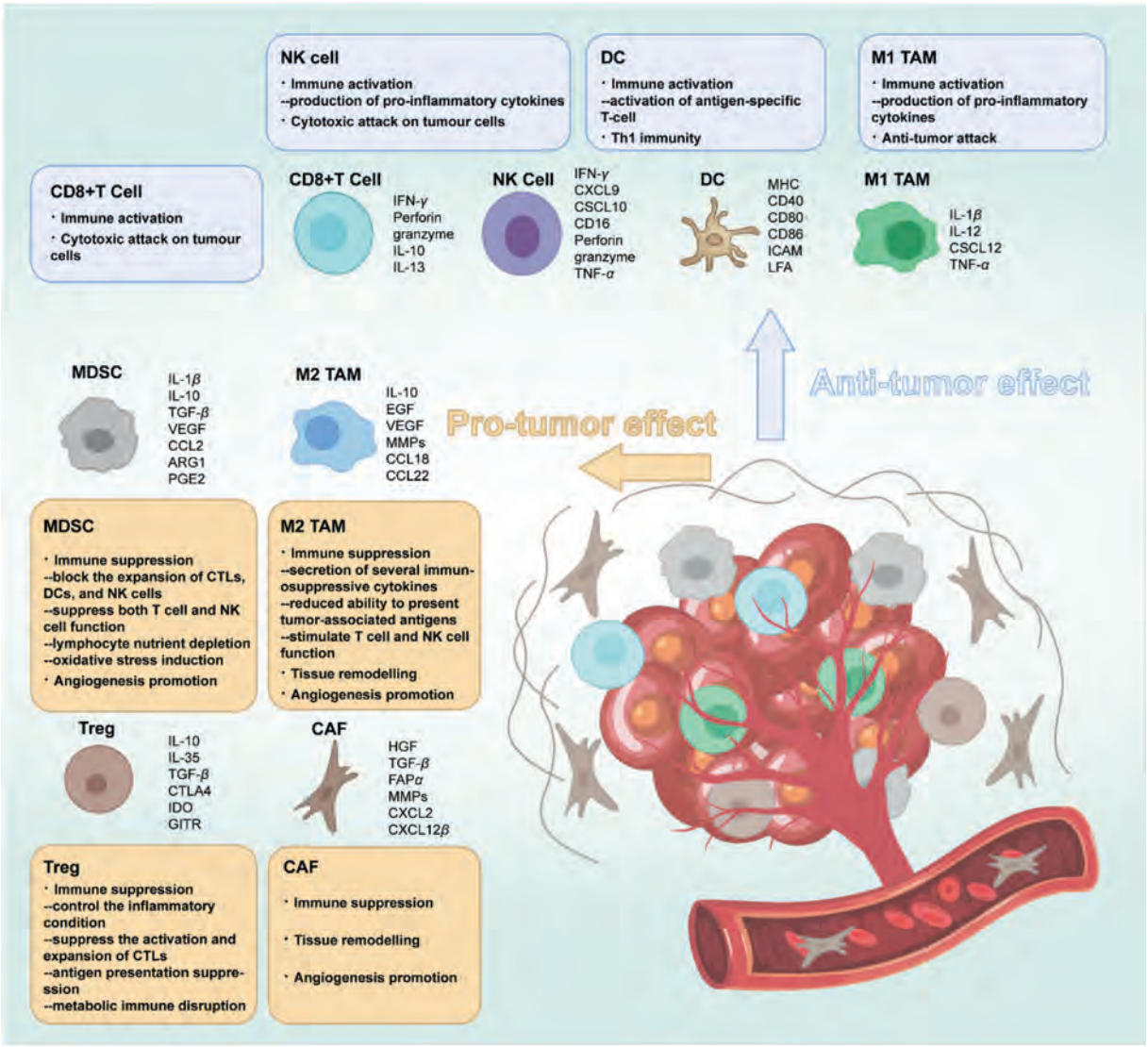

Figure 1 Immune Modulation in Tumor Microenvironment. Natural killer (NK) cells and $CD8^+$ T cells play a crucial role in immune activation and cytotoxic attack on tumor cells, producing pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and activating antigen-specific T-cell responses. Dendritic cells (DC) and M1 tumor-associated macrophages (M1 TAM) contribute to immune activation through the production of cytokines and cytotoxic molecules like perforin and granzyme. Myeloid-derived suppressor cells (MDSC) and M2 tumor-associated macrophages (M2 TAM) are associated with immune suppression, secreting immunosuppressive cytokines like IL-10 and TGF-β, which block the expansion of cytotoxic T lymphocytes (CTLs) and NK cells. They also stimulate angiogenesis and tissue remodeling, promoting a pro-tumor effect. Regulatory T cells (Treg) and cancer-associated fibroblasts (CAF) further contribute to immune suppression through multiple mechanisms, including control of inflammatory conditions, suppression of CTL activation and expansion, metabolic disruption, tissue remodeling and angiogenesis, which are essential for tumor growth and progression.

activity of cytotoxic $CD8^+$ T cells and macrophages[19]. Th2 cells produce cytokines such as interleukin (IL)-4, IL-5, and IL-13, which are involved in promoting humoral immune responses. While Th2 responses are typically associated with allergic and parasitic diseases, they can also play a role in certain tumor contexts[20]. Th17 cells produce cytokines such as IL-17 and IL-22 and are implicated in inflammation and tissue remodeling[21]. In the TIM, Th17 cells can have both pro- and antitumor effects. Tfh cells are specialized $CD4^+$ T cells that provide help to B cells in generating antibody responses[22]. Within the TIM, Tfh cells can contribute to the formation of tertiary lymphoid structures (TLSs), which are organized lymphoid-like structures observed in some tumors. TLSs can facilitate immune cell interactions and promote antitumor immune responses[23].

2.2. *B cells in the TIM*

B cells are a critical component of the adaptive immune system. Within the TIM, tumor-infiltrating B cells (TIL-Bs) display significant heterogeneity and can exert both pro-tumorigenic and anti-tumorigenic effects. TIL-Bs directly influence the anti-tumor immune response through antibody production, antigen presentation, and interaction with other immune cells. TIL-Bs display characteristic features of an active immune response, including

antigen recognition, clonal expansion, phenotypic differentiation, and the production of somatically hypermutated, class-switched antibodies with anti-tumor properties[24].

Firstly, B cells exhibit anti-tumor effects. B cells can recognize tumor-specific antigens and generate antibodies that can bind to and neutralize tumor cells. These antibodies can directly eliminate tumor cells, induce complement-mediated cytotoxicity, or stimulate other immune cells to participate in antibody-dependent cellular cytotoxicity (ADCC). Moreover, B cells can function as APCs within tumors[25]. B cells can process and present antigenic peptides to $CD4^+$ T cells through the MHC class II pathway[26], and also cross-present peptide-MHC I complexes to activate $CD8^+$ T cells[27]. Notably, B cells utilize their surface immunoglobulin to efficiently capture and internalize cognate antigens, allowing them to present low-abundance antigens to T cells more effectively compared to dendritic cells or macrophages[28,29]. TLSs, also known as ectopic lymphoid organs, are commonly found in the peritumoral stromal regions of highly immunogenic tumors[30].

Conversely, B cells can also demonstrate protumor functions within the tumor immune microenvironment. Specific subsets of B cells, termed regulatory B cells (Bregs), possess immunosuppressive properties[31]. Bregs secrete immunosuppressive cytokines such as IL-10, IL-35, and transforming growth factor beta (TGF-β), or release metabolites such as gamma-aminobutyric acid (GABA), which suppress antitumor immune responses and foster immune tolerance[32-34]. Additionally, tumor cells can exploit B cells and antibodies to evade immune surveillance. They can express molecules that bind to the Fc portion of antibodies, preventing their effector functions and neutralization of tumor cells. This mechanism is known as antibody-mediated immune evasion. Additionally, B cells can produce growth factors that promote tumor growth, angiogenesis, and metastasis.

2.3. *Nature killer (NK) cells*

Natural killer (NK) cells are a critical component of the innate immune system, known for their ability to identify and eliminate tumor cells and infected cells without prior sensitization. They achieve this through a balance of signals received from activating and inhibitory receptors, which allows them to discriminate between healthy and stressed or transformed cells[35].

Natural killer (NK) cells are equipped with a variety of activating and inhibitory receptors that play a pivotal role in identifying and eliminating target cells. Activating receptors such as NKG2D, DNAM-1, and NCRs (NKp30, NKp44, NKp46) are crucial for the recognition of target cells, while inhibitory receptors like KIRs and NKG2A interact with MHC class I molecules, maintaining self-tolerance and preventing the NK cells from attacking healthy cells[36].

The activating receptor NKG2D, for instance, is alerted to the presence of cancer cells by the upregulation of its ligands ULBP1 and ULBP2, which is often associated with cellular stress and malignancy. DNAM-1, another activating receptor, is implicated in the NK cell-mediated response against certain tumors and viral infections. Meanwhile, the NCRs, including NKp30, NKp44, and NKp46, contribute to the immediate cytotoxic response against target cells that lack or have downregulated MHC class I molecules, which is a common mechanism of immune evasion in virally infected and malignant cells[37].

On the other hand, inhibitory receptors are equally important for a balanced immune response. Killer cell immunoglobulin-like receptors (KIRs) are one such family of receptors that bind to MHC class I molecules on cells, sending inhibitory signals to prevent the lysis of healthy self-cells. The NKG2A receptor, part of the natural killer group 2 complex, also plays a role in inhibiting NK cell activation, thus helping to avoid overzealous immune responses against the body's tissues[38,39].

The balance between these activating and inhibitory signals is critical for the proper functioning of NK cells. When the activating signals outweigh the inhibitory signals, NK cells become activated and initiate their cytotoxic functions, leading to the release of cytotoxic granules containing perforin and granzymes, which induce apoptosis in target cells. Moreover, NK cells can also mediate antibody-dependent cellular cytotoxicity (ADCC) through their Fc receptors, such as CD16, which bind to the Fc portion of antibodies that are attached to target cells[40].

2.4. *Tumor-associated macrophages (TAMs)*

Macrophages originate from myeloid progenitor cells in the bone marrow and monocytes circulating in the blood. These precursor cells migrate into tissues and differentiate into mature macrophages. Notably, specialized macrophage populations in tissues such as the lungs and liver originate from embryonic progenitors[41-43]. TAMs, which infiltrate tumor tissues or reside within the solid tumor microenvironment[44], play a central role in establishing an immunosuppressive TME.

TAMs can be broadly categorized as M1 and M2 macrophages based on their polarized phenotypes and distinct functional roles[45]. M1 TAMs exhibit anti-tumor properties, promoting inflammation and cytotoxicity by secreting pro-inflammatory cytokines like IL-12, IL-1β, IL-6, IL-23, CXCL-10, IFN-γ, and tumor necrosis factor (TNF-α), and generating nitric oxide (NO) and reactive oxygen species (ROS)[46]. Conversely, M2 TAMs secrete immunosuppressive cytokines such as IL-13, IL-4, and IL-10, transforming growth factor (TGF-β), and matrix metalloproteinases (MMPs) including MMP-2 and MMP-9, as well as growth factors like vascular endothelial growth factor (VEGF). They also express arginase-1, mannose receptor, and scavenger receptors, which contribute to their pro-tumorigenic properties and immunosuppressive role[47-49].

The recruitment and polarization of macrophages are regulated by intricate biological networks. Colony-stimulating factor-1 (CSF-1), C-C motif ligand 2 (CCL2), VEGF-A, and EGFR are well-studied factors that promote macrophage recruitment and polarization towards the M2 phenotype[50-52]. Additionally, monocytes are recruited into tumor tissues under the influence of various cytokines, chemokines, and growth factors such as CCL7, CCL8, CCL3, CCL4, granulocyte-macrophage CSF (GM-CSF), macrophage-stimulating protein (MSP), platelet-derived growth factor (PDGF), and TGF-β1. They may then differentiate into immunosuppressive M2 TAMs in response to IL-4, IL-10, and IL-13[8,53].

Furthermore, TAMs can accumulate in tumor tissues through the influence of hypoxia-induced factors and metabolites, including CCL2, CCL5, CSF-1, VEGF, semaphorin 3A, endothelial cell monocyte-activating polypeptide-II, endothelin, stromal cell-derived factor 1, eotaxin, oncostatin M, lactate, and angiopoietin-2[54]. It is noteworthy that various epigenetic regulators have been implicated in the accumulation, recruitment, and polarization of macrophages. For instance, protein arginine methyltransferase 1, SET and MYND domain-containing protein 3, Jumonji domain-containing protein 3, NAD-dependent protein deacetylase sirtuin-2, and bromodomain and extraterminal

proteins positively regulate M2 polarization by upregulating M2 markers. In contrast, DNA methyltransferase 3B, Jumonji domain-containing protein 1A, histone deacetylase 3 (HDAC3), and HDAC 9 exert opposing effects[55,56].

2.5. MDSCs

MDSCs represent a diverse group of innate immune cells that are activated under pathological conditions and are known for their robust immunosuppressive capabilities[57]. MDSCs are categorized into granulocytes/polymorphonuclear cells (G-MDSCs or PMN-MDSCs) and monocytes (M-MDSCs)[58]. They are rapidly elevated in the TIM during tumorigenesis[59]. MDSCs exert their immunosuppressive effects through multiple mechanisms, such as inhibiting T cell activation and proliferation, suppressing NK cell activity, promoting the development of regulatory T cells (Tregs), and dampening the functions of anti-tumor cells.

MDSCs can produce suppressive cytokines like TGF-β, IL-10, and immunosuppressive enzymes including arginase-1 (ARG1), ROS, iNOS, and PGE2[60]. They also express inhibitory cell surface molecules such as programmed death-ligand 1 (PD-L1). These inhibitory molecules and factors can disrupt the activation and proliferation of T cells and NK cells, enhance the proliferation of circulating tumor cells, promote epithelial-mesenchymal transition (EMT), and induce the expression of matrix metalloproteinases (MMPs) like MMP8 and MMP9, thereby fostering a pro-metastatic microenvironment[61,62].

Furthermore, MDSCs can inhibit the activity of NK cells by producing suppressive cytokines and interacting with NK cells through cell surface molecules such as NKG2D ligands, thus impairing the killing function of NK cells[63]. MDSCs also promote the development of Tregs through the production of cytokines and interaction with molecules such as CTLA-4 and indoleamine 2,3-dioxygenase (IDO)[64]. Lastly, MDSCs can produce suppressive molecules such as acid proteases and oxidases, which directly inhibit the proliferation and function of anti-tumor cells.

2.6. Tregs

Tregs, a specialized subset of T cells, are defined by the expression of the transcription factor FoxP3 and the cell surface marker CD25. These cells are instrumental in preserving immune homeostasis and curbing excessive immune reactions. Tregs can be differentiated into several subpopulations, including non-activated Tregs, effector Tregs, and resting Tregs, which exhibit varying degrees of immunosuppressive capacity[65]. Within the TME, effector Tregs predominate, marked by heightened expression of surface markers such as CTLA-4, PD-1, OX40, and chemokine receptors. These markers facilitate tumor immune evasion[66]. The presence of Tregs within tumors correlates with adverse outcomes, including accelerated tumor growth, metastasis, and diminished responsiveness to immunotherapy. Tumor cells and the TME can enhance the recruitment and proliferation of Tregs by secreting chemokines and other immunosuppressive factors.

Tregs perform their immunosuppressive role through multiple mechanisms. A pivotal mechanism is the secretion of immunosuppressive cytokines, including IL-10, IL-35 (Ebi3−IL-12α heterodimer), and TGF-β. These cytokines attenuate the activation and effector functions of other immune cells, such as cytotoxic $CD8^+$ T cells, NK cells, and APCs[67]. Additionally, Tregs can suppress the function of other immune cells through direct cell-to-cell contact. They express molecules like CTLA-4 and lymphocyte activation gene 3 (LAG-3), which engage with co-stimulatory molecules on target cells, inhibiting their activation and function[68-71]. Moreover, the inhibitory receptors PD-1 and T cell immunoglobulin and ITIM domain (TIGIT) on Tregs can interact with their ligands on effector T cells, resulting in the functional impairment of these cells[72]. Tregs can also induce the expression of IDO in dendritic cells, converting tryptophan into kynurenine, which inhibits T cell proliferation and promoting apoptosis[71,73]. Furthermore, Tregs can directly induce apoptosis in effector T cells *via* the granzyme B/perforin pathway. However, it is essential to recognize that the role of Tregs in cancer is multifaceted and context-dependent. While Tregs are generally linked to immunosuppression and tumor-promoting effects, some subsets of Tregs may exhibit antitumor properties or display functions that vary with context.

3. Mechanisms of nanomedicine in modulating the TME

Nanoparticles, particles with dimensions typically ranging from 1 to 100 nm, can be fabricated from a variety of materials, including metals (*e.g.*, gold, silver, copper, iron), polymers (*e.g.*, poly(lactic-*co*-glycolic acid) (PLGA), polyethylene glycol (PEG), polystyrene (PS), poly(methyl methacrylate) (PMMA)), lipids, inorganic materials (*e.g.*, silica (SiO_2), titanium dioxide (TiO_2), iron oxide (Fe_3O_4)), and composite materials[74]. The nanoscale dimensions endow these particles with distinctive physical, chemical, and biological properties that distinguish them from their bulk forms. Consequently, nanoparticles are a prevalent tool or constituent in nanomedicine. They can be tailored and functionalized to ensure targeted delivery, controlled release, and protection of drugs[75]. In general, the role of nanomedicine in TIM is not independent (Fig. 2). Instead, various cells in the immune microenvironment can be influenced by the interaction of various factors. In the following, we will introduce the interaction of nanoparticles on immune cells with specific cell examples.

3.1. Interaction with T cells

Nanomedicine exhibits substantial potential in modulating the interactions between tumors and T cells, which are integral to the TME. Various mechanisms through which nanomedicine can influence T cell function and activity have been investigated. Nanomedicine can be precisely engineered to deliver immunomodulatory agents, such as checkpoint inhibitors, cytokines, or T cell costimulatory receptor agonists, directly to the TME. This targeted delivery strategy increases the local concentration of these agents while reducing systemic toxicity. For instance, the use of nanomedicine loaded with anti-PD-1 antibodies has been demonstrated to enhance antitumor T cell responses when compared to systemic administration of the antibodies alone[76]. Nanomedicine encapsulating IL-2 has also shown increased T cell activation and proliferation within the TME[77]. Nanomedicine can also be utilized to activate and expand tumor-specific T cells directly. Nanomedicine that is coated with tumor antigens and T cell stimulatory molecules, such as anti-CD3 and anti-CD28 antibodies, have been effective in expanding functional, tumor-reactive T cells *ex vivo* for adoptive cell therapy[78]. Furthermore, nanomedicine that delivers agents stimulating antigen-presenting cells, like toll-like receptor agonists, can boost the priming and expansion of tumor-specific T cells within the TME[79].

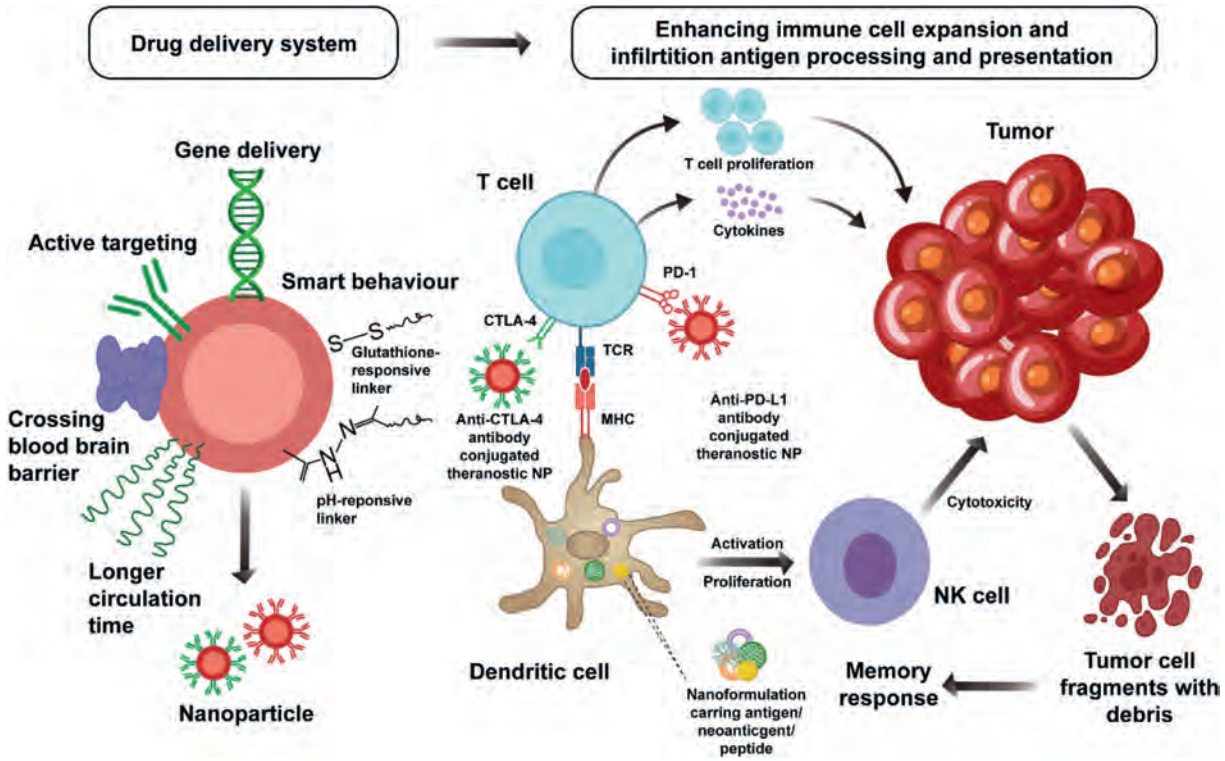

Figure 2 Nanoparticle-mediated tumor immunotherapy. Nanoparticles are engineered to enhance immune cell expansion and deliver therapeutic agents to tumors. They actively target cancer cells, cross the blood−brain barrier, and facilitate gene delivery. These particles promote T cell proliferation and activation, overcome immune checkpoint inhibition, and exhibit smart behavior in response to tumor microenvironments. They also engage dendritic and NK cells, induce memory T cell formation, and respond to tumor fragments to amplify the immune response. This multi-pronged approach leverages nanoparticles to effectively combat tumors through a combination of direct cytotoxicity and immune system engagement.

Nanomedicine also has the capacity to modulate intracellular signaling pathways that govern T-cell function. Nanomedicine encapsulating small molecule inhibitors or small interfering RNA (siRNA) aimed at key signaling nodes, including the PI3K/Akt pathway or the STAT family of transcription factors, have shown promise in enhancing T cell effector functions and potentially reversing T cell exhaustion in the TME[80]. Additionally, nanomaterials can act as tools for *in vivo* monitoring and imaging of T cell responses within the TME. Nanomedicine conjugated with fluorescent or radiolabeled probes have been employed to track T cell trafficking, infiltration, and activation status in both preclinical and clinical studies[81]. This capability can provide valuable insights into the dynamic interactions between T cells and the TME, and guide the optimization of nanomedicine-based immunotherapies.

