Nanoscale Advances

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal

Cite this: DOI: 10.1039/d5na00390c

Nanomedicine revolutionizing cancer immunotherapy: recent advancements in nanotechnological strategies and applications

Jay Bhatt,† Sweny Jain,† Sharad Gupta * and Dhiraj Devidas Bhatia *

The convergence of nanotechnology and cancer immunotherapy represents a promising frontier in the fight against cancer, offering new avenues for enhancing therapeutic efficacy and precise personalized cancer treatments. This review presents recent advancements in nanomedicine that strategically target and modulate various immune cells to enhance anti-tumor responses and overcome barriers posed by the immunosuppressive tumor microenvironment for cancer treatment. By exploring advance strategies such as photoimmunotherapy, sonodynamic therapy, therapeutic nanovaccines, and surface-modified immune cells, we highlight how nanoparticles can go beyond drug delivery to actively reprogram immune pathways. Despite significant advances in cancer immunotherapy, current nanomedicine approaches struggle with poor targeting, immune evasion, systemic toxicity, *etc.* This review highlights recent breakthroughs that address these challenges by focusing on treatment that are induced using effective immune cells, innovative approaches to tumor reduction through targeted drug delivery systems, the development of enhanced combinational immunotherapy techniques, and the modification of immune cells using nanoparticles to enhance their anti-tumor activity through immune cell-specific strategies. These nanotechnological innovations hold the potential to overcome existing limitations in cancer immunotherapy, paving the way for more effective and personalized treatments to reshape cancer immunotherapy through synergistic, targeted, and immune-responsive strategies.

Received 22nd April 2025
Accepted 27th August 2025

DOI: 10.1039/d5na00390c

rsc.li/nanoscale-advances

1. Introduction

Cancer immunotherapy stands at the forefront of modern oncology, representing an innovative approach in the fight against cancer. Nanomedicine provides the distinctive properties of nanomaterials to enhance therapeutic efficacy and minimize adverse effects. This innovative field integrates nanotechnology into cancer treatment, addressing significant challenges such as limited specificity, drug resistance, and systemic toxicity that have historically hindered the effectiveness of traditional cancer therapies. By utilizing nanoparticles that can selectively deliver immunomodulators to tumor sites, researchers aim to improve the activation and persistence of anti-tumor immune responses.[1–3] This review elaborates recent innovations that directly emphasizes immune cell-specific nanoplatforms, and their modifications for nanomedicines while also covering emerging combination strategies like photoimmunotherapy, radioimmunotherapy, and sonodynamic therapy, providing a more integrated and mechanistic perspective not commonly addressed in the existing literature. Cancer immunotherapy has revolutionized the treatment landscape, utilizing the