3.2. *Interaction with B cells*

The strategic engineering of nanomedicine allows for the selective delivery of immunomodulatory agents to tumor-infiltrating B cells. For instance, nanomedicine that is loaded with siRNA directed against the transcription factor Blimp-1, a pivotal regulator in plasma cell differentiation, has been demonstrated to suppress the immunosuppressive functions of tumor-associated plasma cells[79]. Furthermore, the encapsulation of CD40 receptor agonists within nanomedicine has been utilized to augment the antigen-presenting and tumoricidal activities of tumor-infiltrating B cells[82]. Nanomedicine can also induce tumor-specific antibody responses; nanomedicine displaying tumor-associated antigens has effectively primed and activated antigen-specific B cells, culminating in the generation of antibodies that target tumors[81]. These antibodies are capable of mediating ADCC or complement-dependent cytotoxicity against tumor cells within the TME[83]. Mirroring the tactics applied to T cells, nanomedicine can modulate the intracellular signaling pathways that govern B cell function. For example, nanomedicine encapsulating inhibitors of the PI3K/Akt pathway have been shown to boost antitumor antibody production by tumor-infiltrating B cells[80]. Additionally, the delivery of siRNA targeting the transcription factor BCL-6 *via* nanomedicine can foster the differentiation of tumor-infiltrating B cells into plasma cells, thereby amplifying the production of tumor-specific antibodies[84].

3.3. *Interaction with NK cells*

NK cells are a critical component of the immune system that can identify and eliminate cancer cells. The interaction of NK cells with nanomedicine has emerged as a promising strategy for cancer immunotherapy. Cationic nanoparticles (cNPs), for instance, have been shown to activate NK cells, enhancing their cytotoxic activity against triple-negative breast cancer cells both *in vitro* and *in vivo*. This activation was achieved without the need for genetic engineering or cytokine treatment, presenting a significant advantage over conventional methods. The cNPs altered the expression of chemokine receptors CCR4 and CXCR4 on NK cells, which are crucial for their migration towards tumor sites.

Furthermore, cNP-treated NK cells could be effectively tracked *in vivo* using magnetic resonance imaging, highlighting the potential of this approach in monitoring the therapeutic efficacy of NK cell-based cancer immunotherapy[85].

In addition to activation, nanomedicine can be engineered to enhance the chemotropism of NK cells, improving their migration toward tumor sites. This can be achieved by overexpressing chemokine receptors such as CXCR2 on NK cells, which has been shown to promote infiltration into lung metastases *in vivo*. The use of CRISPR/Cas9 technology to upregulate the expression of chemokine receptors like CXCR2 and IL-2 on NK cells has also proven effective in enhancing migration to tumor sites and improving cell killing in preclinical colon cancer models[86].

Innovative approaches, such as the development of chimeric antigen receptors (CARs) for NK cells, have opened new avenues for the precise targeting of tumor cells. These CAR-NK cells, armed with receptors that recognize specific tumor-associated antigens, have shown remarkable potential in eliminating cancer cells both *in vitro* and *in vivo*. Furthermore, the incorporation of NK cell receptor domains into CAR constructs has been explored to improve NK cell activation and cytotoxicity[87,88].

3.4. Interaction with TAMs

TAMs are instrumental in fostering an immunosuppressive microenvironment. Nanomedicine has been engineered to selectively deplete TAMs, curb their recruitment, activate macrophage-mediated phagocytosis of tumor cells, and reprogram their phenotype from the immunosuppressive M2-like to the pro-inflammatory M1-like. Such interventions can attenuate the supportive role of TAMs in tumor growth and metastasis. For instance, clodronate-loaded liposomes can selectively deplete macrophages, including TAMs, by inducing apoptosis[89]. This strategy has been demonstrated to reduce tumor growth across various cancer models. Nanomedicine that targets the CD47−SIRPα interaction can augment macrophage-mediated phagocytosis of tumor cells. Given that CD47 is frequently overexpressed on cancer cells, acting as a "don't eat me" signal, blocking this pathway with nanomedicine can facilitate the clearance of tumor cells by TAMs[90]. Inhibiting the recruitment of TAMs to the TME can significantly reduce their pro-tumorigenic effects. Nanomedicines can interfere with the signaling pathways and chemokines responsible for TAM recruitment. The CCL2/CCR2 signaling pathway is crucial for the recruitment of monocytes and their differentiation into TAMs. Nanoparticles loaded with CCR2 antagonists or siRNA can effectively reduce TAM recruitment[53,91]. CSF-1 and its receptor (CSF-1R) are vital for the survival and recruitment of TAMs. Nanoparticles delivering CSF-1R inhibitors can block this pathway and decrease the infiltration of TAMs into tumors[92,93]. PEGylated gold nanoparticles functionalized with M2pep to deliver sulfated anti-VEGF siRNA have been utilized to target and inhibit the recruitment of immunosuppressive M2-type macrophages[94] (Fig. 3). M2-targeting nanoparticles loaded with siRNA against the CSF-1R receptor and the α-M2pep fusion peptide serve a similar function. The CSF-1R siRNA specifically suppresses M2-like macrophage recruitment, while the α-M2pep enhances nanoparticle binding and uptake by this TAM subpopulation. Importantly, siRNA-carrying M2NPs have down-regulated the expression of exhaustion markers (PD-1 and Tim-3) on infiltrating $CD8^+$ T cells and stimulated their IFN-γ secretion, indicating a restoration of T cell immune function[95]. As previously mentioned, the CD47−SIRPα interaction inhibits macrophage phagocytosis of tumor cells. Nanoparticles designed to block this pathway can "turn on" macrophage-mediated engulfment of tumor cells, promoting their clearance. Studies have shown that anti-CD47 antibody-conjugated nanoparticles can significantly enhance macrophage phagocytosis both *in vitro* and *in vivo*[90,96]. Nanoparticles can also be functionalized with opsonins, such as IgG antibodies, that bind to tumor cells and mark them for phagocytosis, aiding in the recognition and destruction of tumor cells by macrophages[97]. Engineered nanoparticles coated with tumor-specific antibodies can further promote the recognition and engulfment of tumor cells by TAMs[98].

Reprogramming TAMs from a pro-tumorigenic (M2-like) phenotype to an anti-tumorigenic (M1-like) phenotype can significantly bolster anti-tumor immunity. Certain cytokines and small molecules can reprogram TAMs to an M1-like phenotype, and nanoparticles can be engineered to deliver these agents directly to TAMs within the TME. For example, nanoparticles loaded with IFN-γ or TLR agonists have been shown to shift TAMs towards a pro-inflammatory, tumoricidal phenotype (M1)[99]. CRISPR/Cas9-loaded nanoparticles can target and edit specific genes within TAMs to reprogram their function. Knocking out genes that promote the M2 phenotype or upregulating genes associated with the M1 phenotype can effectively reprogram TAMs[100].

Iron-oxide nanoparticles, such as ferumoxytol, can promote the repolarization of immunosuppressive M2 macrophages towards a pro-inflammatory M1 phenotype. This transition is driven by the iron-mediated Fenton reaction, inducing ROS production and tumor cell apoptosis. Notably, the apoptotic tumor cells further stimulate M1 polarization, creating a feedback loop that increases TNF-α and nitric oxide levels. Administration of iron-oxide nanoparticles has also been correlated with elevated M1-associated markers like TNF-α and CD86, as well as decreased M2 markers such as CD206 and IL-10[101]. Additionally, Fe_3O_4/MPs-CpG/liposomes and NK membrane-shrouded photosensitizer-loaded nanoparticles have been reported to repolarize M2 phenotypes to M1 phenotypes. Researchers have developed a modified albumin nanoparticle platform functionalized with two ligands, transferrin receptor-binding peptide and mannose. This platform was used to co-deliver the disulfiram/copper complex and regorafenib, efficiently suppressing cancer cell growth and successfully repolarizing immunosuppressive M2 macrophages towards a pro-inflammatory M1 phenotype[102].

3.5. Interaction with MDSCs

MDSCs constitute a heterogeneous group of immune cells that are pivotal in tumor-induced immunosuppression. Nanoparticles provide a variety of mechanisms to engage with MDSCs and modulate their functionality within the TIME. The capacity to deliver immunomodulatory agents, regulate recruitment and function, promote differentiation, modulate metabolic activity, and inhibit immunosuppressive factors is of significant importance for bolstering anti-tumor immune responses. For example, a formulation of nanoparticles combining low-molecular-weight heparin and tocopherol succinate has been developed to target adhesion molecules essential for vasomotion during MDSC recruitment. These nanoparticles employ a dual mechanism: the hydrophilic end containing low-molecular-weight heparin interferes with the binding of granulocytic MDSCs (G-MDSCs) to vascular endothelial cells, impeding their penetration and adhesion to blood

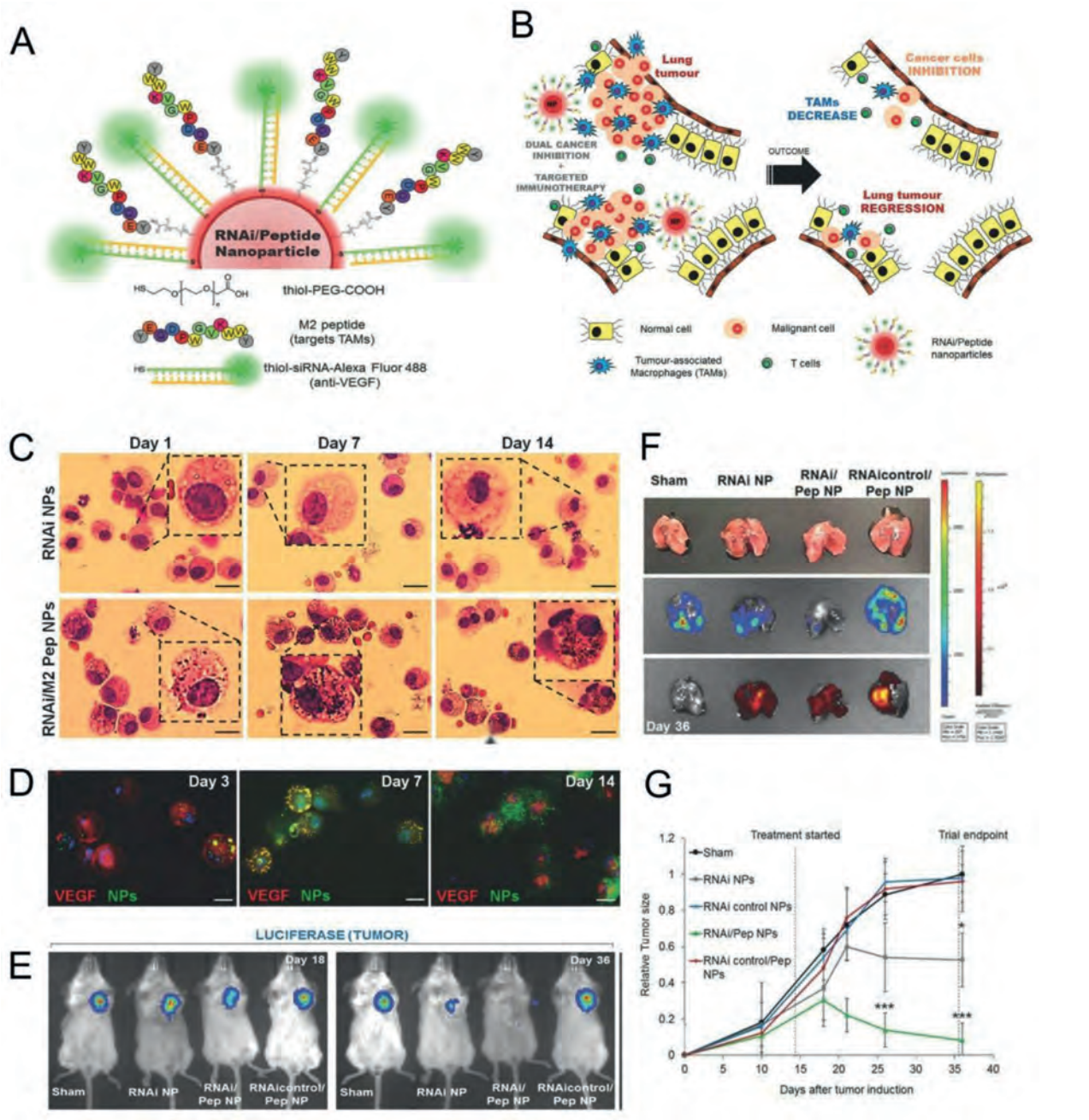

Figure 3 RNAi-M2pep-AuNPs hinder lung cancer progression by silencing tumor-associated macrophages and cancer cells. (A) Gold nanoparticles (AuNPs, ≈15 nm) functionalized with thiolated-PEG-COOH conjugated to TAMs-targeting peptide (M2pep) and thiolated anti-VEGF siRNA labeled with Alexa Fluor 488. (B) Schematic of the outcome of the proposed combined silencing therapy (immunotherapy targeting TAMs and cancer cells) *in vivo via* highly specific and potent nanoparticles administered directly to bronchial airways. (C) Representative light microscopy images of BAL cells, specifically murine macrophages recovered from bronchoalveolar lavage illustrating cells from mice treated with RNAi- and RNAi-M2pep-AuNPs (0.05 mg/kg of siRNA) for days 1, 7, and 14. Black spots on macrophages treated with only RNAi-M2pep-AuNPs represent internalized NPs. Scale bars: 15 μm. (D) Immunofluorescence microscopy images of recovered macrophages from BAL fluid show RNAi-M2pep-AuNPs (green) internalization and VEGF (red) expression during 14 d of exposure. Nuclei are stained with DAPI (blue). Scale bars: 10 μm. These pictures are a composite of stylized images captured with a confocal microscope. (E) Live imaging of BALB/c nude mice bearing A549-luciferase-C8 human lung adenocarcinoma tumors nontreated (Sham) and treated with both RNAi- and RNAi-M2pep-AuNPs and with RNAicontrol-M2pep-AuNPs (dose of 0.05 mg/kg of siRNA). Representative imaging of individual mice from each treated group ($n = 6$ animals) is shown at days 18 and 36. (F) Bioluminescence and epi-fluorescence analysis of *ex vivo* lungs from nontreated and treated mice. (G) Relative tumor size in BALB/c nude mice bearing lung tumor xenografts treated with the RNAi- and RNAi-M2pep-AuNPs, compared to untreated mice (sham), RNAicontrol-AuNPs, and RNAicontrol-M2Pep-AuNPs. The mice were treated through repeated intratracheal instillation at 0.05 mg/kg of siRNA on Days 14, 18, and 21. The tumor volume was monitored by luciferase bioluminescence ($n = 6$, $^{*}P < 0.05$, $^{***}P < 0.005$). Reprinted with the permission from Ref. 94. Copyright © 2015 Wiley.

vessels, while the hydrophobic end with α-tocopheryl succinate (TOS) suppresses MMP-9 expression in G-MDSCs, thereby hindering the remodeling of the tumor immune microenvironment[103]. Nano-cur, formed from curcumin coupled to an FFE-ss-EE peptide, downregulates ARG1 and iNOS expression, and inhibits ROS production and IL-10 release, thus suppressing MDSC recruitment and differentiation in the TIME[104]. Given that MDSC recruitment is governed by multiple signaling axes, targeting a single receptor or cytokine often yields limited effects. Strategies that broadly adsorb MDSC-related cytokines or remodel the tumor immune microenvironment, such as employing bionic sponges[105] or platelet membrane-coated nanoparticles[106], can effectively inhibit MDSC accumulation and enhance antitumor immunity. These approaches aim to disrupt the diverse ligand−receptor interactions that facilitate MDSC recruitment and create an unfavorable microenvironment for MDSC infiltration.

SCM-HPAD NPs, which have a core of DOX/HPAD polymer and are coated with cancer cell membranes, can deplete MDSCs more effectively than free DOX, while also reducing drug dosage, toxicity, and production costs[107]. DS@HLipo is a liposomal nanoparticle encapsulating DOX nanoparticles and free sunitinib, which rapidly releases sunitinib upon near-infrared light exposure to target tumor vasculature and MDSCs, followed by the release of DOX-NPs to eliminate tumor cells[108]. SUNb-PM is a sunitinib-encapsulated polymeric micellar nano delivery system that diminishes MDSC infiltration and induces tumor cell apoptosis[109]. High-density lipoprotein (HDL) nanoparticles, designed to mimic the properties of natural HDL, bind more effectively to the highly expressed B-1 scavenger receptor (SCARB1) on MDSCs. This binding effectively reduces the expression of ARG1, NOS2, and CCL5 in MDSCs, thereby activating the adaptive antitumor immune response[110].

All-*trans* retinoic acid (ATRA) suppresses retinoic acid signaling and promotes glutathione (GSH) accumulation in MDSCs, reducing ROS expression and stimulating MDSC differentiation into mature myeloid cells. Clinical trials have evaluated ATRA in combination with chemotherapy or immunotherapy to reverse the immunosuppressive TIME. Biodegradable hollow mesoporous silica nanoparticles coated with a lipid bilayer (dHMLB) can simultaneously deliver DOX, ATRA, and IL-2, depleting immune-suppressing cells and activating immune effector cells[111]. The iNCVs (R848) are biodegradable silica nanoparticles coated with a lipid bilayer, loaded with the TLR7/8 agonist R848 and the drug doxorubicin. The primary function of iNCVs (R848) is to remodel the TME by converting immunosuppressive MDSCs into antigen-presenting cells, thereby reducing tumor immunosuppression[112].

3.6. Interaction with Tregs

Tregs are a subset of immune cells that play a crucial role in maintaining immune homeostasis and suppressing excessive immune responses. However, their accumulation and immunosuppressive function within the TME can hinder anti-tumor immune responses. The interaction with nanoparticles within the TME can be manipulated to disrupt this suppression. They are able to deliver immunomodulatory agents, regulate recruitment and function, modulate metabolism, and inhibit immunosuppressive factors. Biomimetic nanoparticles that mimic the behavior of Tregs have been developed, which can directly interact with overactive immune cells, inhibiting their activation and reducing the immunosuppressive effects within the TME.

Indiscriminate systemic depletion of Tregs in cancer immunotherapy can increase the risk of autoimmune-related toxicity. Nanotechnology can help increase the specificity of Treg targeting in the TME to reduce side effects. The researchers utilized bare gold nanoparticles generated by laser ablation as carriers, and functionalized them with locked nucleic acid (LNA) oligonucleotides and nuclear localization signal (NLS) peptides to achieve efficient siRNA delivery into murine Tregs. This AuNP-LNA-NLS conjugate was able to effectively enter Tregs and suppress eGFP expression by up to 50% in Foxp3-eGFP transgenic mice[113]. A charge-reversible polymeric nanomodulator ($SP_{DMC}N$) was designed to release a PP2A inhibitor (DMC) selectively in the acidic TME, downregulating FoxP3 to reduce Tregs and increase the CTL/Treg ratio[114]. A bivalent aptamer-peptide (AptCD28-P60) targeting CD28 on Tregs was used to improve the specificity and efficacy of a FoxP3 inhibitor peptide, enhancing tumor immunity when combined with a tumor vaccine[115].

3.7. Interaction with non-cellular components

Nanomedicine's interaction with the TIM extends beyond cellular components, significantly impacting non-cellular elements such as the ECM and various signaling molecules. The ECM's physical properties, including its density and stiffness, can be altered by nanomedicine, facilitating immune cell behavior and trafficking. For instance, nanoparticles have been shown to disrupt the ECM and enhance the penetration of therapeutic agents into the tumor[116].

Moreover, nanomedicine can interact with signaling molecules like cytokines and chemokines, affecting immune cell signaling pathways and reshaping the TIM to foster a more conducive environment for immune responses against cancer cells. Research indicates that nanoparticles can be engineered to respond to the tumor immune microenvironment, releasing immunomodulatory agents to counteract immunosuppressive factors such as transforming growth factor-beta (TGF-β) and reducing tumor-associated fibroblast (TAF) activity, thereby enhancing the efficacy of immunotherapies[117].

Furthermore, nanomedicine has the potential to act as a bridge between cellular and non-cellular elements within the TIM. By integrating the complex signaling network, it offers a more comprehensive approach to cancer immunotherapy. This includes the development of strategies that target both the tumor cells and the surrounding ECM, as well as the modulation of immune cell activity, creating a synergistic effect that can improve the efficacy of immunotherapies[118].

4. Immunotherapy trials targeting tumor immune microenvironment

4.1. Targeting T cells

The therapeutic potential of T cells in immunotherapy is under intense investigation, with a focus on modulating the TME. ADP-A2M4, a novel agent, is designed to enhance T cell targeting of tumor cells by countering the TME's immunosuppressive mechanisms, particularly in advanced synovial sarcoma or myxoid/round cell liposarcoma, in conjunction with lymphodepleting chemotherapy[119]. Another strategy employs blinatumomab (BLINCYTO), a bispecific antibody that simultaneously binds to CD19 on B cells and CD3 on T cells, redirecting T cell-mediated

cytotoxicity towards B cell-positive malignancies. This drug has been used in relapsed/refractory B-ALL and MRD^+ B-ALL, with trials indicating its potential to improve outcomes in these conditions[120]. Cibisatamab, a CEA-CD3 bispecific antibody, is being tested clinically, either as a single agent or combined with obinutuzumab, for advanced CEA-positive solid tumors. This precision medicine approach utilizes the specificity of T cells to target and eliminate CEA-expressing tumor cells, offering a tailored therapeutic strategy for certain solid tumors[121]. IGM-2323, a CD20 x CD3 bispecific DART molecule, is being evaluated in a phase I study for its safety, tolerability, and preliminary signs of antitumor activity in patients with relapsed or refractory B cell malignancies[122]. This innovative approach aims to harness the natural killing ability of T cells while minimizing off-target effects.

In the quest to augment the therapeutic potency of immunotherapy and concurrently attenuate its adverse effects, a multitude of clinical trials have been initiated, with a particular emphasis on the modulation of T cell activity within the tumor immune microenvironment. One such investigational agent is AMG 424, which is currently under scrutiny as a monotherapy for patients with relapsed or refractory multiple myeloma. This clinical study, launched in 2019, endeavors to elucidate the safety profile and therapeutic efficacy of AMG 424 within this specific patient cohort[123]. MGD024, a CD123 x CD3 bispecific DART molecule, is also under evaluation in a phase I clinical trial for patients with relapsed or refractory CD123-positive hematologic malignancies, which began in 2022. The trial is assessing the safety, tolerability, and early anti-neoplastic activity of MGD024[124]. PRS-343, engaging HER2 and 4−1BB, is the subject of a phase I clinical trial for patients with HER2-positive malignancies, which started in 2019. This trial is conducting a thorough assessment of various therapeutic indicators relevant to PRS-343's potential[125]. For a comprehensive overview of clinical trials targeting the tumor immune microenvironment, refer to Table 1[119-157]. These trials exemplify the diverse strategies being explored to harness T cells for cancer immunotherapy, reflecting the dynamic and evolving landscape of cancer treatment.

4.2. Targeting B cells

Targeting B cells has emerged as a pivotal strategy in cancer immunotherapy, with clinical trials focusing on inhibiting their activity or relieving their inhibitory effects on lymphocytes. Idelalisib, a potent PI3Kδ inhibitor, has been investigated in combination with rituximab for the treatment of relapsed chronic lymphocytic leukemia (CLL), follicular B-cell NHL, and small lymphocytic lymphoma (SLL), demonstrating its efficacy in a phase II study conducted in 2017[129].

Icatolimab (TAB004/JS004), a novel anti-BTLA antibody, is being assessed for its capacity to relieve the inhibitory effects on lymphocytes in advanced unresectable or metastatic solid tumors. The drug has been combined with toripalimab, a PD-1 inhibitor, in a phase I clinical trial initiated in 2022[128]. Belzutifan (MK-6482, PT2977), a HIF-2α inhibitor, has shown promise as a single agent in treating renal cell carcinoma, CNS hemangioblastomas, and pancreatic neuroendocrine tumors associated with von Hippel-Lindau (VHL) disease. This drug is currently in a phase II study that started in 2021, further exploring its potential in cancer treatment[127]. Crizotinib, a kinase inhibitor targeting ALK, ROS1, and MET, is being studied as a single agent for the treatment of hematologic cancers, solid tumors, and metastatic cancer. The phase II trial, which began in 2024, aims to evaluate the drug's effectiveness in these conditions[126].

4.3. Targeting NK cells

Natural killer (NK) cells are critical components of the innate immune system, capable of identifying and eliminating cancer cells without prior sensitization. The targeting of NK cells in the TME has become a promising strategy in immunotherapy. Several clinical trials are underway to explore the potential of engaging NK cells *via* different mechanisms to enhance their antitumor activity. AFM28, a bispecific antibody, is being investigated as a single agent for the treatment of relapsed/refractory acute myeloid leukemia (AML). This therapy aims to harness the power of NK cells by engaging them with CD123-expressing targets, a strategy that is currently in phase I of clinical development, with studies initiated in 2022[133]. Similarly, AFM24 is being explored in combination with atezolizumab, an anti-PD-L1 antibody, for the treatment of advanced EGFR-expressing solid tumors. This approach seeks to leverage the cytotoxic potential of NK cells while overcoming the immunosuppressive TME, and the trial is in phase I/II, as of 2024[132]. DF1001 represents a novel tri-specific NK cell engager therapy that targets HER2-expressing tumors. This therapy is designed to redirect NK cells to cancer cells, enhancing their cytotoxic effects. The phase I/II clinical trial of DF1001 is focused on patients with advanced solid tumors that express at least HER2 1^+, with the trial initiated in 2023[131]. SAR445514, another bispecific antibody, is under investigation for its safety and efficacy in patients with relapsed/refractory multiple myeloma (RRMM) and relapsed/refractory light chain amyloidosis (RRLCA). This therapy is being evaluated as a single agent and in combination with pembrolizumab, an anti-PD-1 therapy, for patients with advanced solid tumors, including those with head and neck squamous cell carcinoma, non-small cell lung cancer, and renal cell carcinoma. The trial is in phase 1/2 and was initiated in 2023[130].

4.4. Targeting TAMs

In the TIM, tumor-associated macrophages (TAMs) are key factors affecting tumor growth and the response to immunotherapy. Recent clinical trials have focused on studying various strategies to target TAMs to enhance immune responses and therapeutic efficacy.

Initially, the recruitment of TAMs was inhibited using the anti-CCL2 antibody Carlumab/CNTO 888, in combination with multiple chemotherapy drugs such as docetaxel, gemcitabine, and paclitaxel[149]. Additionally, the CCR2 antagonist PF-04136309, when combined with chemotherapy drugs oxaliplatin, irinotecan, leucovorin, and fluorouracil, showed potential in a phase I clinical trial for pancreatic neoplasms in 2016[137]. Maraviroc, as a CCR5 antagonist, was initiated in a clinical trial in 2022 in combination with Pembrolizumab for metastatic colorectal cancer[157].

Beyond inhibiting TAM recruitment, clinical trials are also exploring how to deplete and suppress TAMs. For instance, the CSF-1R inhibitor Pexidartinib/PLX3397, as a monotherapy, entered a phase III clinical trial for tenosynovial giant cell tumor or related lesions in 2019[135]. ARRY-382, another CSF-1R inhibitor, entered a phase II clinical trial in 2022 in combination with Pembrolizumab for advanced solid tumors[156].

Reprogramming the function of TAMs is also a hot topic of current research. The GAS6-AXL signaling pathway inhibitor

Table 1 Clinical trials of drugs targeting the tumor immune microenvironment.

Target	Mechanism	Drug	Strategy (combination drugs)	Conditions	Phase	Year	Identifier	Ref
T Cells	Improving tumour targeting	ADP-A2M4	Lymphodepleting chemotherapy (fludarabine and cyclophosphamide)	Advanced synovial sarcoma or MRCLS	II	2024	NCT03132922	119
		Blinatumomab (BLINCYTO)	Chemotherapy	Relapsed/refractory B-ALL; MRD + B-ALL	III	2023	NCT02101853	120
		Cibisatamab	Single agent with or without obinutuzumab	Advanced CEA-positive solid tumors	I	2024	NCT02324257	121
		IGM-2323	Single agent	Relapsed or refractory FL, DLBCL, MZL	I	2023	NCT04082936	122
	Restricting T cell stimulation to mitigate adverse effects.	AMG 424	Single agent	Relapsed or refractory multiple myeloma	I	2019	NCT03445663	123
		MGD024	Single agent	Relapsed or refractory CD123-positive hematologic malignancies	I	2022	NCT05362773	124
		PRS-343	Single agent	Solid tumors (gastric, breast, gynecological, colorectal, gallbladder, bladder, pancreatic, salivary duct, melanoma)	I	2019	NCT03330561	125
B Cells	Inhibit B cell activity	Idelalisib	Combined rituximab (for CLL)	Relapsed CLL; relapsed follicular B-cell NHL; relapsed SLL	III	2017	NCT01659021	129
	Relieve the inhibitory effect on lymphocytes	Icatolimab (TAB004/JS004)	Toripalimab	Advanced unresectable solid tumour; Metastatic solid tumour	I	2022	NCT04137900	128
		Belzutifan (MK-6482, PT2977)	Single agent	Renal cell carcinoma, CNS hemangioblastomas, pancreatic neuroendocrine tumors associated with VHL disease	II	2021	NCT03401788	127
		Crizotinib	Single agent	Haematologic cancers; solid tumours; Metastatic cancer	II	2024	NCT02034981	126
NK cells	Engaging NK cells *via* one activating receptor	AFM28	Single agent	Relapsed/Refractory AML	I	2022	NCT05817058	133
		AFM24	Combination with atezolizumab	Advanced EGFR-expressing solid tumors	I/II	2024	NCT04259450	132
	Engaging NK cells *via* two activating receptors	DF1001	Single agent	Advanced solid tumors, at least HER2 1+ expressing tumors	I/II	2023	NCT04143711	131
		SAR445514 (IPH64)	Single agent	Relapsed/refractory multiple myeloma and relapsed/refractory light chain amyloidosis	I/II	2023	NCT05839626	130

(*continued on next page*)

Table 1 (*continued*)

Target	Mechanism	Drug	Strategy (combination drugs)	Conditions	Phase	Year	Identifier	Ref
TAMs	Inhibit recruitment	Carlumab/CNTO 888 (anti-CCL2 antibody)	Combined chemotherapy (docetaxel/ gemcitabine/ Paclitaxel and carboplatin/DOXIL®/ Caelyx® doxorubicin HCL liposome injection)	Solid tumors	I	2015	NCT01204996	149
		PF-04136309 (CCR2 antagonist)	Combined chemotherapy (Oxaliplatin/ Irinotecan/ Leucovorin/ Fluorouracil)	Pancreatic neoplasms	I	2016	NCT01413022	137
		Maraviroc (CCR5 antagonist)	Combined immunotherapy (Pembrolizumab)	Metastatic colorectal cancer	I	2022	NCT03274804	157
	Deplete and suppress TAMs	Pexidartinib/ PLX3397 (CSF-1R inhibitor)	Monotherapy	PVNS or GCT-TS	III	2019	NCT02371369	135
		ARRY-382 (CSF-1R inhibitor)	Combined immunotherapy (Pembrolizumab)	Advanced solid tumors	II	2022	NCT02880371	156
		Lacnotuzumab (MCS110)	Combined immunotherapy (Spartalizumab, PDR001)	Solid tumors	I/II	2024	NCT02807844	145
		PY314 (anti-TREM2 mab)	Combined immunotherapy (Pembrolizumab)	Advanced renal cell carcinoma	I	2024	NCT04691375	141
	Reprogramming TAM function	AVB-S6-500 (GAS6-AXL signaling pathway inhibitor)	Combined chemotherapy (Pegylated liposomal doxorubicin/ Paclitaxel)	Ovarian cancer	I	2021	NCT03639246	155
		R484/Resiquimod (TLR7/8 agonist)	Monotherapy	CTCL	I/II	2015	NCT01676831	147
		Olaparib (PARP inhibitor)	Combined immunotherapy (Durvalumab) and angiogenesis (Cediranib)	Advanced leiomyosarcoma	II	2023	NCT03851614	144
		ONCOS-102 (expressing GM-CSF)	Combination therapy with oncolytic virus and chemotherapy (Pemetrexed)	Malignant pleural mesothelioma	II	2023	NCT02879669	143
	Block immune checkpoints	Magrolimab/ Hu5F9-G4 (anti-CD47 mab)	Monotherapy	Hematological malignancies	I	2023	NCT04778397	154
			Monotherapy	Solid tumor	I	2019	NCT02216409	134
			Combined immunotherapy and Chemotherapy (Rituximab/ Rituximab + Gemcitabine)	B-cell non-Hodgkin's lymphoma	I/II	2018	NCT02953509	136
		Bintrafusp alfa	Bifunctional fusion protein therapy (anti TGF-β and PD-L1)	Non-small cell lung cancer	I	2024	NCT02517398	142
MDSCs	Inhibit recruitment	AZD5069 (CXCR2 inhibitor)	Combined enzalutamide	Metastatic castration resistant prostate cancer	I/II	2023	NCT03177187	148

Table 1 (*continued*)

Target	Mechanism	Drug	Strategy (combination drugs)	Conditions	Phase	Year	Identifier	Ref
		BL-8040 (CXCR4 antagonists)	Combined immunotherapy (Pembrolizumab)	Metastatic pancreatic cancer	II	2021	NCT02826486	150, 153
	Deplete MDSCs	Tadalafil (ATRA)	Combined cancer vaccine	Head and neck cancer	I	2014	NCT02544880	146
		Entinostat (hdaci)	Combined immunotherapy (Pembrolizumab)	MDS or AML	I	2024	NCT02936752	140
	Reprogramming TAM function	VT1021 (TSP-1 activator)	Monotherapy	Advanced solid tumors	I	2024	NCT03364400	139
Tregs	Targeting recruitment factors	Mogamulizumab (Anti-CCR84 antibody)	Combined immunotherapy (Nivolumab)	Solid tumor	I	2019	NCT02476123	152
	Targeting immune checkpoints	Tiragolumab (Anti-TIGIT mab)	Combined immunotherapy (Atezolizumab)	Non-small cell lung cancer	II	2022	NCT03563716	151
	Deplete Tregs	Mogamulizumab (Anti-CCR4 igg1 antibody)	Monotherapy	Advanced solid tumors CCR4-negative	I	2023	NCT01929486	138

TAMs, tumor-associated macrophages; MDS, myelodysplastic syndromes/neoplasms; AML, acute myeloid leukemia; MRCLS, myxoid/round cell liposarcoma; B-ALL, B-cell acute lymphoblastic leukemia; MRD, minimal residual disease; CEA, carcinoembryonic antigen; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; MZL, marginal zone lymphoma; CLL, chronic lymphocytic leukemia; NHL, non-hodgkin's lymphoma; SLL, small lymphocytic lymphoma; CNS, central nervous system; VHL, Von Hippel-Lindau; EGFR, epidermal growth factor receptor; CCL2, C−C motif chemokine ligand 2; CCR2, chemokine receptor 2; CSF-1R, colony-stimulating factor 1 receptor; PVNS, pigmented villonodular synovitis; GCT-TS, tenosynovial giant cell tumor of the tendon sheath; TREM2, triggering receptor expressed on myeloid cells 2; GAS6, growth arrest-specific 6; TLR7/8, toll-like receptor 7/8; CTCL, cutaneous T-cell lymphoma; PARP, poly(ADP-ribose) polymerase; GM-CSF, granulocyte-macrophage colony-stimulating factor; anti-CD47 mAb, anti-CD47 monoclonal antibody; B-cell NHL, B-cell non-hodgkin's lymphoma; CXCR2, C−X−C motif chemokine receptor 2; CXCR4, C−X−C motif chemokine receptor 4; ATRA, all-*trans* retinoic acid; PDE-5, phosphodiesterase type 5; MDSCs, myeloid-derived suppressor cells; HDACi, histone deacetylase inhibitor; TSP-1, thrombospondin-1; Anti-CCR4, IgG1 antibody anti-C−C chemokine receptor 4 immunoglobulin G1 antibody; Anti-TIGIT mab, anti-t cell immunoreceptor with IG and ITIM domains monoclonal antibody.

AVB-S6-500, when used in combination with chemotherapy drugs, showed promise in a clinical trial for ovarian cancer[155]. Furthermore, the TLR7/8 agonist R484, Resiquimod, as a monotherapy, entered phases I and II of a clinical trial for cutaneous T-cell lymphoma in 2015[147]. Using the "β-Elemene@Stanene" strategy for enhancing cancer chemo-immunotherapy, researchers overcome immunosuppression and enhance the effectiveness of chemo-immunotherapy. This approach is significant as it not only demonstrates the therapeutic efficacy of STNSP-based nano drug delivery systems against immunosuppressive tumors but also establishes a versatile platform for 2D nanomaterial-mediated cancer chemo-immunotherapy[158].

Immune checkpoint inhibitors also play a significant role in cancer therapy. Magrolimab/Hu5F9-G4, a monoclonal antibody targeting CD47, entered phase I of a clinical trial for hematological malignancies in 2023[154]. Moreover, Magrolimab is also used as a single therapy or in combination with Rituximab and Gemcitabine for the treatment of B-cell non-Hodgkin's lymphoma in clinical trials[136]. Bintrafusp alfa, as a bifunctional fusion protein targeting TGF-β and PD-L1, has demonstrated potential in the second-line treatment of non-small cell lung cancer[142].

4.5. Targeting MDSCs

Myeloid-derived suppressor cells (MDSCs) play a significant role in the TME by inhibiting the immune response against cancer. Various strategies are being explored to target MDSCs and enhance the efficacy of immunotherapy. One approach to inhibit the recruitment of MDSCs is the use of AZD5069, a CXCR2 inhibitor, which is being studied in combination with enzalutamide for metastatic castration-resistant prostate cancer (mCRPC). This clinical trial is in phase I/II and was initiated in 2023[148]. Another strategy involves the use of BL-8040, a CXCR4 antagonist, which is being combined with pembrolizumab, an anti-PD-1 therapy, for the treatment of metastatic pancreatic cancer. This trial is in phase II and began in 2021[150,153]. To deplete MDSCs, Tadalafil, also known as ATRA, is being investigated in combination with a cancer vaccine for head and neck cancer. This phase I trial started in 2014[146]. Entinostat, a histone deacetylase inhibitor (HDACi), is being explored in combination with pembrolizumab for the treatment of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). This phase I trial was initiated in 2024[140]. Lastly, the reprogramming of MDSCs is being targeted with VT1021, a TSP-1 activator, which is being used as a monotherapy for advanced solid tumors. This phase I trial started in 2024[139].

4.6. Targeting Tregs

Regulatory T cells (Tregs) are a subset of T cells that play a critical role in maintaining immune tolerance and suppressing excessive immune responses, including those against tumors. Targeting Tregs has emerged as a promising strategy to enhance the efficacy of cancer immunotherapy. One approach to target Tregs involves the use of mogamulizumab, an anti-CCR8 antibody, which is being investigated in combination with nivolumab,

an immune checkpoint inhibitor, for the treatment of solid tumors. This clinical trial is in phase I and was initiated in 2019[152]. Another strategy aims to target immune checkpoints by using tiragolumab, an anti-TIGIT monoclonal antibody, in combination with atezolizumab for non-small cell lung cancer. This trial is in phase II and began in 2022[151]. Depletion of Tregs is also being explored as a therapeutic approach. Mogamulizumab, an anti-CCR4 IgG1 antibody, is being studied as a monotherapy for advanced solid tumors that are CCR4-negative. This phase I trial started in 2023[138]. Published clinical trials for cancer nanoparticles are shown in Table 2[159-183].

5. Role of nanomedicine in overcoming tumor immunosuppression

5.1. Inhibiting immunosuppressive cell recruitment and function

The engagement of immunosuppressive cells within the TME is a pivotal factor propelling cancer progression and impeding therapeutic efficacy. Nanomedicine presents groundbreaking methods to regulate these processes, thus amplifying the potency of cancer therapies. Inhibiting the recruitment of immunosuppressive cells can be achieved through nanoparticles that disrupt the signaling pathways guiding their migration toward tumors. For instance, nanoparticles designed to deliver siCCR2 have been effectively utilized to target inflammatory monocytes, consequently reducing their accumulation in the TME and altering the immunosuppressive milieu[184]. Another strategy encompasses the deployment of nanoparticles laden with pCCL2 LPD NP, which are directed at TAMs, suppressing the expression of tumor-associated antigens while simultaneously promoting T-cell infiltration and depleting M2 macrophages[91].

Nanomedicine possesses the capability to target the functionality of immunosuppressive cells already entrenched within the TME. For example, M2pep/anti-VEGF siRNA nanoparticles have been crafted to specifically hone in on M2 macrophages, thereby silencing VEGF mRNA and neutralizing their immunosuppressive capabilities[94]. Along similar lines, α-M2pep/cholsiCD115 nanoparticles have been engineered for dual-targeted delivery to M2-type TAMs, enhancing the precision of therapeutic interventions[95]. Beyond inhibition, it can also modulate the phenotype of immunosuppressive cells, directing them toward a more beneficial state. For example, DOX/αGC PLT/DOX/αGC NPs have shown the capacity to impede the adhesion between granulocytic myeloid-derived suppressor cells (G-MDSCs) and endothelial cells, which leads to a reduction in MMP-9 expression in G-MDSCs and a subsequent compromise of their immunosuppressive activity[103].

5.2. Depletion and suppression of immunosuppressive cells

The targeted depletion and suppression of immunosuppressive cells are essential in cancer therapy, aimed at normalizing the TME and bolstering antitumor immune responses. Nanomedicine facilitates this strategy through the development of targeted delivery systems designed to selectively eliminate or modulate the activity of these cells. ALN-BSP conjugated polymer nanoparticles have been specifically engineered to target and deplete TAMs, thereby inhibiting angiogenesis and enhancing local immune surveillance[185]. BLZ-945, a CSF-1R inhibitor, when delivered *via* nanocarriers, enhances the targeting of TAMs and contributes to their depletion[186]. MDSCs are immature myeloid cells that accumulate in various cancers and are pivotal in immune suppression. DSB PSNP nanoparticles simulate apoptosome-mediated phagocytosis for tumor-specific macrophage targeting, resulting in the depletion of immunosuppressive cells[187]. Additionally, DOX S-CM-HPAD NPs have been formulated to suppress the activity of MDSCs, regulate tumor immune evasion, and stimulate T-cell proliferation and cytokine production[188].

Combination therapies targeting both tumor vascular epithelial cells and MDSCs have shown promising results. An example of this is the DOX-NP/Sunitinib DS@HLipo liposomes, which are crafted to target multiple cellular components, dismantling the immunosuppressive network and amplifying the collective antitumor defense[107]. Beyond cell depletion, the modulatory potential of MDSCs is also utilized to reduce their immunosuppressive impact. SCARB1-targeted HDL NP therapy illustrates this approach, where the activity of MDSCs is dampened, thus fostering a more favorable TME for effective immune reactions[109].

5.3. Reprogramming immunosuppressive cells

Within the TME, macrophages can assume a spectrum of phenotypes, with M2 macrophages often manifesting immunosuppressive characteristics. The reprogramming of these cells from a suppressive to an activated state, such as the pro-inflammatory M1 phenotype, can leverage their potential in the fight against cancer. Nanomedicine plays a pivotal role in this strategy by enabling the targeted delivery of reprogramming agents that induce this phenotypic shift towards antitumor activity. For example, micelles containing Poly I:C and ZnPP have been used to reprogram TAMs by modulating the expression of ROS and STAT3, promoting a shift towards the M1 phenotype[189]. SiRNA can be employed to target specific genes that contribute to the immunosuppressive phenotype of cells. Nanoparticles, such as AS/IKKβ siRNA ST-AS&Si, have been engineered to co-deliver M2-targeted IKKβ siRNA and the pH-sensitive STAT6 inhibitor AS, enabling precise drug release and effectively repolarizing M2 macrophages[117]. The delivery of specific genes can also reprogram immunosuppressive cells. Nanoparticles like IRF5/IKKβ mRNA NPs have been engineered to provide genes encoding master regulators of macrophage polarization, which can instruct macrophages to adopt a more antitumor phenotype[190-192]. Combining reprogramming agents with other therapies can enhance the overall effect. For example, liposomes such as GEF/VOR tLGV have been applied to reprogram TAMs and activate a specific signaling axis for drug-resistant non-small cell lung cancer, integrating the reprogramming effect with chemotherapeutic agents[193]. Moreover, Dendritic cells can also be reprogrammed to enhance their antigen-presenting capabilities. Nanoparticles, such as CpG ODN/anti-IL-10 ODN/anti-IL-10R ODN PDO, have been used to effectively educate macrophages without impacting systemic immunity, fostering a more robust immune response against cancer[194].

5.4. Activating phagocytic function of immune cells

The innate ability of immune cells to engulf and neutralize tumor cells through phagocytosis is a vital component of the body's defense mechanisms against cancer. Nanomedicine can be utilized to enhance this function, thereby improving the body's innate ability to combat cancer. One approach involves the use of nanoparticles to deliver agents that can directly enhance the

Table 2 Published clinical trials for cancer nanoparticles.

Active component	Name	Ligand target	Nanocarrier	Payload	Indication	Trial registration	Year	Status	Ref
Chemotherapy Drugs	Doxil	NA	Liposome	DOX	Karposi's sarcoma, ovarian cancer, multiple myeloma	NA	1995	Approved by FDA	169
	Daunoxome	NA	Liposome	Daunorubicin	Karposi's sarcoma	NA	1996	Approved by FDA	168
	Marqibo	NA	Liposome	Vincristine	Acute lymphoblastic leukemia	NCT00495079	2012	Approved by FDA	159
	Onivyde	DNA topoisomerase I inhibitor	Liposome	Irinotecan	Pancreatic cancer	NCT00813072	2015	Approved by FDA	166
	MBP-426	Transferrin receptor	Liposome	Oxaliplatin	Gastric, oesophageal and gastro-oesophageal adenocarcinoma	NCT00355888	2009	Phase I	165
	Thermodox	NA	Liposome	DOX	Hepatocellular carcinoma	NCT02112656	2009	Phase III	164
	Genexol-PM	NA	Polymeric nanoparticles	Paclitaxel	Breast cancer and NSCLC	NA	2007	Approved in South Korea	163
	Opaxio	NA	Polymeric nanoparticles	Paclitaxel	Head and neck cancer; Glioblastoma	NA	2012	Approved by FDA	162
Antibodies	Targomirs	Anti-EGFR	Minicell	Mir-16-based microRNA mimic	NSCLC, MPM	NCT02369198	2017	Phase I	178
	AB160	Anti-VEGF	Nab-paclitaxel	Bevacizumab	GUC	NCT02020707	2024	Phase I	171
Antibody fragments	C225-ils-DOX	Anti-EGFR Fab'	Liposome	DOX	Solid tumors	NCT01702129	2012	Phase I	177
	MM-302	Anti-HER2 scfv	Liposome	DOX	Breast cancer	NCT01304797	2018	Phase I	179
	SGT-53	Anti-TFR scfv	Liposome	P53 plasmid	Solid tumors	NCT00470613	2013	Phase I	175
					Pancreatic cancer	NCT02340117	2008	Phase II	173
	SGT-94	Anti-TFR scfv	Liposome	RB94 plasmid	GUC	NCT01517464	2016	Phase I	176
	Lipovaxin-MM	Anti-DC-SIGN VH	Liposome	Melanoma antigens and IFN-γ	Melanoma	NCT01052142	2018	Phase I	181
Proteins	MBP-426	Tf	Liposome	Oxaliplatin	Solid tumors	NCT00355888	2009	Phase I	183
					AGC or EAC	NCT00964080	2009	Phase I/II	182
	CALAA-01	Tf	Polymeric nanoparticles	RRM2 siRNA	Solid tumors	NCT00689065	2014	Phase I	174
Peptides	Mepact	NA	Liposome	Muramyl tripeptide phosphatidyl ethanolamine	Non-metastatic osteosarcoma	NA	2009	Approved in Europe	167
	Rexin-G	Vwf-derived motif	Retroviral vector	Dn-CCNG1	Osteosarcoma	NCT00572130	2009	Phase II	160
				Dn-CCNG1	Sarcoma	NCT00505713	2019	Phase I/II	180
				Dn-CCNG1	Pancreatic cancer	NCT00504998	2019	Phase I/II	180
Inorganic nanoparticles	Aguix	Radiotherapy	Diethylene glycol	Gadolinium	Metastatic brain tumor	NCT02820454	2021	Phase I	170
	NBTXR3	Radiotherapy		Hafnium oxide NPs	Adult soft tissue sarcoma	NCT01433068	2019	Approved in Europe	161
	^{188}Re-liposome	NA	Liposome	^{188}Re	^{188}Re	Approved in Taiwan, China. MA1101G0	2019	Phase 0	172

AGC, advanced gastric cancer; dn-CCNG1, dominant-negative mutant construct of cyclin G1; DOX, doxorubicin; EAC, esophageal adenocarcinoma; GUC, genitourinary cancers; HER2, growth factor receptor 2; MPM, malignant pleural mesothelioma; NSCLC, non-small cell lung cancer; NP, nanoparticles; Tf, transferrin; vWF, von Willebrand factor.

phagocytic activity of macrophages. Notably, recombinant CALR/aCD47 nanoparticles have demonstrated the capacity to enhance macrophage-mediated phagocytosis, thereby bolstering antitumor effectiveness[195]. CD47, a protein frequently overexpressed on cancer cells, can suppress macrophage phagocytosis by engaging with its receptor on macrophages, signal regulatory protein alpha (SIRPα). To counteract this, nanoparticles like vSIRPα-probe have been formulated to obstruct this interaction, promoting CD47-targeted cancer visualization and stimulating anticancer immune responses reliant on phagocytosis[196]. Additionally, the concept of programming macrophages into CAR-M1 macrophages through nanocomplexes represents a groundbreaking tactic. This has been realized through the conveyance of the CAR gene MPEI/pCAR−IFN-γ, which provides macrophages with chimeric antigen receptors capable of specifically identifying and phagocytosing tumor cells[197]. Dendrimer-based proton sponge nanocomposites exemplify another avant-garde strategy. The combination of G5AcP dendrimer with Cu(II) and DOX has illustrated the potential to curb autophagy and reprogram the TME to foster macrophage activation, leading to the efficacious eradication of tumors[198]. These advancements underscore the transformative potential of nanomedicine in invigorating the phagocytic function of immune cells and, by extension, the overall immune response against cancer.

5.5. *Modulating Treg function*

Tregs play a critical role in preserving immune system balance, yet their abundance within the TME. can hinder the body's antitumor defenses. Nanomedicine offers sophisticated, targeted methods to influence Treg behavior, either by reinforcing their function to strengthen tumor immunity or by diminishing their suppressive effects to boost the potency of cancer therapies. Gold nanoparticle conjugates have been employed to effectively deliver nucleic acids into Tregs, thereby modulating their function and amplifying the immune response against tumors[113]. Charge-conversion polymer nanoparticles, like SPDMCN, have been crafted for improved stability and the ability to penetrate the TME more deeply. These particles are capable of releasing their cargo, dimethylchitosan (DMC), under the acidic conditions prevalent in the TME, thereby suppressing the expression of FoxP3 and reducing the immunosuppressive impact of Tregs[114]. Aptamer-peptide chimeras, such as AptCD28-P60, have been developed to improve the precision targeting of Tregs, enabling a decrease in the required dosage while simultaneously amplifying the immune response[115]. By employing these nanotechnological strategies, researchers can more effectively manage the presence and function of Tregs in the TME, tipping the scales in favor of a more robust immune response against cancer.

5.6. *Combine with traditional therapies*

The fusion of nanomedicine with traditional cancer therapies has shown great potential in overcoming the constraints of current therapeutic options and improving patient outcomes. This integration combines the precision of nanoscale drug delivery systems with the established efficacy of conventional treatments, creating a synergistic approach to cancer therapy. For instance, engineered platelets displaying PD-1 have been utilized to enhance cancer immunotherapy following surgery. This method leverages the immune system's ability to target any residual cancer cells that may remain after surgical intervention[199]. The application of nanoparticle-mediated hyperthermia has been employed to deplete tumor-associated Tregs, which can significantly boost the effects of ICB cancer immunotherapy. This approach can re-energize the immune system's ability to detect and destroy cancer cells[200]. The encapsulation of chemotherapeutic agents like MTO/IND within liposomes can halt cancer progression by inducing immunogenic cell death (ICD) and inhibiting the IDO-1 pathway simultaneously. This combined therapeutic strategy can trigger a robust immune response against the tumor[201]. Normalization of the tumor's acidic microenvironment through the use of nanoparticles, such as those delivering siLdha, can improve the effectiveness of traditional therapies. This is achieved by optimizing drug delivery and enhancing the functionality of immune cells[202]. Liposomes co-encapsulating Dox and alendronate can increase the sensitivity to both chemotherapy and immunotherapy by repolarizing TAMs and activating gamma-delta T lymphocytes. This dual-targeted strategy can significantly increase the overall effectiveness of cancer treatment[203]. Chimeric peptide-engineered self-delivery nanomedicines for photodynamic therapy have been developed to eradicate primary tumor growth and reprogram M2-type TAMs to the M1-type, thereby stimulating T cell-mediated antitumor immunity. This multifaceted therapeutic approach can provide substantial improvements over traditional treatments[204].

The integration of nanomedicine with oncolytic virus-like particles has opened new avenues for enhancing tumor immunotherapy. A recent study presents an innovative approach using an ion-enhanced nanoplatform, PolyIC@ZIF-8, which not only mimics the function of an oncolytic virus by inducing tumor cell apoptosis and recruiting T cells in a tumor antigen-dependent manner but also releases $Zn2^{+}$ to further enhance T cell recruitment and activation in a tumor antigen-independent manner[205]. This strategy signifies a promising direction for the development of new immunotherapies that can effectively target and eradicate tumors. The interaction between intracellular microbiota (ITM) and TME provides a new approach for tumor immunotherapy. The presence of ITM in TME can promote the delivery of antigens to tumor cells, provide cross-antigens to promote immune cells to attack tumors, and also affect the activity of immune cells and stromal cells. This type of treatment mainly works by deleting harmful bacteria, increasing beneficial bacteria, and changing microbial metabolites[59]. The innovative approach utilizing colistin crosslinked gemcitabine micelles (CCGM) presents a significant advancement in overcoming tumor drug resistance induced by intratumoral microorganisms. The study develops a co-delivery system of an antibiotic and an anticancer drug, encapsulated within micelles that are designed to release their payload in response to the tumor's microenvironment. Specifically, the CCGM is triggered by intracellular glutathione levels within the tumor to release colistin and gemcitabine, thereby inhibiting microbial growth and reversing drug resistance[206].

5.7. *Multifaceted biomimetic systems*

Incorporating biomimetic systems into nanomedicine has paved innovative paths in cancer therapy. These systems harness the body's inherent mechanisms to refine treatment efficacy[207]. Biomimetic nano-RBCs, which imitate red blood cells, have shown promise in homing in on endogenous TAMs. By doing so, they reprogram the immunosuppressive TME to enhance chemo-immunotherapy. These biomimetic systems are capable of depleting M2-type TAMs and impeding their recruitment, which in turn, escalates the impact of traditional chemotherapy and

immunotherapy agents[208]. The *in situ* generation of ROS-responsive scaffolds, embedded with therapeutic agents like gemcitabine and checkpoint inhibitors, represents an integrated therapy approach. This method utilizes biomaterials to escalate the potency of treatments. Such scaffolds can boost the tumor's immunogenic properties and increase the levels of proinflammatory cytokines, leading to a synergistic effect when paired with immunotherapy[209]. CXCR4-targeting nanocomplexes, such as FX/paclitaxel, have been designed to enhance T-cell infiltration and support antigen presentation. These nanocomplexes work to reduce the presence of MDSCs and Tregs, thereby amplifying the effectiveness of anti-PD-L1 immunotherapy[210]. The development of multifunctional redox-responsive nanoplatforms stands as an advanced biomimetic strategy. These platforms have the potential to activate both macrophages and T cells for antitumor immunotherapy. They can be customized to respond to specific stimuli within the TME, releasing their therapeutic payloads in a controlled manner to ensure maximum therapeutic benefits (Fig. 4)[211]. The strategies on nanomedicine targeting the tumor immune microenvironment are shown in Table 3[91,94,95,103-105,107-110,113-115,117,158,184-190,193-206,208-222].

6. Future directions of nanomedicine in immunotherapy

6.1. *Development of multifunctional nanoplatforms*

The progression of nanomedicine is characterized by a significant trend towards the development of sophisticated multifunctional nanoplatforms, which are set to revolutionize cancer therapy[223,224]. These cutting-edge platforms are expected to lead a therapeutic transformation by overcoming the limitations of conventional single-agent treatments and adopting integrated systems that can perform simultaneous diagnosis, drug delivery, and therapeutic intervention. The multifunctionality of these nanoplatforms will be achieved through the strategic integration of various components, each playing a distinct role in the therapeutic sequence. For instance, the integration of imaging agents into nanoplatforms allows for the real-time tracking of therapeutic outcomes[225,226]. This feature empowers medical professionals to promptly assess the effectiveness of treatments and make informed decisions on patient care.

Moreover, these nanoplatforms are crafted to ensure the precise delivery of a wide range of therapeutic agents. This includes

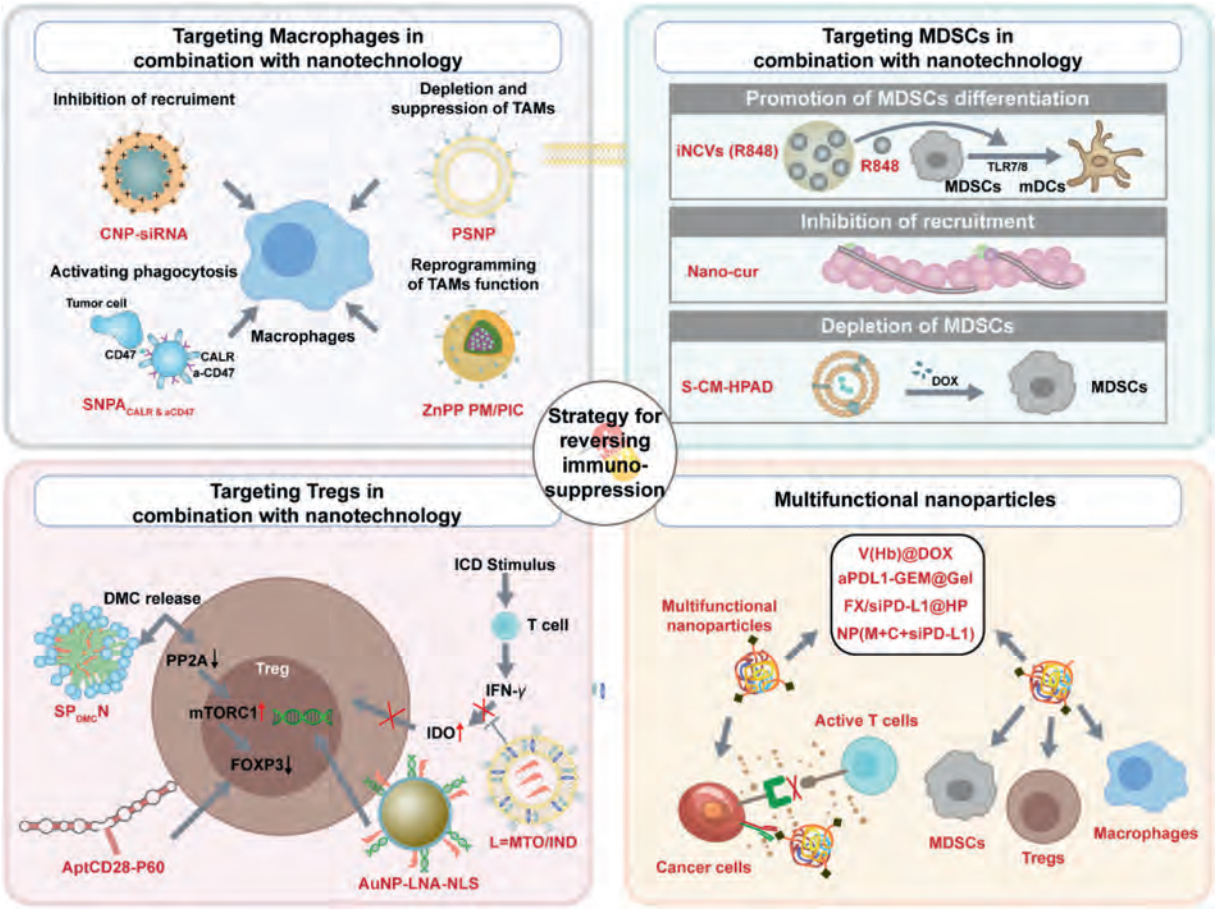

Figure 4 Strategy for reversing immunosuppression in tumor microenvironment. Nanotechnology is employed to reverse immunosuppression within the tumor microenvironment, enhancing the body's natural ability to combat cancer. This strategy involves targeting immune-suppressive cells such as tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) with nanoparticles designed to deplete or reprogram these cells. Additionally, regulatory T cells (Tregs) are targeted to reduce their immunosuppressive effects. Multifunctional nanoparticles are used to deliver therapeutic agents that activate T cells, induce cancer cell death, and stimulate an immune response. By modulating the tumor microenvironment and enhancing immune cell function, this approach aims to overcome the immunosuppressive barriers that tumors often use to evade immune detection and destruction.

Table 3 Strategies on nanomedicine targeting the tumor microenvironment.

Mechanism	Delivery system	Payload	Immune niche	Function	Year	Ref
Inhibit recruitment	Nanoparticle	Siccr2 CNP-siRNA	TAMs	Increase the sensitivity of chemotherapy	2018	184
	Nanoparticle	Pccl2 LPD NP	TAMs	Suppresses TAMs, increases T-cell infiltration and decreases the population of M2 macrophages	2021	91
	Nanoparticle	M2pep/anti-VEGF siRNA	M2 macrophages	Silence VEGF mRNA in M2 macrophages and M2pep to increase its M2 TAMs targeting	2015	94
	Nanoparticle	A-M2pep/cholsicd115	M2-type TAMs	Dual-targeted delivery of cholinesterase CD115 to M2-type TAMs	2017	95
	Nanoparticle	DOX/αGC PLT/DOX/αGC NPs	MDSCs	Inhibit the adhesion between G-MDSCs and endothelial cells and reduce the expression of MMP-9 in G-MDSCs	2020	103
	Nano-filament	Curcumin Nano-cur	MDSCs	Relieve the tumor burden by regulating and improving the TME	2022	104
	Nanosized sponge	Pcss	Neutrophils	Inhibit most membrane receptors on neutrophils to neutralize MDSC-related cytokine effects	2020	105
	Nanoparticle	Bi2-WO6-NP PM-biw nps	MDSCs	Integrate radiation therapy, PTT and PDT to overcome the immunosuppression caused by MDSCs.	2020	218
Deplete and suppress immunosuppressive cell	Conjugated polymer	ALN-BSP	TAMs	Eliminates TAMs, inhibits angiogenesis, and restores local immune surveillance	2014	185
	Conjugated polymer	BLZ-945	TAMs	Enhance targeting of the highly selective CSF-1R inhibitor BLZ-945 with nanocarriers	2017	186
	Nanoparticle	DSB PSNP	Tumor-specific macrophages	Mimics apoptosome-mediated phagocytosis for tumor-specific macrophage targeting	2020	187
	Conjugated polymer	DOX PAMB/DOX	Macrophages	Stepwise-responsive; TME hypoxia and high ROS for targeted delivery; PEG modification to reduce hepatic accumulation	2020	188
	Nanoparticle	DOX S-CM-HPAD NPs	MDSCs	Inhibit MDSCs to regulate tumor immune escape; improve T-cell proliferation and stimulate cytokine secretion to alter TME	2019	107
	Liposome	DOX-NP/Sunitinib DS@hlipo	Tumor vascular epithelial cells and MDSCs	Target multiple regions, including tumor vascular epithelial cells and MDSCs	2022	108
	Micelle	Sunitinib sunb-PM	MDSCs	Reduce MDSCs in TME and inhibit Stat3 and AKT signaling pathways to induce apoptosis in tumor cells	2017	109

Table 3 (*continued*)

Mechanism	Delivery system	Payload	Immune niche	Function	Year	Ref
	Nanoparticle	HDL nps SCARB1-targeted HDL NP therapy	MDSCs	Inhibited MDSC activity	2018	110
Reprogramming immunosuppressive cells	Micelle	Poly I:C Znpp PM/PIC	TAMs	Repolarize TAMs through modulating the expression of ROS and STAT3	2018	189
	Nanoparticle	AS/IKKβ siRNA ST-AS&Si	M2 macrophages	Codelivery of M2-targeted IKKβ siRNA and STAT6 inhibitor AS; pH-sensitive for precise drug release	2020	117
	Nanoparticle	IRF5/IKKβ mRNA IRF5/IKKβ mRNA nps	Macrophages	Provide with genes encoding master regulators of macrophage polarization.	2019	190
	Liposome	GEF/VOR TLGV	TAMs	Repolarize TAMs and trigger ROS/MSRA/EGFRT790 M axis for drug-resistant NSCLC	2017	193
	Nanoparticle	Cpg ODN/anti-IL-10 ODN/anti-IL-10R ODN PDO	TAMs	Delivery of ODN to TAMs effectively re-educated macrophages without affecting systemic immunity	2012	194
	2D stanene-based nanosheets (STNSP)	*B*-Elemene	TAMs	Overcome immunosuppression and enhance chemo-immunotherapy	2023	158
	Nanoparticle	CpG ODNs MCMC/HA/PS/ODN NPs	Macrophages	Dual-targeting delivery system enhanced secretion of proinflammatory cytokines and shifted to M1	2017	222
	Nanocomplex	CpG ONDs GGIC	Macrophages	Provide synergistic photothermal and immunological effects under NIR	2014	217
	Microparticles	SR-B1 targeting peptide/P5091	Brain macrophages	Cross the BBB and target M2 to reprogram it	2023	221
	Hydrogel scaffold	KN93 MRK hydrogel	Tumor-associated macrophages	Provide a synergistic tumor suppression effect against through reshaping TMEs.	2020	195
	Injectable hydrogel	PP2/R848 PR-Gel	Tumor tissue	Improve the drug accumulation at the tumor tissue and enable more enduring drug level	2021	216
	Engineered-TAA	Telratolimod telratolimod@adipcyt	TAMs	TAA are engineered to promote the polarization of TAMs to M1	2023	220
	Milk exosome (MEXO) system	7D12-MEXO-M2pep-siPDL1	M2 macrophages	Inducing reprogramming of M2-type TAMs to M1-type macrophages	2024	215
	Engineered extracellular vesicles	AIE-active photosensitizers	Macrophages	Improving tumor immunosuppressive microenvironment and overcoming immune escape through photodynamic therapy (PDT)	2024	214

(*continued on next page*)

Table 3 (*continued*)

Mechanism	Delivery system	Payload	Immune niche	Function	Year	Ref
	Poly(2-alkyl cyanoacrylate) (PACA) nanoparticles	Cabazitaxel (CBZ)	Myeloid cells, especially macrophages	Enhanced effect of drug-loaded PEBCA variants compared with free drug and PEHCA NPs, contributing to an inflammatory, immune activated tumor microenvironment	2024	213
	Cyclodextrin-modified poly(D,L-lactide-*co*-glycolide) (PLGA) nanoparticles	R848	TAMs	Promoting M1 polarization of TAMs and enhancing the efficacy of colon cancer treatment	2024	212
Activate phagocytic function	Nanoparticle	Recombinant CALR/aCD47	Macrophages	Enhance the phagocytosis and improved antitumor efficacy	2020	219
	Activatable prob	vSIRPα-probe	Macrophages	Facilitate CD47-targeted cancer imaging and elicit anticancer immune responses depending on phagocytosis	2020	196
	Nano-complexes	CAR gene MPEI/pCAR-IFN-γ	Macrophages	Program macrophages into CAR-M1 macrophages displaying enhanced cancer-directed phagocytosis	2021	197
	Dendrimer-based proton sponge nanocomposites	Proton sponge g5acp dendrimer, Cu(II), and DOX	TAMs	Inhibiting autophagy and reconstructing TME toward macrophage activation for effective tumor elimination	2024	198
Enhancing Treg efficiently	Nanoparticle	LNA/NLS AuNP-LNA-NLS	Tregs	Import nucleic acids into Tregs efficiently	2016	113
	Nanomodulator	DMC SPDMCN	Tregs	Charge conversion improved stability and tumor infiltration, low-pH triggered the release of DMC to inhibit FoxP3 expression	2021	114
	Aptamer-peptide chimera	Aptcd28-P60	Tregs	Enhance targeting to reduce dose and strengthen patient immunity	2016	115
Combine with traditional therapies	Engineered platelet	PD-1	−	Enhance cancer immunotherapy after surgery	2018	199
	Nanoparticle	Ionps	Tregs	Deplete Tregs and collaboratively enhance ICB cancer immunotherapy	2020	200
	Liposome	MTO/IND	−	Inhibit cancer progression in model mice through concurrent induction of ICD and inhibition of the Ido-1 pathway	2020	201
	Nanoparticle	siLdha	−	Normalize tumor acidic microenvironment	2019	202
	Liposomes	Doxorubicin (Dox) and alendronate (Ald)	TAMs and gamma-delta T lymphocytes	Enhance the sensitivity of chemotherapy and immunotherapy by repolarizing TAMs and activating gamma-delta T lymphocytes	2023	203

Table 3 (*continued*)

Mechanism	Delivery system	Payload	Immune niche	Function	Year	Ref
	Chimeric peptide-engineered self-delivery nanomedicine	Photosensitizer chlorine e6 (Ce6) and TLR7/8 agonist imiquimod (R837)	TAMs	Eradication of primary tumor growth through PDT, polarization of M2-type TAMs to M1-type, activation of T cell antitumor immunity	2023	204
	Oncolytic virus like	Polyic and Zn^{2+}	T Cells	Induced tumor cell apoptosis; enhanced T cell-mediated antitumor response	2022	205
	Nano-micelle	Colistin and gemcitabine	Tumor microbe	Intracellular glutathione triggers the release of colistin and gemcitabine, inhibiting tumor microbe growth and eliminating drug resistance.	2022	206
More than one biomimetic system	Biomimetic cell	DOX/O2 V [162] @DOX	TAMs	Deplete M2-type TAMs and reduce the recruitment of TAMs	2021	208
	Scaffold	Apdl1/GEM	−	Boost tumor immunogenicity and upregulate expression of proinflammatory factors	2018	209
	Nanocomplex	FX/paclitaxel	T Cells	Increase T-cell infiltration; to promote antigen presentation and decrease the number of MDSCs/Tregs	2020	210
	Nanoparticle	Motolimod/catalase/ siPD-L1	TAMs, MDSCs, T cells	Combined immunotherapy targeting TAMs, MDSCs and T cells to activate both innate and adaptive immunity	2023	211

TAAs, tumor-associated antigens; M2 macrophages, M2-type tumor-associated macrophages; VEGF mRNA, vascular endothelial growth factor messenger RNA; M2pep, M2-targeting peptide; TAMs, tumor-associated macrophages; CSF-1R, colony-stimulating factor 1 receptor; ROS, reactive oxygen species; TME, tumor microenvironment; PEG, polyethylene glycol; IKKβ, inhibitor of nuclear factor kappa-b kinase beta; ODN, oligodeoxynucleotide; NIR, near-infrared; BBB, blood−brain barrier; MDSCs, myeloid-derived suppressor cells; MMP-9, matrix metalloproteinase-9; PTT, photothermal therapy; PDT, photodynamic therapy; ICD, immunogenic cell death; IDO-1, indoleamine 2,3-dioxygenase 1; DOX, doxorubicin; ATRA, all-*trans* retinoic acid; IL-2, interleukin-2; Tregs, regulatory t cells; DMC, dimethylchitosan; FoxP3, forkhead box p3.

the targeted delivery of traditional chemotherapeutic agents to cancer cells, thus minimizing harm to healthy cells. Additionally, the incorporation of immune modulators is intended to strengthen the patient's immune response, enhancing its capacity to identify and combat cancer cells more effectively[211]. The targeted delivery of immune modulators could counteract the immune evasion strategies used by tumors, thereby reinforcing the body's natural defenses against cancer. Furthermore, some researchers have developed a light-triggered sequential delivery strategy that has shown great promise in multimodal cancer therapy targeting multiple aspects, including the delivery of DOX, photosensitizer porphyrin-phospholipid (PoP), and sunitinib, in distinct spatial locations within the tumor microenvironment[108].

6.2. *The emergence of theranostics*

Theranostics marks a pivotal fusion of diagnostic and therapeutic modalities, ushering in a new age of personalized medicine[227]. This holistic strategy facilitates a simultaneous approach to cancer treatment and diagnosis, supplying vital data for crafting individualized patient care plans. The amalgamation of these two functionalities within NPs is a cutting-edge advancement, presenting considerable promise for the advancement of oncology care. Theranostic NPs are meticulously designed to traverse biological barriers and target tumor immune microenvironments with precision. They are capable of being laden with a range of therapeutic agents, including chemotherapy drugs, immunotherapies, or gene-editing technologies, all intended for direct delivery to cancerous cells. Simultaneously, these NPs can also be embedded with diagnostic markers that facilitate the assessment of treatment efficacy and the genetic and environmental profiling of tumors[111,195].

The diagnostic component of theranostic nanoparticles often includes imaging agents that are traceable through a variety of imaging techniques such as magnetic resonance imaging (MRI)[228], positron emission tomography (PET)[229], or fluorescence imaging[230]. These agents provide real-time imaging of the tumor and the therapeutic agents' distribution, thus allowing for the accurate monitoring of drug delivery and treatment results.

Moreover, theranostic nanoparticles can be tailored to react to specific stimuli present in the tumor immune microenvironment. For instance, they can be engineered to discharge their therapeutic cargo upon encountering the acidic pH[231] or the hypoxic conditions characteristic of tumors[232]. This responsive drug delivery system enhances the precision and potency of the treatment while minimizing the impact on healthy tissues. A remarkable feature of theranostic nanoparticles is their ability to map the genetic makeup of tumors. By incorporating molecular probes or nucleic acid sensors, these nanoparticles are able to identify specific genetic anomalies or expression profiles within the tumor. Such insights are crucial for the selection of targeted therapeutics and the development of personalized treatment plans[233].

6.3. *Precision engineering of nanoparticles*

The advancement of nanomedicine is significantly contingent upon the precision engineering of NPs, a pivotal strategy to enhance the effectiveness of cancer treatments. Central to this strategy is the meticulous optimization of NP dimensions. Nanoparticles with diameters ranging from 10 to 200 nm can effectively accumulate in tumors *via* the enhanced permeability and retention (EPR) effect[234]. Nonetheless, to facilitate deeper penetration into the tumor mass, smaller nanoparticles may offer benefits[235]. Current research is dedicated to pinpointing the ideal size that strikes a balance between efficient tumor accumulation and the ability to traverse compact tumor tissues. The shape of nanoparticles is another crucial factor influencing their interaction with biological systems. Rod-shaped or discoidal NPs have demonstrated superior cellular uptake and tissue penetration compared to spherical NPs[236]. This superior penetration is credited to their ability to navigate more readily between cells. Current research is investigating the effects of various NP shapes on biodistribution, cellular internalization, and therapeutic efficacy.

The surface charge of nanoparticles is a tunable feature that significantly influences their engagement with the TME[237]. Cationic NPs can more effectively interact with the negatively charged cell membranes, potentially boosting cellular uptake. However, this may also lead to increased clearance by the reticuloendothelial system[238]. Consequently, the formulation of methods to mask the positive charge under normal physiological conditions, while enabling charge exposure in the acidic TME, is a burgeoning field of research. Additionally, the decoration of NP surfaces with targeting ligands, such as antibodies, peptides, or small molecules, promotes the active targeting of specific cells within the TME. This targeted approach can enhance binding and uptake by the desired cell population, thus elevating the therapeutic index of the treatment[87]. Moreover, the integration of stimuli-responsive linkers that trigger the release of therapeutic agents in response to TME-specific stimuli, like pH fluctuations or enzymatic activity, is a promising strategy to enhance precision medicine[202].

6.4. *Application of nanotechnology in immune cell engineering*

The convergence of nanotechnology and immune cell engineering is paving innovative avenues in the field of oncology[208]. Leveraging the unique properties of nanomaterials, scientists are developing strategies to enhance the precision targeting of tumors by immune cells, including T lymphocytes and NK cells[239]. A significant application in this domain is the use of nanotechnology for the genetic modification of immune cells. Techniques such as CRISPR/Cas9 can be combined with nanocarriers to precisely edit the genomes of T or NK cells, endowing them with improved abilities to detect and destroy cancerous cells[240]. These genetically modified immune cells, when equipped with nanomaterials, can serve as vectors for the targeted delivery of therapeutic agents to tumor sites[241,242]. Another technique was the development of the nanovaccines[243]. Recent research utilizes multi-lamellar RNA lipid particle aggregates that can significantly enhance the immunogenicity of tumor mRNA antigens, as demonstrated in both canine and human glioblastoma patients (Fig. 5)[244].

Moreover, nanotechnology is being utilized to fabricate advanced scaffolds and substrata that promote the proliferation and activation of immune cells[245]. These biomaterials can be designed to provide the necessary signals and environmental conditions that support the growth and maturation of immune cells, thereby increasing their effectiveness in targeting tumors. Additionally, nanoparticles are being investigated for the delivery of immunomodulatory agents. They can be engineered to encapsulate cytokines, immune checkpoint inhibitors, or other immunoenhancing substances, and deliver them with precision to the tumor immune microenvironment[246]. This targeted delivery may help to modulate the local immune response, overcoming the immunosuppressive barriers posed by the tumor and boosting the potency of the engineered immune cells.

6.5. *Targeted drug delivery to metastatic sites*

Navigating the complexities of metastatic tumor management in oncology is a formidable task, compounded by their varied characteristics and propensity for widespread dissemination. As we venture into the future of nanomedicine, a significant focus will be on developing targeted strategies that can preferentially direct therapeutic agents to these metastatic sites[243]. This will involve the use of sophisticated homing devices, which are designed to navigate the intricate and often elusive pathways that characterize metastatic spread. One innovative approach is the development of nanovaccines that specifically target lymph nodes, which are common sites for metastatic spread and crucial in the initiation of systemic immune responses[247]. These nanovaccines can be engineered to not only deliver therapeutic agents but also to activate the immune system in a targeted manner. By capitalizing on the lymphatic system's inherent cell and molecule trafficking, these nanovaccines can concentrate at metastatic locales, thereby amplifying the local therapeutic and immunostimulatory agent density.

The construction of nanovaccines is underpinned by the application of biomaterials and surface engineering strategies that facilitate the precise targeting of receptors or antigens present on metastatic cells or within the tumor immune microenvironment. Moreover, the integration of stimuli-responsive components paves the way for the conditional release of therapeutic agents, triggered by localized cues at the metastatic site, such as pH alterations or the presence of specific enzymatic activities[248]. Additionally, the convergence of nanotechnology with immune cell engineering promises a synergistic enhancement between cellular immunotherapy and nanoscale drug delivery. Immune cells, genetically modified and fortified with nanomaterials, can be navigated to metastatic sites where they can interact with indigenous immune cells, thereby aiding in the annihilation of tumor cells[111,208]. The forthcoming horizon of nanomedicine targeting metastatic sites is poised to embrace the incorporation of cutting-edge imaging

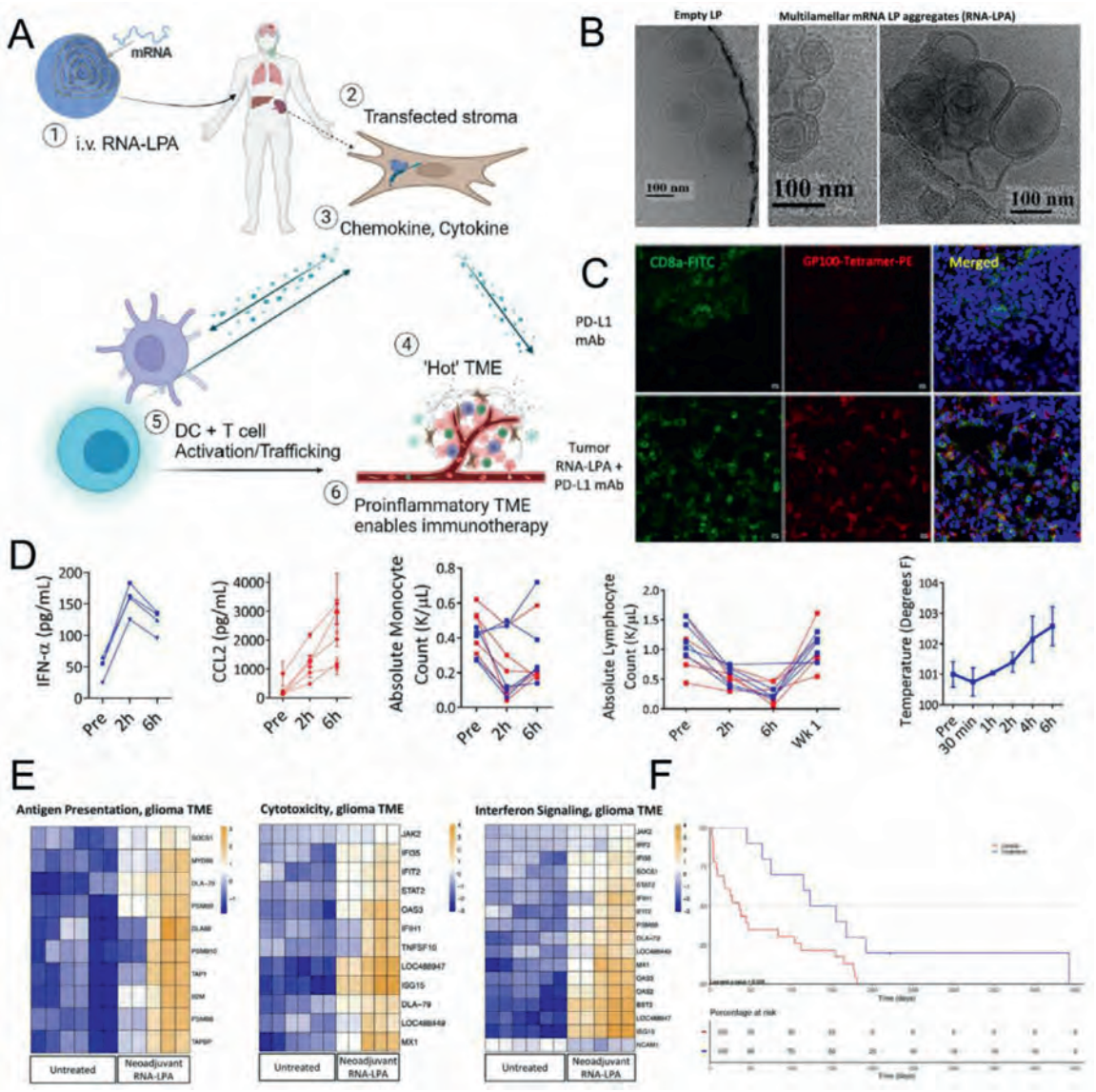

Figure 5 Multi-lamellar RNA lipid particle aggregates enhance the payload packaging and immunogenicity of tumor mRNA antigens. (A) The illustration of the Mechanism of multi-lamellar RNA lipid particle in tumor microenvironment. (B) NanoSight size distributions. (C) C57Bl/6 mice bearing pulmonary B16F0 melanomas treated with anti-PD-L1 mAbs, with or without B16F0 tumor-derived RNA-LPAs. (D) Serum from canines was obtained for analysis of IFN-α, CCL2, monocyte count, lymphocyte count, and temperature in dogs. (E) Heatmaps displaying differential gene expression of antigen presentation in human. (F) Kaplan-Meier curve of receiving RNA-LPA compared with historical control of canines receiving supportive care. Reprinted with the permission from Ref. 203. Copyright © 2024 CellPress.

technologies. These will serve to monitor the biodistribution and therapeutic efficacy of nanovaccines in real-time, enabling the dynamic recalibration of treatment approaches. Such adaptations will ensure the optimization of therapeutic agent delivery, thereby striving to achieve the most favorable outcomes for individuals confronting metastatic disease.

6.6. Overcoming drug resistance

Drug resistance is a formidable barrier to the effectiveness of cancer therapies, as tumor cells often develop ways to counteract the lethal effects of chemotherapeutic agents[249]. The advent of nanotechnology offers innovative tactics to tackle this issue, with nanoparticles being meticulously engineered to target and overcome drug resistance mechanisms. One such approach involves the simultaneous delivery of chemotherapeutic drugs along with substances that can dismantle resistance. These nanoparticles can be expertly designed to encapsulate both the therapeutic medication and molecules that counteract the molecular foundations of drug resistance[250]. These molecules could include inhibitors of efflux pumps, such as P-glycoprotein, which are often associated with resistance, or agents that disrupt the survival pathways activated in treatment-resistant cancer cells.

Moreover, the application of nanotechnology in molecular targeting has given rise to immunoliposomes[251]. These are specialized liposomes linked with antibodies that bind specifically

to receptors overexpressed on cancer cells. The interaction between the antibody and the antileukocyte antibody promotes the internalization of the liposome, resulting in the intracellular release of the drug and potentially circumventing efflux pump mechanisms[252]. Additionally, the deployment of nanocarriers for the concurrent delivery of drugs and siRNA or gene therapies has become an influential method for regulating the expression of drug resistance genes[253]. By suppressing the expression of genes that drive drug expulsion or trigger survival pathways, this method can re-sensitize resistant cancer cells to chemotherapy (Fig. 6).

6.7. Nanoformulations from preclinical studies to clinical approval

The translation of nanomedicine from bench to bedside is fraught with intricacies and challenges. Ensuring the safe and effective transition of these therapies requires meticulous attention to several key issues. A primary challenge is the development of nanocarriers that are more targeted and less toxic. The design must enable specific targeting of disease sites while minimizing off-target effects and toxicity to healthy tissues, necessitating a profound understanding of the interactions between nanocarriers and biological systems, including immune responses and biodistribution[254].

The elevated production costs also erect a significant barrier to clinical adoption. The creation and fabrication of nanocarriers frequently entail sophisticated procedures that necessitate state-of-the-art equipment and materials[255]. Achieving scalability while maintaining quality and affordability is a formidable challenge. Additionally, the establishment of quality control measures and standardized protocols further increases the cost and complexity of bringing these therapies to market[256]. Navigating the regulatory approval processes is another intricate hurdle for the clinical integration of nanomedicines. The regulatory frameworks for nanomedicines are in a state of evolution, necessitating clearer guidelines and standards for their safety, efficacy, and manufacturing[257]. The long-term effects of nanomaterials on the human body remain incompletely understood. There is a prevalent negative perception of nano-level waste, concerning both human health and the environment[258,259]. While nanomedicines hold significant therapeutic potential, concerns exist regarding their long-term safety profiles. The potential for accumulation, toxicity, and unforeseen interactions with biological systems must be

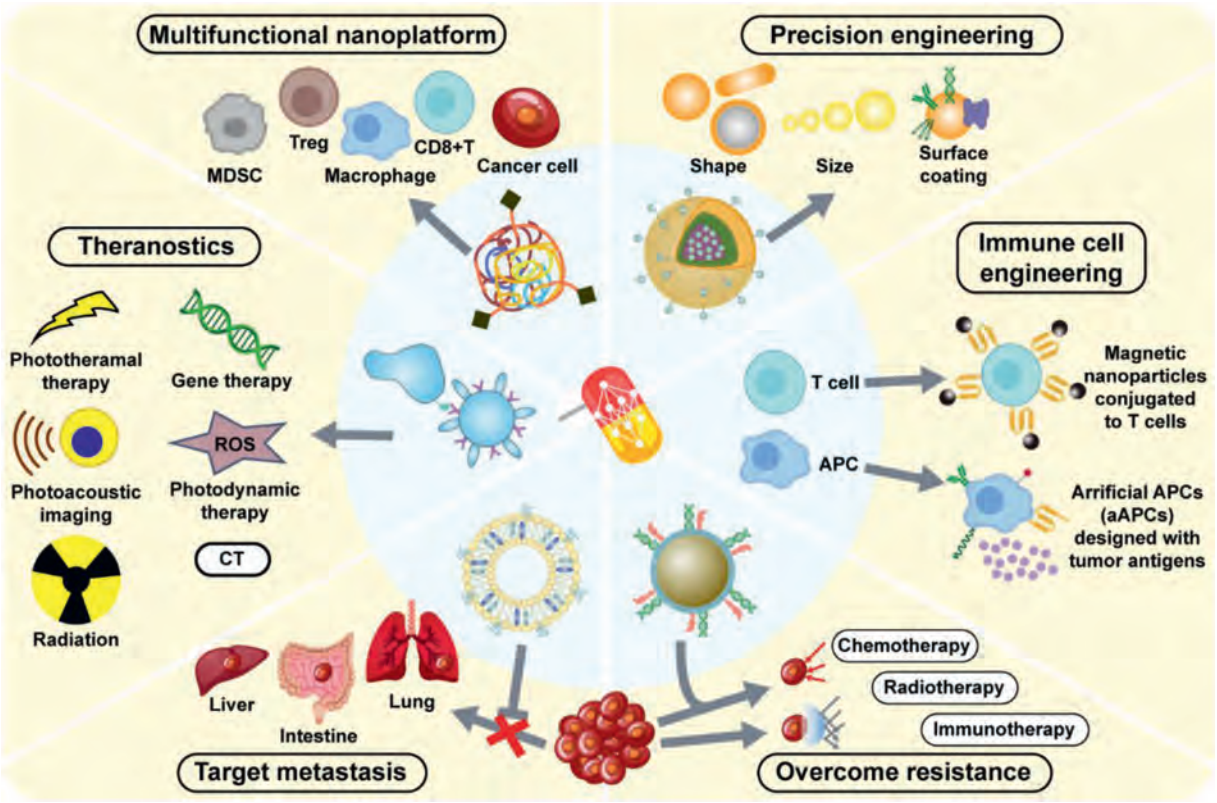

Figure 6 The future of nanoparticles in tumor microenvironment. Multifunctional nanoplatforms means integrating various therapeutic agents and imaging modalities onto a single particle, enabling a synergistic attack on cancer cells and real-time monitoring of treatment efficacy. Theranostics means advancing to a new level, where nanoparticles not only treat but also diagnose, providing a comprehensive tool for personalized medicine. Targeting metastasis means involving the development of nanoparticles capable of homing in on cancer cells that have spread to distant organs, such as the liver, lung, and intestine, thereby tackling one of the most aggressive aspects of cancer. Overcoming resistance means designing nanoparticles that can bypass or reverse the mechanisms that tumors use to evade therapeutic agents, ensuring sustained treatment effectiveness. Precision engineering means refining the size, shape, and surface properties of nanoparticles to maximize their interaction with target cells and minimize side effects on healthy tissues. Finally, immune cell engineering means harnessing the power of the immune system by designing nanoparticles that can activate and direct immune cells like T cells and macrophages to attack cancer cells more effectively.

thoroughly investigated through preclinical and clinical studies. A comprehensive grasp of the biodistribution and clearance mechanisms of nanocarriers is vital for safety assessment and for crafting nanomedicines with superior pharmacokinetics.

Beyond these challenges, additional factors complicate the clinical translation of nanomedicines. These include the need for more robust preclinical models that accurately replicate human diseases[260], the development of sensitive and specific analytical techniques for tracking nanomedicines *in vivo*[261], and a deeper comprehension of the mechanisms by which nanoparticles can enhance drug delivery and therapeutic outcomes[262].

7. Conclusions

The integration of nanomedicine with cancer immunotherapy has shown remarkable progress, as demonstrated by the ability to effectively alter the TIM and enhance treatment outcomes. This article reviews the strategic application of nanotechnology to target and reshape the intricate cellular and molecular components of the TIM. Notably, the incorporation of nanomedicine in boosting immunotherapy has been illustrated through the use of liposomal doxorubicin (Doxil®), which has shown increased safety and tolerability in clinical applications, and has the potential to be combined with traditional chemotherapy and immune checkpoint inhibitors[169,263,264]. Furthermore, paclitaxel protein-bound particles, such as Abraxane®, have been formulated using innovative nanoplatforms, reducing solvent-related side effects and improving drug delivery and efficacy[265-267]. The emergence of theranostic nanoparticles marks a significant advancement in personalized medicine, allowing for the simultaneous performance of diagnostics and therapeutics. These nanoparticles, equipped with various imaging agents and therapeutic payloads, have been shown to increase the accuracy of cancer treatments and offer insights into the effectiveness of therapies[223,227,230]. Precision engineering of nanoparticles is also highlighted as a key strategy for optimizing cancer treatments. By adjusting the size, shape, and surface characteristics of nanoparticles, researchers have managed to improve their biodistribution, cellular uptake, and overall therapeutic efficacy[234-236].

Despite the promise of nanomedicine in clinical translation, challenges remain, including the need for more targeted and less toxic nanocarriers, the high costs of production, and the dynamic regulatory environment[257]. It is also essential to ensure the safety and biocompatibility of nanomaterials, with ongoing studies focusing on their biodistribution, clearance, and long-term effects within the human body[268-270]. The future of nanomedicine in cancer therapy holds immense potential. The ongoing development of multifunctional nanoplatforms, the incorporation of theranostics into clinical practice, and the precision engineering of nanoparticles are expected to push the boundaries of personalized and effective cancer treatments. However, to realize this potential, it is necessary to overcome the current challenges and deepen the understanding of the intricate interactions between nanomedicines and biological systems.

Authors contributions

Nan Lin: Conceptualization, Writing − original draft. Keqin Tan: Conceptualization, Writing − original draft. Yuhao Wei: Data curation, Writing − original draft, Conceptualization. Songtao Xie: Writing − review & editing, Resources. Jiaming Liu: Writing − review & editing. Xuelei Ma: Writing − original draft, Conceptualization, Writing − review & editing.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Elzoghby AO, Samir O, Emam HE, Soliman A, Abdelgalil RM, Elmorshedy YM, et al. Engineering nanomedicines for immunogenic eradication of cancer cells: recent trends and synergistic approaches. *Acta Pharm Sin B* 2024;**14**:2475−504.
2. Li Y, Chen W, Kang Y, Zhen X, Zhou Z, Liu C, et al. Nanosensitizer-mediated augmentation of sonodynamic therapy efficacy and anti-tumor immunity. *Nat Commun* 2023;**14**:6973.
3. Liao M, Yao D, Wu L, Luo C, Wang Z, Zhang J, et al. Targeting the Warburg effect: a revisited perspective from molecular mechanisms to traditional and innovative therapeutic strategies in cancer. *Acta Pharm Sin B* 2024;**14**:953−1008.
4. Jin Y, Huang Y, Ren H, Huang H, Lai C, Wang W, et al. Nano-enhanced immunotherapy: targeting the immunosuppressive tumor microenvironment. *Biomaterials* 2024;**305**:122463.
5. Sun B, Hyun H, Li LT, Wang AZ. Harnessing nanomedicine to overcome the immunosuppressive tumor microenvironment. *Acta Pharmacol Sin* 2020;**41**:970−85.
6. Wang J, Li Y, Nie G. Multifunctional biomolecule nanostructures for cancer therapy. *Nat Rev Mater* 2021;**6**:766−83.
7. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;**144**:646−74.
8. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. *Nat Med* 2013;**19**:1423−37.
9. Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. *Nat Med* 2018;**24**:541−50.
10. Coulie PG, Van den Eynde BJ, van der Bruggen P, Boon T. Tumour antigens recognized by T lymphocytes: at the core of cancer immunotherapy. *Nat Rev Cancer* 2014;**14**:135−46.
11. Broz ML, Binnewies M, Boldajipour B, Nelson AE, Pollack JL, Erle DJ, et al. Dissecting the tumor myeloid compartment reveals rare activating antigen-presenting cells critical for T cell immunity. *Cancer Cell* 2014;**26**:638−52.
12. Nagaraj S, Gupta K, Pisarev V, Kinarsky L, Sherman S, Kang L, et al. Altered recognition of antigen is a mechanism of CD8+ T cell tolerance in cancer. *Nat Med* 2007;**13**:828−35.
13. Hamann D, Baars PA, Rep MH, Hooibrink B, Kerkhof-Garde SR, Klein MR, et al. Phenotypic and functional separation of memory and effector human CD8+ T cells. *J Exp Med* 1997;**186**:1407−18.
14. Schietinger A, Philip M, Krisnawan VE, Chiu EY, Delrow JJ, Basom RS, et al. Tumor-Specific T cell dysfunction is a dynamic antigen-driven differentiation program initiated early during tumorigenesis. *Immunity* 2016;**45**:389−401.
15. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell* 2015;**161**:205−14.
16. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell* 2015;**27**:450−61.
17. Zhu J, Paul WE. CD4 T cells: fates, functions, and faults. *Blood* 2008;**112**:1557−69.
18. Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations (*). *Annu Rev Immunol* 2010;**28**:445−89.
19. Chowdhury D, Lieberman J. Death by a thousand cuts: granzyme pathways of programmed cell death. *Annu Rev Immunol* 2008;**26**:389−420.
20. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008;**454**:436−44.

21. Muranski P, Restifo NP. Essentials of Th17 cell commitment and plasticity. *Blood* 2013;**121**:2402−14.
22. Crotty S. Follicular helper CD4 T cells (TFH). *Annu Rev Immunol* 2011;**29**:621−63.
23. Dieu-Nosjean MC, Goc J, Giraldo NA, Sautès-Fridman C, Fridman WH. Tertiary lymphoid structures in cancer and beyond. *Trends Immunol* 2014;**35**:571−80.
24. Harris RJ, Cheung A, Ng JCF, Laddach R, Chenoweth AM, Crescioli S, et al. Tumor-infiltrating B lymphocyte profiling identifies igG-biased, clonally expanded prognostic phenotypes in triple-negative breast cancer. *Cancer Res* 2021;**81**:4290−304.
25. Kambayashi T, Laufer TM. Atypical MHC class II-expressing antigen-presenting cells: can anything replace a dendritic cell?. *Nat Rev Immunol* 2014;**14**:719−30.
26. Hong S, Zhang Z, Liu H, Tian M, Zhu X, Zhang Z, et al. B cells are the dominant antigen-presenting cells that activate naive CD4(+) T Cells upon immunization with a virus-derived nanoparticle antigen. *Immunity* 2018;**49**:695−708.e4.
27. Mariño E, Tan B, Binge L, Mackay CR, Grey ST. B-cell cross-presentation of autologous antigen precipitates diabetes. *Diabetes* 2012;**61**:2893−905.
28. Avalos AM, Ploegh HL. Early BCR events and antigen capture, processing, and loading on MHC class II on B cells. *Front Immunol* 2014;**5**:92.
29. Lanzavecchia A, Bove S. *Specific B lymphocytes efficiently pick up, process and present antigen to T cells*. Behring Inst Mitt; 1985. p. 82−7.
30. Rodriguez AB, Engelhard VH. Insights into tumor-associated tertiary lymphoid structures: novel targets for antitumor immunity and cancer immunotherapy. *Cancer Immunol Res* 2020;**8**:1338−45.
31. Michaud D, Steward CR, Mirlekar B, Pylayeva-Gupta Y. Regulatory B cells in cancer. *Immunol Rev* 2021;**299**:74−92.
32. Matsumoto M, Baba A, Yokota T, Nishikawa H, Ohkawa Y, Kayama H, et al. Interleukin-10-producing plasmablasts exert regulatory function in autoimmune inflammation. *Immunity* 2014;**41**: 1040−51.
33. Nouël A, Pochard P, Simon Q, Ségalen I, Le Meur Y, Pers JO, et al. B-cells induce regulatory T cells through TGF-β/IDO production in a CTLA-4 dependent manner. *J Autoimmun* 2015;**59**:53−60.
34. Zhang B, Vogelzang A, Miyajima M, Sugiura Y, Wu Y, Chamoto K, et al. B cell-derived GABA elicits IL-10(+) macrophages to limit anti-tumour immunity. *Nature* 2021;**599**:471−6.
35. Crinier A, Narni-Mancinelli E, Ugolini S, Vivier E. SnapShot: natural killer cells. *Cell* 2020;**180**:1280−1280.e1.
36. Wolf NK, Kissiov DU, Raulet DH. Roles of natural killer cells in immunity to cancer, and applications to immunotherapy. *Nat Rev Immunol* 2023;**23**:90−105.
37. Page A, Chuvin N, Valladeau-Guilemond J, Depil S. Development of NK cell-based cancer immunotherapies through receptor engineering. *Cell Mol Immunol* 2024;**21**:315−31.
38. Liu X, Zuo F, Song J, Tang L, Wang X, Liu X, et al. Immune checkpoints HLA-E:CD94-NKG2A and HLA-C:KIR2DL1 complementarily shield circulating tumor cells from NK-mediated immune surveillance. *Cell Discov* 2024;**10**:16.
39. Liu X, Song J, Zhang H, Liu X, Zuo F, Zhao Y, et al. Immune checkpoint HLA-E:CD94-NKG2A mediates evasion of circulating tumor cells from NK cell surveillance. *Cancer Cell* 2023; **41**:272.
40. Münz C. Natural killer cell responses to human oncogenic γ-herpesvirus infections. *Semin Immunol* 2022;**60**:101652.
41. Liu Y, Cao X. The origin and function of tumor-associated macrophages. *Cell Mol Immunol* 2015;**12**:1−4.
42. Wynn TA, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. *Nature* 2013;**496**:445−55.
43. Sharma SK, Chintala NK, Vadrevu SK, Patel J, Karbowniczek M, Markiewski MM. Pulmonary alveolar macrophages contribute to the premetastatic niche by suppressing antitumor T cell responses in the lungs. *J Immunol* 2015;**194**:5529−38.
44. Singh S, Mehta N, Lilan J, Budhthoki MB, Chao F, Yong L. Initiative action of tumor-associated macrophage during tumor metastasis. *Biochim Open* 2017;**4**:8−18.
45. Lin Y, Xu J, Lan H. Tumor-associated macrophages in tumor metastasis: biological roles and clinical therapeutic applications. *J Hematol Oncol* 2019;**12**:76.
46. Khan MM, Li Y, Zhou Z, Ni A, Saiding Q, Qin D, et al. Macrophage-modulating nanomedicine for cancer immunotherapy. *Nanoscale* 2024;**16**:7378−86.
47. Lorenzo-Sanz L, Muñoz P. Tumor-Infiltrating immunosuppressive cells in cancer-cell plasticity, tumor progression and therapy response. *Cancer Microenviron* 2019;**12**:119−32.
48. Movahedi K, Laoui D, Gysemans C, Baeten M, Stangé G, Van den Bossche J, et al. Different tumor microenvironments contain functionally distinct subsets of macrophages derived from Ly6C(high) monocytes. *Cancer Res* 2010;**70**:5728−39.
49. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. *Cell* 2010;**141**:39−51.
50. Abraham D, Zins K, Sioud M, Lucas T, Schäfer R, Stanley ER, et al. Stromal cell-derived CSF-1 blockade prolongs xenograft survival of CSF-1-negative neuroblastoma. *Int J Cancer* 2010;**126**:1339−52.
51. Linde N, Lederle W, Depner S, van Rooijen N, Gutschalk CM, Mueller MM. Vascular endothelial growth factor-induced skin carcinogenesis depends on recruitment and alternative activation of macrophages. *J Pathol* 2012;**227**:17−28.
52. Zhang W, Chen L, Ma K, Zhao Y, Liu X, Wang Y, et al. Polarization of macrophages in the tumor microenvironment is influenced by EGFR signaling within colon cancer cells. *Oncotarget* 2016;**7**: 75366−78.
53. Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. *Nature* 2011;**475**:222−5.
54. Henze AT, Mazzone M. The impact of hypoxia on tumor-associated macrophages. *J Clin Investig* 2016;**126**:3672−9.
55. Hoeksema MA, de Winther MP. Epigenetic regulation of monocyte and macrophage function. *Antioxid Redox Signal* 2016;**25**: 758−74.
56. Kapellos TS, Iqbal AJ. Epigenetic control of macrophage polarisation and soluble mediator gene expression during inflammation. *Mediat Inflamm* 2016;**2016**:6591703.
57. Bronte V, Brandau S, Chen SH, Colombo MP, Frey AB, Greten TF, et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. *Nat Commun* 2016;**7**: 12150.
58. Condamine T, Mastio J, Gabrilovich DI. Transcriptional regulation of myeloid-derived suppressor cells. *J Leukoc Biol* 2015;**98**:913−22.
59. Fu Y, Li J, Cai W, Huang Y, Liu X, Ma Z, et al. The emerging tumor microbe microenvironment: from delineation to multidisciplinary approach-based interventions. *Acta Pharm Sin B* 2024;**14**: 1560−91.
60. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. *Nat Rev Immunol* 2012;**12**: 253−68.
61. Papadaki MA, Aggouraki D, Vetsika EK, Xenidis N, Kallergi G, Kotsakis A, et al. Epithelial-to-mesenchymal transition heterogeneity of circulating tumor cells and their correlation with MDSCs and Tregs in HER2-negative metastatic breast cancer patients. *Anticancer Res* 2021;**41**:661−70.
62. Wang Y, Ding Y, Guo N, Wang S. MDSCs: key criminals of tumor pre-metastatic niche formation. *Front Immunol* 2019;**10**:172.
63. Groh V, Wu J, Yee C, Spies T. Tumour-derived soluble MIC ligands impair expression of NKG2D and T-cell activation. *Nature* 2002;**419**: 734−8.
64. Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells: linking inflammation and cancer. *J Immunol* 2009;**182**:4499−506.
65. Wing JB, Tanaka A, Sakaguchi S. Human FOXP3(+) Regulatory T Cell heterogeneity and function in autoimmunity and cancer. *Immunity* 2019;**50**:302−16.

66. Li C, Jiang P, Wei S, Xu X, Wang J. Regulatory T cells in tumor microenvironment: new mechanisms, potential therapeutic strategies and future prospects. *Mol Cancer* 2020;**19**:116.
67. Sullivan JA, Tomita Y, Jankowska-Gan E, Lema DA, Arvedson MP, Nair A, et al. Treg-cell-derived IL-35-coated extracellular vesicles promote infectious tolerance. *Cell Rep* 2020;**30**:1039.
68. Workman CJ, Vignali DA. Negative regulation of T cell homeostasis by lymphocyte activation gene-3 (CD223). *J Immunol* 2005;**174**: 688−95.
69. Huang CT, Workman CJ, Flies D, Pan X, Marson AL, Zhou G, et al. Role of LAG-3 in regulatory T cells. *Immunity* 2004;**21**:503−13.
70. Liang B, Workman C, Lee J, Chew C, Dale BM, Colonna L, et al. Regulatory T cells inhibit dendritic cells by lymphocyte activation gene-3 engagement of MHC class II. *J Immunol* 2008;**180**:5916−26.
71. Fallarino F, Grohmann U, Hwang KW, Orabona C, Vacca C, Bianchi R, et al. Modulation of tryptophan catabolism by regulatory T cells. *Nat Immunol* 2003;**4**:1206−12.
72. Kurtulus S, Sakuishi K, Ngiow SF, Joller N, Tan DJ, Teng MW, et al. TIGIT predominantly regulates the immune response *via* regulatory T cells. *J Clin Investig* 2015;**125**:4053−62.
73. Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. *Nat Rev Immunol* 2004;**4**:762−74.
74. Brouillard A, Deshpande N, Kulkarni AA. Engineered multifunctional nano- and biological materials for cancer immunotherapy. *Adv Healthcare Mater* 2021;**10**:e2001680.
75. Hu X, Zhu H, He X, Chen J, Xiong L, Shen Y, et al. The application of nanoparticles in immunotherapy for hepatocellular carcinoma. *J Control Release* 2023;**355**:85−108.
76. Smith TT, Stephan SB, Moffett HF, McKnight LE, Ji W, Reiman D, et al. In situ programming of leukaemia-specific T cells using synthetic DNA nanocarriers. *Nat Nanotechnol* 2017;**12**:813−20.
77. Xie YQ, Arik H, Wei L, Zheng Y, Suh H, Irvine DJ, et al. Redox-responsive interleukin-2 nanogel specifically and safely promotes the proliferation and memory precursor differentiation of tumor-reactive T-cells. *Biomater Sci* 2019;**7**:1345−57.
78. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov* 2021;**20**:101−24.
79. Xu Z, Ramishetti S, Tseng YC, Guo S, Wang Y, Huang L. Multifunctional nanoparticles co-delivering Trp2 peptide and CpG adjuvant induce potent cytotoxic T-lymphocyte response against melanoma and its lung metastasis. *J Control Release* 2013;**172**: 259−65.
80. Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. *Nat Rev Immunol* 2012;**12**: 269−81.
81. Perica K, Bieler JG, Schütz C, Varela JC, Douglass J, Skora A, et al. Enrichment and expansion with nanoscale artificial antigen presenting cells for adoptive immunotherapy. *ACS Nano* 2015;**9**: 6861−71.
82. Yan H, Lin G, Liu Z, Gu F, Zhang Y. Nano-adjuvants and immune agonists promote antitumor immunity of peptide amphiphiles. *Acta Biomater* 2023;**161**:213−25.
83. Hafeez U, Parakh S, Gan HK, Scott AM. Antibody-drug conjugates for cancer therapy. *Molecules* 2020;**25**:4764.
84. Xie Y, Bagby TR, Cohen MS, Forrest ML. Drug delivery to the lymphatic system: importance in future cancer diagnosis and therapies. *Expet Opin Drug Deliv* 2009;**6**:785−92.
85. Kim KS, Han JH, Choi SH, Jung HY, Park JD, An HJ, et al. Cationic nanoparticle-mediated activation of natural killer cells for effective cancer immunotherapy. *ACS Appl Mater Interfaces* 2020;**12**: 56731−40.
86. Kim ME, Kim DH, Lee JS. FoxO transcription factors: applicability as a novel immune cell regulators and therapeutic targets in oxidative stress-related diseases. *Int J Mol Sci* 2022;**23**:11877.
87. Hu Y, Tian ZG, Zhang C. Chimeric antigen receptor (CAR)-transduced natural killer cells in tumor immunotherapy. *Acta Pharmacol Sin* 2018;**39**:167−76.
88. Dana H, Chalbatani GM, Jalali SA, Mirzaei HR, Grupp SA, Suarez ER, et al. CAR-T cells: early successes in blood cancer and challenges in solid tumors. *Acta Pharm Sin B* 2021;**11**:1129−47.
89. Van Rooijen N, Sanders A. Liposome mediated depletion of macrophages: mechanism of action, preparation of liposomes and applications. *J Immunol Methods* 1994;**174**:83−93.
90. Chao MP, Alizadeh AA, Tang C, Myklebust JH, Varghese B, Gill S, et al. Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate Non-Hodgkin lymphoma. *Cell* 2010;**142**: 699−713.
91. Liu Y, Tiruthani K, Wang M, Zhou X, Qiu N, Xiong Y, et al. Tumor-targeted gene therapy with lipid nanoparticles inhibits tumor-associated adipocytes and remodels the immunosuppressive tumor microenvironment in triple-negative breast cancer. *Nanoscale Horiz* 2021;**6**:319−29.
92. Ries CH, Cannarile MA, Hoves S, Benz J, Wartha K, Runza V, et al. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. *Cancer Cell* 2014;**25**: 846−59.
93. Zhu Y, Knolhoff BL, Meyer MA, Nywening TM, West BL, Luo J, et al. CSF1/CSF1R blockade reprograms tumor-infiltrating macrophages and improves response to T-cell checkpoint immunotherapy in pancreatic cancer models. *Cancer Res* 2014;**74**:5057−69.
94. Conde J, Bao C, Tan Y, Cui D, Edelman ER, Azevedo HS, et al. Dual targeted immunotherapy *via in vivo* delivery of biohybrid RNAi-peptide nanoparticles to tumour-associated macrophages and cancer cells. *Adv Funct Mater* 2015;**25**:4183−94.
95. Qian Y, Qiao S, Dai Y, Xu G, Dai B, Lu L, et al. Molecular-targeted immunotherapeutic strategy for melanoma *via* dual-targeting nanoparticles delivering small interfering RNA to tumor-associated macrophages. *ACS Nano* 2017;**11**:9536−49.
96. Liu X, Pu Y, Cron K, Deng L, Kline J, Frazier WA, et al. CD47 blockade triggers T cell-mediated destruction of immunogenic tumors. *Nat Med* 2015;**21**:1209−15.
97. Bournazos S. IgG Fc receptors: evolutionary considerations. *Curr Top Microbiol Immunol* 2019;**423**:1−11.
98. Wang C, Ye Y, Hu Q, Bellotti A, Gu Z. Tailoring biomaterials for cancer immunotherapy: emerging trends and future outlook. *Adv Mater* 2017;**29**:1606036.
99. Rodell CB, Ahmed MS, Garris CS, Pittet MJ, Weissleder R. Development of adamantane-conjugated TLR7/8 agonists for supramolecular delivery and cancer immunotherapy. *Theranostics* 2019;**9**:8426−36.
100. Wang H, Yang H, Shivalila CS, Dawlaty MM, Cheng AW, Zhang F, et al. One-step generation of mice carrying mutations in multiple genes by CRISPR/Cas-mediated genome engineering. *Cell* 2013;**153**: 910−8.
101. Zanganeh S, Hutter G, Spitler R, Lenkov O, Mahmoudi M, Shaw A, et al. Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues. *Nat Nanotechnol* 2016;**11**:986−94.
102. Zhao P, Wang Y, Kang X, Wu A, Yin W, Tang Y, et al. Dual-targeting biomimetic delivery for anti-glioma activity *via* remodeling the tumor microenvironment and directing macrophage-mediated immunotherapy. *Chem Sci* 2018;**9**:2674−89.
103. Long Y, Lu Z, Xu S, Li M, Wang X, Zhang Z, et al. Self-delivery micellar nanoparticles prevent premetastatic niche formation by interfering with the early recruitment and vascular destruction of granulocytic myeloid-derived suppressor cells. *Nano Lett* 2020;**20**: 2219−29.
104. Wang T, Wang J, Jiang H, Ni M, Zou Y, Chen Y, et al. Targeted regulation of tumor microenvironment through the inhibition of MDSCs by curcumin loaded self-assembled nano-filaments. *Mater Today Bio* 2022;**15**:100304.
105. Li S, Wang Q, Shen Y, Hassan M, Shen J, Jiang W, et al. Pseudo-neutrophil cytokine sponges disrupt myeloid expansion and tumor trafficking to improve cancer immunotherapy. *Nano Lett* 2020;**20**: 242−51.

106. Han H, Bártolo R, Li J, Shahbazi MA, Santos HA. Biomimetic platelet membrane-coated nanoparticles for targeted therapy. *Eur J Pharm Biopharm* 2022;**172**:1−15.
107. Wu M, Liu X, Bai H, Lai L, Chen Q, Huang G, et al. Surface-layer protein-enhanced immunotherapy based on cell membrane-coated nanoparticles for the effective inhibition of tumor growth and metastasis. *ACS Appl Mater Interfaces* 2019;**11**:9850−9.
108. Lai X, Liu XL, Pan H, Zhu MH, Long M, Yuan Y, et al. Light-triggered efficient sequential drug delivery of biomimetic nano-system for multimodal chemo-, antiangiogenic, and anti-MDSC therapy in melanoma. *Adv Mater* 2022;**34**:e2106682.
109. Huo M, Zhao Y, Satterlee AB, Wang Y, Xu Y, Huang L. Tumor-targeted delivery of sunitinib base enhances vaccine therapy for advanced melanoma by remodeling the tumor microenvironment. *J Control Release* 2017;**245**:81−94.
110. Plebanek MP, Bhaumik D, Bryce PJ, Thaxton CS. Scavenger receptor type B1 and lipoprotein nanoparticle inhibit myeloid-derived suppressor cells. *Mol Cancer Therapeut* 2018;**17**:686−97.
111. Kong M, Tang J, Qiao Q, Wu T, Qi Y, Tan S, et al. Biodegradable hollow mesoporous silica nanoparticles for regulating tumor microenvironment and enhancing antitumor efficiency. *Theranostics* 2017;**7**:3276−92.
112. Phuengkham H, Song C, Lim YT. A designer scaffold with immune nanoconverters for reverting immunosuppression and enhancing immune checkpoint blockade therapy. *Adv Mater* 2019;**31**:e1903242.
113. Gamrad L, Rehbock C, Westendorf AM, Buer J, Barcikowski S, Hansen W. Efficient nucleic acid delivery to murine regulatory T cells by gold nanoparticle conjugates. *Sci Rep* 2016;**6**:28709.
114. He S, Li J, Cheng P, Zeng Z, Zhang C, Duan H, et al. Charge-reversal polymer nano-modulators for photodynamic immunotherapy of cancer. *Angew Chem Int Ed Engl* 2021;**60**:19355−63.
115. Lozano T, Soldevilla MM, Casares N, Villanueva H, Bendandi M, Lasarte JJ, et al. Targeting inhibition of Foxp3 by a CD28 2′-Fluro oligonucleotide aptamer conjugated to P60-peptide enhances active cancer immunotherapy. *Biomaterials* 2016;**91**:73−80.
116. Zhang Y, Han X, Nie G. Responsive and activable nanomedicines for remodeling the tumor microenvironment. *Nat Protoc* 2021;**16**:405−30.
117. Xiao H, Guo Y, Li B, Li X, Wang Y, Han S, et al. M2-Like tumor-associated macrophage-targeted codelivery of STAT6 inhibitor and IKKβ siRNA induces M2-to-M1 repolarization for cancer immunotherapy with low immune side effects. *ACS Cent Sci* 2020;**6**:1208−22.
118. Martin JD, Cabral H, Stylianopoulos T, Jain RK. Improving cancer immunotherapy using nanomedicines: progress, opportunities and challenges. *Nat Rev Clin Oncol* 2020;**17**:251−66.
119. D'Angelo SP, Araujo DM, Abdul Razak AR, Agulnik M, Attia S, Blay JY, et al. Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): an international, open-label, phase 2 trial. *Lancet* 2024;**403**:1460−71.
120. Hogan LE, Brown PA, Ji L, Xu X, Devidas M, Bhatla T, et al. Children's Oncology group AALL1331: phase III trial of blinatumomab in children, adolescents, and young adults with low-risk B-cell ALL in first relapse. *J Clin Oncol* 2023;**41**:4118−29.
121. Segal NH, Melero I, Moreno V, Steeghs N, Marabelle A, Rohrberg K, et al. CEA-CD3 bispecific antibody cibisatamab with or without atezolizumab in patients with CEA-positive solid tumours: results of two multi-institutional Phase 1 trials. *Nat Commun* 2024;**15**:4091.
122. Budde E, Gopal AK, Flinn IW, Nastoupil LJ, Gordon MS, Pang C-F, et al. Preliminary results of a phase 1 dose escalation study of the first-in-class IgM based bispecific antibody Igm-2323 (anti-CD20 x anti-CD3) in patients with advanced B-Cell malignancies. *Blood* 2020;**136**:45−6.
123. Zuch de Zafra CL, Fajardo F, Zhong W, Bernett MJ, Muchhal US, Moore GL, et al. Targeting multiple myeloma with AMG 424, a novel anti-CD38/CD3 bispecific t-cell-recruiting antibody optimized for cytotoxicity and cytokine release. *Clin Cancer Res* 2019;**25**:3921−33.
124. Winer ES, Maris M, Sharma MR, Kaminker P, Zhao E, Ward A, et al. A phase 1, first-in-human, dose-escalation study of MGD024, a CD123 x CD3 bispecific dart® molecule, in patients with relapsed or refractory CD123-positive (+) hematologic malignancies. *Blood* 2022;**140**:11753−4.
125. Piha-Paul S, Bendell J, Tolcher A, Hurvitz S, Patnaik A, Shroff R, et al. O82 A phase 1 dose escalation study of PRS-343, a HER2/4−1BB bispecific molecule, in patients with HER2-positive malignancies. *J Immunother Cancer* 2020;**8**:A1−2.
126. Brugières L, Cozic N, Houot R, Rigaud C, Sibon D, Arfi-Rouche J, et al. Efficacy and safety of crizotinib in ALK-positive systemic anaplastic large-cell lymphoma in children, adolescents, and adult patients: results of the French AcSé-crizotinib trial. *Eur J Cancer* 2023;**191**:112984.
127. Jonasch E, Donskov F, Iliopoulos O, Rathmell WK, Narayan VK, Maughan BL, et al. Belzutifan for renal cell carcinoma in von Hippel-Lindau disease. *N Engl J Med* 2021;**385**:2036−46.
128. Schilder RJ, Powderly JD, Park H, Bilen MA, McKean M, May R, et al. Phase Ia dose-escalation study of the anti-BTLA antibody icatolimab as a monotherapy in patients with advanced solid tumor. *J Clin Oncol* 2022;**40**:2643.
129. Jones JA, Robak T, Brown JR, Awan FT, Badoux X, Coutre S, et al. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. *Lancet Haematol* 2017;**4**:e114−26.
130. Selwyn Stein A, Jongen-Lavrencic M, Garciaz S, G AH, Maiti A, Boissel N, et al. P494: a first-in-human study of CD123 nk cell engager SAR443579 in relapsed or refractory acute myeloid leukemia, b-cell acute lymphoblastic leukemia or high risk-myelodysplasia. *Hemasphere* 2023;**7**:7005.
131. Safran H, Cassier PA, Vicier C, Forget F, Gomez-Roca CA, Penel N, et al. Phase 1/2 Study of DF1001, a novel tri-specific, NK cell engager therapy targeting HER2, in patients with advanced solid tumors: phase 1 DF1001 monotherapy dose-escalation results. *J Clin Oncol* 2023;**41**:2508.
132. Santa Gadea OS, Christenson E, El-Khoueiry AB, Cervantes A, Raab C, Gaertner U, et al. AFM24 in combination with atezolizumab in patients with advanced EGFR-expressing solid tumors: phase 1/2a study design and rationale. *J Clin Oncol* 2022;**40**:TPS2673.
133. Schmitt N, Siegler J-J, Wagner L, Schulze N, Beck A, Hofmann W-K, et al. The novel bispecific innate cell engager (ICE®) AFM28 efficiently directs allogeneic nk cells to CD123+ leukemic stem- and progenitor cells in AML. *Blood* 2022;**140**:8815−6.
134. Sikic BI, Lakhani N, Patnaik A, Shah SA, Chandana SR, Rasco D, et al. First-in-human, first-in-class phase I trial of the anti-CD47 antibody Hu5F9-G4 in patients with advanced cancers. *J Clin Oncol* 2019;**37**:946−53.
135. Tap WD, Gelderblom H, Palmerini E, Desai J, Bauer S, Blay JY, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet* 2019;**394**:478−87.
136. Advani R, Flinn I, Popplewell L, Forero A, Bartlett NL, Ghosh N, et al. CD47 Blockade by Hu5F9-G4 and rituximab in non-hodgkin's lymphoma. *N Engl J Med* 2018;**379**:1711−21.
137. Nywening TM, Wang-Gillam A, Sanford DE, Belt BA, Panni RZ, Cusworth BM, et al. Targeting tumour-associated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer: a single-centre, open-label, dose-finding, non-randomised, phase 1b trial. *Lancet Oncol* 2016;**17**:651−62.
138. Fujikawa K, Saito T, Kurose K, Kojima T, Funakoshi T, Sato E, et al. Integrated analysis of phase 1a and 1b randomized controlled trials; Treg-targeted cancer immunotherapy with the humanized anti-CCR4 antibody, KW-0761, for advanced solid tumors. *PLoS One* 2023;**18**:e0291772.

139. Mahalingam D, Harb W, Patnaik A, Bullock A, Watnick RS, Vincent MY, et al. First-in-human phase I dose escalation trial of the first-in-class tumor microenvironment modulator VT1021 in advanced solid tumors. *Commun Med* 2024;**4**:10.
140. Bewersdorf JP, Shallis RM, Sharon E, Park S, Ramaswamy R, Roe CE, et al. A multicenter phase Ib trial of the histone deacetylase inhibitor entinostat in combination with pembrolizumab in patients with myelodysplastic syndromes/neoplasms or acute myeloid leukemia refractory to hypomethylating agents. *Ann Hematol* 2024;**103**: 105−16.
141. Beckermann KE, Patnaik A, Winer I, Tan W, Bashir B, Kyriakopoulos CE, et al. A phase 1b open-label study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of py314 in combination with pembrolizumab in patients with advanced renal cell carcinoma. *Invest N Drugs* 2024;**42**:179−84.
142. Rajan A, Abdul Sater H, Rahma O, Agajanian R, Lassoued W, Marté JL, et al. Efficacy, safety, and biomarker analyses of bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1, in patients with advanced non-small cell lung cancer. *J Immunother Cancer* 2024;**12**:e008480.
143. Ponce S, Cedrés S, Ricordel C, Isambert N, Viteri S, Herrera-Juarez M, et al. ONCOS-102 plus pemetrexed and platinum chemotherapy in malignant pleural mesothelioma: a randomized phase 2 study investigating clinical outcomes and the tumor microenvironment. *J Immunother Cancer* 2023;**11**:e007552.
144. Salawu A, Wang BX, Han M, Geady C, Heirali A, Berman HK, et al. Safety, immunologic, and clinical activity of durvalumab in combination with olaparib or cediranib in advanced leiomyosarcoma: results of the DAPPER clinical trial. *Clin Cancer Res* 2023;**29**: 4128−38.
145. Ahmed J, Stephen B, Yang Y, Kwiatkowski E, Ejezie CL, Pant S. Phase Ib/II study of lacnotuzumab in combination with spartalizumab in patients with advanced malignancies. *J Immunother Precis Oncol* 2024;**7**:73−81.
146. Weed DT, Zilio S, Reis IM, Sargi Z, Abouyared M, Gomez-Fernandez CR, et al. The reversal of immune exclusion mediated by tadalafil and an anti-tumor vaccine also induces PDL1 upregulation in recurrent head and neck squamous cell carcinoma: interim analysis of a phase i clinical trial. *Front Immunol* 2019;**10**:1206.
147. Rook AH, Gelfand JM, Wysocka M, Troxel AB, Benoit B, Surber C, et al. Topical resiquimod can induce disease regression and enhance T-cell effector functions in cutaneous T-cell lymphoma. *Blood* 2015; **126**:1452−61.
148. Guo C, Sharp A, Gurel B, Crespo M, Figueiredo I, Jain S, et al. Targeting myeloid chemotaxis to reverse prostate cancer therapy resistance. *Nature* 2023;**623**:1053−61.
149. Brana I, Calles A, LoRusso PM, Yee LK, Puchalski TA, Seetharam S, et al. Carlumab, an anti-C-C chemokine ligand 2 monoclonal antibody, in combination with four chemotherapy regimens for the treatment of patients with solid tumors: an open-label, multicenter phase 1b study. *Targeted Oncol* 2015;**10**:111−23.
150. Bockorny B, Semenisty V, Macarulla T, Borazanci E, Wolpin BM, Stemmer SM, et al. BL-8040, a CXCR4 antagonist, in combination with pembrolizumab and chemotherapy for pancreatic cancer: the COMBAT trial. *Nat Med* 2020;**26**:878−85.
151. Cho BC, Abreu DR, Hussein M, Cobo M, Patel AJ, Secen N, et al. Tiragolumab plus atezolizumab versus placebo plus atezolizumab as a first-line treatment for PD-L1-selected non-small-cell lung cancer (CITYSCAPE): primary and follow-up analyses of a randomised, double, phase 2 study. *Lancet Oncol* 2022;**23**:781−92.
152. Doi T, Muro K, Ishii H, Kato T, Tsushima T, Takenoyama M, et al. A phase I study of the anti-CC chemokine receptor 4 antibody, mogamulizumab, in combination with nivolumab in patients with advanced or metastatic solid tumors. *Clin Cancer Res* 2019;**25**: 6614−22.
153. Bockorny B, Macarulla T, Semenisty V, Borazanci E, Feliu J, Ponz-Sarvise M, et al. Motixafortide and pembrolizumab combined to nanoliposomal irinotecan, fluorouracil, and folinic acid in metastatic pancreatic cancer: the COMBAT/KEYNOTE-202 trial. *Clin Cancer Res* 2021;**27**:5020−7.
154. Daver NG, Vyas P, Kambhampati S, Al Malki MM, Larson RA, Asch AS, et al. Tolerability and efficacy of the anticluster of differentiation 47 antibody magrolimab combined with azacitidine in patients with previously untreated AML: phase Ib results. *J Clin Oncol* 2023;**41**:4893−904.
155. Fuh KC, Bookman MA, Liu JF, Coleman RL, Herzog TJ, Thaker PH, et al. Phase 1b study of AVB-500 in combination with paclitaxel or pegylated liposomal doxorubicin platinum-resistant recurrent ovarian cancer. *Gynecol Oncol* 2021;**163**:254−61.
156. Johnson M, Dudek AZ, Sukari A, Call J, Kunk PR, Lewis K, et al. ARRY-382 in combination with pembrolizumab in patients with advanced solid tumors: results from a phase 1b/2 study. *Clin Cancer Res* 2022;**28**:2517−26.
157. Haag GM, Springfeld C, Grün B, Apostolidis L, Zschäbitz S, Dietrich M, et al. Pembrolizumab and maraviroc in refractory mismatch repair proficient/microsatellite-stable metastatic colorectal cancer - the PICCASSO phase I trial. *Eur J Cancer* 2022;**167**: 112−22.
158. Chen W, Li Y, Liu C, Kang Y, Qin D, Chen S, et al. In situ engineering of tumor-associated macrophages *via* a nanodrug-delivering-drug (β-Elemene@Stanene) strategy for enhanced cancer chemo-immunotherapy. *Angew Chem Int Ed Engl* 2023;**62**:e202308413.
159. Silverman JA, Deitcher SR. Marqibo®(vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine. *Cancer Chemother Pharmacol* 2013;**71**:555−64.
160. Chawla SP, Chua VS, Fernandez L, Quon D, Saralou A, Blackwelder WC, et al. Phase I/II and phase II studies of targeted gene delivery *in vivo*: intravenous Rexin-G for chemotherapy-resistant sarcoma and osteosarcoma. *Mol Ther* 2009;**17**:1651−7.
161. Bonvalot S, Pechoux CL, Baere TD, Buy X, Italiano A, Stockle E, et al. Phase I study of NBTXR3 nanoparticles, in patients with advanced soft tissue sarcoma (STS). *J Clin Oncol* 2014;**32**:10563.
162. Bonomi P. Paclitaxel poliglumex (PPX, CT-2103): macromolecular medicine for advanced non-small-cell lung cancer. *Expet Rev Anticancer Ther* 2007;**7**:415−22.
163. Kim D-W, Kim S-Y, Kim H-K, Kim S-W, Shin S, Kim J, et al. Multicenter phase II trial of Genexol-PM, a novel cremophor-free, polymeric micelle formulation of paclitaxel, with cisplatin in patients with advanced non-small-cell lung cancer. *Ann Oncol* 2007;**18**: 2009−14.
164. Poon RT, Borys N. Lyso-thermosensitive liposomal doxorubicin: a novel approach to enhance efficacy of thermal ablation of liver cancer. *Expet Opin Pharmacother* 2009;**10**:333−43.
165. Sankhala K, Mita A, Adinin R, Wood L, Beeram M, Bullock S, et al. A phase I pharmacokinetic (PK) study of MBP-426, a novel liposome encapsulated oxaliplatin. *J Clin Oncol* 2009;**27**:2535.
166. Zhang H. Onivyde for the therapy of multiple solid tumors. *OncoTargets Ther* 2016:3001−7.
167. Meyers PA. Muramyl tripeptide (mifamurtide) for the treatment of osteosarcoma. *Expet Rev Anticancer Ther* 2009;**9**:1035−49.
168. Forssen EA. The design and development of DaunoXome® for solid tumor targeting *in vivo*. *Adv Drug Deliv Rev* 1997;**24**:133−50.
169. Barenholz Y. Doxil®–the first FDA-approved nano-drug: lessons learned. *J Control Release* 2012;**160**:117−34.
170. Verry C, Dufort S, Villa J, Gavard M, Iriart C, Grand S, et al. Theranostic AGuIX nanoparticles as radiosensitizer: a phase I, dose-escalation study in patients with multiple brain metastases (NANO-RAD trial). *Radiother Oncol* 2021;**160**:159−65.
171. Kalogera E, Nevala WK, Finnes HD, Suman VJ, Schimke JM, Strand CA, et al. A phase I trial of nab-paclitaxel/bevacizumab (AB160) nano-immunoconjugate therapy for gynecologic malignancies. *Clin Cancer Res* 2024;**30**:2623−35.
172. Wang SJ, Huang WS, Chuang CM, Chang CH, Lee TW, Ting G, et al. A phase 0 study of the pharmacokinetics, biodistribution, and dosimetry of (188)Re-liposome in patients with metastatic tumors. *EJNMMI Res* 2019;**9**:46.

173. Pirollo KF, Rait A, Zhou Q, Zhang XQ, Zhou J, Kim CS, et al. Tumor-targeting nanocomplex delivery of novel tumor suppressor RB94 chemosensitizes bladder carcinoma cells *in vitro* and *in vivo*. *Clin Cancer Res* 2008;**14**:2190−8.
174. Zuckerman JE, Gritli I, Tolcher A, Heidel JD, Lim D, Morgan R, et al. Correlating animal and human phase Ia/Ib clinical data with CALAA-01, a targeted, polymer-based nanoparticle containing siRNA. *Proc Natl Acad Sci U S A* 2014;**111**:11449−54.
175. Senzer N, Nemunaitis J, Nemunaitis D, Bedell C, Edelman G, Barve M, et al. Phase I study of a systemically delivered p53 nanoparticle in advanced solid tumors. *Mol Ther* 2013;**21**:1096−103.
176. Siefker-Radtke A, Zhang XQ, Guo CC, Shen Y, Pirollo KF, Sabir S, et al. A phase l study of a tumor-targeted systemic nanodelivery system, SGT-94, in genitourinary cancers. *Mol Ther* 2016;**24**:1484−91.
177. Mamot C, Ritschard R, Wicki A, Stehle G, Dieterle T, Bubendorf L, et al. Tolerability, safety, pharmacokinetics, and efficacy of doxorubicin-loaded anti-EGFR immunoliposomes in advanced solid tumours: a phase 1 dose-escalation study. *Lancet Oncol* 2012;**13**: 1234−41.
178. van Zandwijk N, Pavlakis N, Kao SC, Linton A, Boyer MJ, Clarke S, et al. Safety and activity of microRNA-loaded minicells in patients with recurrent malignant pleural mesothelioma: a first-in-man, phase 1, open-label, dose-escalation study. *Lancet Oncol* 2017;**18**:1386−96.
179. Munster P, Krop IE, LoRusso P, Ma C, Siegel BA, Shields AF, et al. Safety and pharmacokinetics of MM-302, a HER2-targeted antibody-liposomal doxorubicin conjugate, in patients with advanced HER2-positive breast cancer: a phase 1 dose-escalation study. *Br J Cancer* 2018;**119**:1086−93.
180. Chawla SP, Bruckner H, Morse MA, Assudani N, Hall FL, Gordon EM. A phase I-II study using Rexin-G tumor-targeted retrovector encoding a dominant-negative cyclin G1 inhibitor for advanced pancreatic cancer. *Mol Ther Oncolytics* 2019;**12**:56−67.
181. Gargett T, Abbas MN, Rolan P, Price JD, Gosling KM, Ferrante A, et al. Phase I trial of Lipovaxin-MM, a novel dendritic cell-targeted liposomal vaccine for malignant melanoma. *Cancer Immunol Immunother* 2018;**67**:1461−72.
182. Senzer NN, Matsuno K, Yamagata N, Fujisawa T, Wasserman E, Sutherland W, et al. MBP-426, a novel liposome-encapsulated oxaliplatin, in combination with 5-FU/leucovorin (LV): phase I results of a Phase I/Il study in gastro-esophageal adenocarcinoma, with pharmacokinetics. *Mol Cancer Therapeut* 2009;**8**:C36.
183. Sankhala KK, Mita AC, Adinin R, Wood L, Beeram M, Bullock S, et al. A phase I pharmacokinetic (PK) study of MBP-426, a novel liposome encapsulated oxaliplatin. *J Clin Oncol* 2009;**27**:2535.
184. Shen S, Zhang Y, Chen KG, Luo YL, Wang J. Cationic polymeric nanoparticle delivering CCR2 siRNA to inflammatory monocytes for tumor microenvironment modification and cancer therapy. *Mol Pharm* 2018;**15**:3642−53.
185. Zhan X, Jia L, Niu Y, Qi H, Chen X, Zhang Q, et al. Targeted depletion of tumour-associated macrophages by an alendronate-glucomannan conjugate for cancer immunotherapy. *Biomaterials* 2014;**35**:10046−57.
186. Shen S, Li HJ, Chen KG, Wang YC, Yang XZ, Lian ZX, et al. Spatial targeting of tumor-associated macrophages and tumor cells with a pH-sensitive cluster nanocarrier for cancer chemoimmunotherapy. *Nano Lett* 2017;**17**:3822−9.
187. Liu Y, Wang J, Zhang J, Marbach S, Xu W, Zhu L. Targeting tumor-associated macrophages by MMP2-sensitive apoptotic body-mimicking nanoparticles. *ACS Appl Mater Interfaces* 2020;**12**: 52402−14.
188. Guo N, Zhou Y, Wang T, Lin M, Chen J, Zhang Z, et al. Specifically eliminating tumor-associated macrophages with an extra- and intracellular stepwise-responsive nanocarrier for inhibiting metastasis. *ACS Appl Mater Interfaces* 2020;**12**:57798−809.
189. Liu L, He H, Liang R, Yi H, Meng X, Chen Z, et al. ROS-inducing micelles sensitize tumor-associated macrophages to TLR3 stimulation for potent immunotherapy. *Biomacromolecules* 2018;**19**: 2146−55.
190. Zhang F, Parayath NN, Ene CI, Stephan SB, Koehne AL, Coon ME, et al. Genetic programming of macrophages to perform anti-tumor functions using targeted mRNA nanocarriers. *Nat Commun* 2019;**10**: 3974.
191. Qu Y, Xu J, Zhang T, Chen Q, Sun T, Jiang C. Advanced nano-based strategies for mRNA tumor vaccine. *Acta Pharm Sin B* 2024;**14**: 170−89.
192. Zhang W, Jiang Y, He Y, Boucetta H, Wu J, Chen Z, et al. Lipid carriers for mRNA delivery. *Acta Pharm Sin B* 2023;**13**:4105−26.
193. Peng H, Chen B, Huang W, Tang Y, Jiang Y, Zhang W, et al. Reprogramming tumor-associated macrophages to reverse EGFR (T790M) resistance by dual-targeting codelivery of gefitinib/vorinostat. *Nano Lett* 2017;**17**:7684−90.
194. Huang Z, Zhang Z, Jiang Y, Zhang D, Chen J, Dong L, et al. Targeted delivery of oligonucleotides into tumor-associated macrophages for cancer immunotherapy. *J Control Release* 2012;**158**:286−92.
195. Dai X, Meng J, Deng S, Zhang L, Wan C, Lu L, et al. Targeting CAMKII to reprogram tumor-associated macrophages and inhibit tumor cells for cancer immunotherapy with an injectable hybrid peptide hydrogel. *Theranostics* 2020;**10**:3049−63.
196. Ko YJ, Lee JW, Kim H, Cho E, Yang Y, Kim IS, et al. Versatile activatable vSIRPα-probe for cancer-targeted imaging and macrophage-mediated phagocytosis of cancer cells. *J Control Release* 2020;**323**:376−86.
197. Kang M, Lee SH, Kwon M, Byun J, Kim D, Kim C, et al. Nanocomplex-mediated *in vivo* programming to chimeric antigen receptor-M1 macrophages for cancer therapy. *Adv Mater* 2021;**33**:e2103258.
198. Duan Y, Zhang W, Ouyang Y, Yang Q, Zhang Q, Zhao S, et al. Proton sponge nanocomposites for synergistic tumor elimination *via* autophagy inhibition-promoted cell apoptosis and macrophage repolarization-enhanced immune response. *ACS Appl Mater Interfaces* 2024;**16**:17285−99.
199. Zhang X, Wang J, Chen Z, Hu Q, Wang C, Yan J, et al. Engineering PD-1-presenting platelets for cancer immunotherapy. *Nano Lett* 2018;**18**:5716−25.
200. Chen H, Luan X, Paholak HJ, Burnett JP, Stevers NO, Sansanaphongpricha K, et al. Depleting tumor-associated Tregs *via* nanoparticle-mediated hyperthermia to enhance anti-CTLA-4 immunotherapy. *Nanomedicine* 2020;**15**:77−92.
201. Mei KC, Liao YP, Jiang J, Chiang M, Khazaieli M, Liu X, et al. Liposomal delivery of mitoxantrone and a cholesteryl indoximod prodrug provides effective chemo-immunotherapy in multiple solid tumors. *ACS Nano* 2020;**14**:13343−66.
202. Zhang YX, Zhao YY, Shen J, Sun X, Liu Y, Liu H, et al. Nanoenabled modulation of acidic tumor microenvironment reverses anergy of infiltrating t cells and potentiates anti-PD-1 therapy. *Nano Lett* 2019;**19**:2774−83.
203. Gabizon A, Shmeeda H, Draper B, Parente-Pereira A, Maher J, Carrascal-Miniño A, et al. Harnessing nanomedicine to potentiate the chemo-immunotherapeutic effects of doxorubicin and alendronate co-encapsulated in pegylated liposomes. *Pharmaceutics* 2023;**15**:2606.
204. Liu YB, Chen XY, Yu BX, Cen Y, Huang CY, Yan MY, et al. Chimeric peptide-engineered self-delivery nanomedicine for photodynamic-triggered breast cancer immunotherapy by macrophage polarization. *Small* 2023:e2309994.
205. Wu F, Li Y, Meng Y, Cai X, Shi J, Li J, et al. An ion-enhanced oncolytic virus-like nanoparticle for tumor immunotherapy. *Angew Chem Int Ed Engl* 2022;**61**:e202210487.
206. Qiu Q, Lu D, Liu G, Yang X, Li J, Ren H, et al. Colistin crosslinked gemcitabine micelles to eliminate tumor drug resistance caused by intratumoral microorganisms. *Bioconjug Chem* 2022;**33**:1944−52.
207. Zhang Y, Luo Y, Zhao J, Zheng W, Zhan J, Zheng H, et al. Emerging delivery systems based on aqueous two-phase systems: a review. *Acta Pharm Sin B* 2024;**14**:110−32.
208. Wang Y, Yu J, Luo Z, Shi Q, Liu G, Wu F, et al. Engineering endogenous tumor-associated macrophage-targeted biomimetic nano-RBC to reprogram tumor immunosuppressive microenvironment for enhanced chemo-immunotherapy. *Adv Mater* 2021;**33**:e2103497.

209. Wang C, Wang J, Zhang X, Yu S, Wen D, Hu Q, et al. *In situ* formed reactive oxygen species-responsive scaffold with gemcitabine and checkpoint inhibitor for combination therapy. *Sci Transl Med* 2018;**10**: eaan3682.
210. Li Z, Wang Y, Shen Y, Qian C, Oupicky D, Sun M. Targeting pulmonary tumor microenvironment with CXCR4-inhibiting nanocomplex to enhance anti-PD-L1 immunotherapy. *Sci Adv* 2020;**6**:eaaz9240.
211. Zhang W, Liu X, Cao S, Zhang Q, Chen X, Luo W, et al. Multifunctional redox-responsive nanoplatform with dual activation of macrophages and t cells for antitumor immunotherapy. *ACS Nano* 2023;**17**:14424−41.
212. Yuan H, Gui H, Chen S, Zhu L, Wang C, Jing Q, et al. Regulating tumor-associated macrophage polarization by cyclodextrin-modified PLGA nanoparticles loaded with R848 for treating colon cancer. *Int J Nanomed* 2024;**19**:3589−605.
213. Valsalakumari R, Pandya AD, Prasmickaite L, Kvalvaag A, Myrann AG, Åslund AKO, et al. Preclinical efficacy of cabazitaxel loaded poly(2-alkyl cyanoacrylate) nanoparticle variants. *Int J Nanomed* 2024;**19**:3009−29.
214. Sun Z, Sun Z, Liu J, Gao X, Jiao L, Zhao Q, et al. Engineered extracellular vesicles expressing siglec-10 camouflaged AIE photosensitizer to reprogram macrophages to active M1 phenotype and present tumor-associated antigens for photodynamic immunotherapy. *Small* 2024;**20**:e2307147.
215. Chen Y, Gong L, Cao Y, Liu Z, Wang Y, Cheng H, et al. Reprogramming tumor-associated macrophages by a dually targeted milk exosome system as a potent monotherapy for cancer. *J Control Release* 2024;**366**:395−409.
216. Yang Y, Yang Y, Chen M, Chen J, Wang J, Ma Y, et al. Injectable shear-thinning polylysine hydrogels for localized immunotherapy of gastric cancer through repolarization of tumor-associated macrophages. *Biomater Sci* 2021;**9**:6597−608.
217. Tao Y, Ju E, Ren J, Qu X. Immunostimulatory oligonucleotides-loaded cationic graphene oxide with photothermally enhanced immunogenicity for photothermal/immune cancer therapy. *Biomaterials* 2014;**35**:9963−71.
218. Zhang C, Xia D, Liu J, Huo D, Jiang X, Hu Y. Bypassing the immunosuppression of myeloid-derived suppressor cells by reversing tumor hypoxia using a platelet-inspired platform. *Adv Funct Mater* 2020;**30**:2000189.
219. Zhang YR, Luo JQ, Zhang JY, Miao WM, Wu JS, Huang H, et al. Nanoparticle-enabled dual modulation of phagocytic signals to improve macrophage-mediated cancer immunotherapy. *Small* 2020; **16**:e2004240.
220. Wen D, Liang T, Chen G, Li H, Wang Z, Wang J, et al. Adipocytes encapsulating telratolimod recruit and polarize tumor-associated macrophages for cancer immunotherapy. *Adv Sci (Weinh)* 2023;**10**: e2206001.
221. Lu L, Zi H, Zhou J, Huang J, Deng Z, Tang Z, et al. Engineered microparticles for treatment of murine brain metastasis by reprograming tumor microenvironment and inhibiting MAPK Pathway. *Adv Sci (Weinh)* 2023;**10**:e2206212.
222. He XY, Liu BY, Wu JL, Ai SL, Zhuo RX, Cheng SX. A dual macrophage targeting nanovector for delivery of oligodeoxynucleotides to overcome cancer-associated immunosuppression. *ACS Appl Mater Interfaces* 2017;**9**:42566−76.
223. Yuan G, Liu Z, Wang W, Liu M, Xu Y, Hu W, et al. Multifunctional nanoplatforms application in the transcatheter chemoembolization against hepatocellular carcinoma. *J Nanobiotechnol* 2023;**21**:68.
224. Lu X, Liu J, Wu X, Ding B. Multifunctional DNA origami nanoplatforms for drug delivery. *Chem Asian J* 2019;**14**:2193−202.
225. Lin Y, Zhong W, Wang M, Chen Z, Lu C, Yang H. Multifunctional carbon monoxide prodrug-loaded nanoplatforms for effective photoacoustic imaging-guided photothermal/gas synergistic therapy. *ACS Appl Bio Mater* 2021;**4**:4557−64.
226. Gao B, Xu J, Zhou J, Zhang H, Yang R, Wang H, et al. Multifunctional pathology-mapping theranostic nanoplatforms for US/MR imaging and ultrasound therapy of atherosclerosis. *Nanoscale* 2021;**13**:8623−38.
227. Lecocq Q, De Vlaeminck Y, Hanssens H, D'Huyvetter M, Raes G, Goyvaerts C, et al. Theranostics in immuno-oncology using nanobody derivatives. *Theranostics* 2019;**9**:7772−91.
228. Anani T, Rahmati S, Sultana N, David AE. MRI-traceable theranostic nanoparticles for targeted cancer treatment. *Theranostics* 2021;**11**: 579−601.
229. de Aguiar Ferreira C, Heidari P, Ataeinia B, Sinevici N, Granito A, Kumar HM, et al. Immune checkpoint inhibitor-mediated cancer theranostics with radiolabeled anti-granzyme B peptide. *Pharmaceutics* 2022;**14**:1460.
230. Zhao DH, Li CQ, Hou XL, Xie XT, Zhang B, Wu GY, et al. Tumor microenvironment-activated theranostics nanozymes for fluorescence imaging and enhanced chemo-chemodynamic therapy of tumors. *ACS Appl Mater Interfaces* 2021;**13**:55780−9.
231. Zhao X, Yang CX, Chen LG, Yan XP. Dual-stimuli responsive and reversibly activatable theranostic nanoprobe for precision tumor-targeting and fluorescence-guided photothermal therapy. *Nat Commun* 2017;**8**:14998.
232. Feng L, Cheng L, Dong Z, Tao D, Barnhart TE, Cai W, et al. Theranostic liposomes with hypoxia-activated prodrug to effectively destruct hypoxic tumors post-photodynamic therapy. *ACS Nano* 2017;**11**:927−37.
233. Singh S, Chauhan V, Barik P. Nano-based theranostics approach in the management of cancer: review. *Pharm Nanotechnol* 2025;**13**: 633−47.
234. Kang H, Rho S, Stiles WR, Hu S, Baek Y, Hwang DW, et al. Size-dependent EPR effect of polymeric nanoparticles on tumor targeting. *Adv Healthcare Mater* 2020;**9**:e1901223.
235. Chen H, Liu YC, Zhang Z, Li M, Du L, Wu PC, et al. Mouse Strain- and charge-dependent vessel permeability of nanoparticles at the lower size limit. *Front Chem* 2022;**10**:944556.
236. Li X, Montague EC, Pollinzi A, Lofts A, Hoare T. Design of smart size-, surface-, and shape-switching nanoparticles to improve therapeutic efficacy. *Small* 2022;**18**:e2104632.
237. Roshanzadeh A, Park S, Ganjbakhsh SE, Park J, Lee DH, Lee S, et al. Surface charge-dependent cytotoxicity of plastic nanoparticles in alveolar cells under cyclic stretches. *Nano Lett* 2020;**20**: 7168−76.
238. Bilardo R, Traldi F, Vdovchenko A, Resmini M. Influence of surface chemistry and morphology of nanoparticles on protein corona formation. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 2022;**14**:e1788.
239. Nakamura T, Sato T, Endo R, Sasaki S, Takahashi N, Sato Y, et al. STING agonist loaded lipid nanoparticles overcome anti-PD-1 resistance in melanoma lung metastasis *via* NK cell activation. *J Immunother Cancer* 2021;**9**:e002852.
240. Rosenblum D, Gutkin A, Kedmi R, Ramishetti S, Veiga N, Jacobi AM, et al. CRISPR-Cas9 genome editing using targeted lipid nanoparticles for cancer therapy. *Sci Adv* 2020;**6**:eabc9450.
241. Kazemian P, Yu SY, Thomson SB, Birkenshaw A, Leavitt BR, Ross CJD. Lipid-nanoparticle-based delivery of CRISPR/Cas9 genome-editing components. *Mol Pharm* 2022;**19**:1669−86.
242. Zou Y, Sun X, Yang Q, Zheng M, Shimoni O, Ruan W, et al. Blood-brain barrier-penetrating single CRISPR-Cas9 nanocapsules for effective and safe glioblastoma gene therapy. *Sci Adv* 2022;**8**: eabm8011.
243. Li Y, Li S, Jiang Z, Tan K, Meng Y, Zhang D, et al. Targeting lymph node delivery with nanovaccines for cancer immunotherapy: recent advances and future directions. *J Nanobiotechnol* 2023;**21**: 212.
244. Mendez-Gomez HR, DeVries A, Castillo P, von Roemeling C, Qdaisat S, Stover BD, et al. RNA aggregates harness the danger response for potent cancer immunotherapy. *Cell* 2024;**187**:2521.
245. Sun R, Chen H, Zheng J, Yoshitomi T, Kawazoe N, Yang Y, et al. Composite scaffolds of gelatin and Fe(3) O(4) nanoparticles for magnetic hyperthermia-based breast cancer treatment and adipose tissue regeneration. *Adv Healthcare Mater* 2023;**12**:e2202604.
246. Molina-Peña R, Haji Mansor M, Najberg M, Thomassin JM, Gueza B, Alvarez-Lorenzo C, et al. Nanoparticle-containing

electrospun nanofibrous scaffolds for sustained release of SDF-1α. *Int J Pharm* 2021;**610**:121205.
247. Xiang Y, Tian M, Huang J, Li Y, Li G, Li X, et al. LMP2-mRNA lipid nanoparticle sensitizes EBV-related tumors to anti-PD-1 therapy by reversing T cell exhaustion. *J Nanobiotechnol* 2023;**21**:324.
248. Ding H, Tan P, Fu S, Tian X, Zhang H, Ma X, et al. Preparation and application of pH-responsive drug delivery systems. *J Control Release* 2022;**348**:206−38.
249. Wang C, Li F, Zhang T, Yu M, Sun Y. Recent advances in anti-multidrug resistance for nano-drug delivery system. *Drug Deliv* 2022;**29**:1684−97.
250. Xiao Y, Li X, Mao J, Zheng H, Ji R, Wang Z, et al. Reverse anti-breast cancer drug resistance effects by a novel two-step assembled nano-celastrol medicine. *Nanoscale* 2022;**14**:7856−63.
251. Rahman MM, Wang J, Wang G, Su Z, Li Y, Chen Y, et al. Chimeric nanobody-decorated liposomes by self-assembly. *Nat Nanotechnol* 2024;**19**:818−24.
252. Georgievski A, Bellaye PS, Tournier B, Choubley H, Pais de Barros JP, Herbst M, et al. Valrubicin-loaded immunoliposomes for specific vesicle-mediated cell death in the treatment of hematological cancers. *Cell Death Dis* 2024;**15**:328.
253. Charbe NB, Amnerkar ND, Ramesh B, Tambuwala MM, Bakshi HA, Aljabali AAA, et al. Small interfering RNA for cancer treatment: overcoming hurdles in delivery. *Acta Pharm Sin B* 2020;**10**:2075−109.
254. Zhou Y, Yuan J, Xu K, Li S, Liu Y. Nanotechnology reprogramming metabolism for enhanced tumor immunotherapy. *ACS Nano* 2024;**18**: 1846−64.
255. Stoller M, Di Palma L, Vuppala S, Verdone N, Vilardi G. Process intensification techniques for the production of nano- and sub-micronic particles for food and medical applications. *Curr Pharm Des* 2018;**24**:2329−38.
256. Fu S, Li G, Zang W, Zhou X, Shi K, Zhai Y. Pure drug nano-assemblies: a facile carrier-free nanoplatform for efficient cancer therapy. *Acta Pharm Sin B* 2022;**12**:92−106.
257. Ramos TI, Villacis-Aguirre CA, López-Aguilar KV, Santiago Padilla L, Altamirano C, Toledo JR, et al. The Hitchhiker's guide to human therapeutic nanoparticle development. *Pharmaceutics* 2022;**14**:247.
258. Chen D, Wei Z, Wang Z, Yang Y, Chen L, Wang X, et al. Long-term exposure to nanoplastics reshapes the microbial interaction network of activated sludge. *Environ Pollut* 2022;**314**:120205.
259. Kong T, Zhang SH, Zhang C, Zhang JL, Yang F, Wang GY, et al. Long-term effects of unmodified 50 nm ZnO in mice. *Biol Trace Elem Res* 2019;**189**:478−89.
260. Khoobchandani M, Katti KK, Karikachery AR, Thipe VC, Srisrimal D, Dhurvas Mohandoss DK, et al. New approaches in breast cancer therapy through green nanotechnology and nano-ayurvedic medicine - pre-clinical and pilot human clinical investigations. *Int J Nanomed* 2020;**15**:181−97.
261. Liu SL, Wang ZG, Xie HY, Liu AA, Lamb DC, Pang DW. Single-virus tracking: from imaging methodologies to virological applications. *Chem Rev* 2020;**120**:1936−79.
262. Chen Y, Zhang X, Liu W. Effect of metal and metal oxide engineered nano particles on nitrogen bio-conversion and its mechanism: a review. *Chemosphere* 2022;**287**:132097.
263. Wang L, Luo R, Onyshchenko K, Rao X, Wang M, Menz B, et al. Adding liposomal doxorubicin enhances the abscopal effect induced by radiation/αPD1 therapy depending on tumor cell mitochondrial DNA and cGAS/STING. *J Immunother Cancer* 2023;**11**:e006235.
264. Alimohammadi R, Alibeigi R, Nikpoor AR, Chalbatani GM, Webster TJ, Jaafari MR, et al. Encapsulated checkpoint blocker before chemotherapy: the optimal sequence of anti-CTLA-4 and doxil combination therapy. *Int J Nanomed* 2020;**15**: 5279−88.
265. Sparreboom A, Scripture CD, Trieu V, Williams PJ, De T, Yang A, et al. Comparative preclinical and clinical pharmacokinetics of a cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in Cremophor (Taxol). *Clin Cancer Res* 2005;**11**:4136−43.
266. Zhang Q, Huang XE, Gao LL. A clinical study on the premedication of paclitaxel liposome in the treatment of solid tumors. *Biomed Pharmacother* 2009;**63**:603−7.
267. Björn N, Jakobsen Falk I, Vergote I, Gréen H. ABCB1 Variation affects myelosuppression, progression-free survival and overall survival in paclitaxel/carboplatin-treated Ovarian Cancer patients. *Basic Clin Pharmacol Toxicol* 2018;**123**:277−87.
268. Raj S, Khurana S, Choudhari R, Kesari KK, Kamal MA, Garg N, et al. Specific targeting cancer cells with nanoparticles and drug delivery in cancer therapy. *Semin Cancer Biol* 2021;**69**: 166−77.
269. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: an updated review. *Pharmaceutics* 2017; **9**:12.
270. Drabczyk A, Kudłacik-Kramarczyk S, Jamroży M, Krzan M. Biomaterials in drug delivery: advancements in cancer and diverse therapies-review. *Int J Mol Sci* 2024;**25**:3126.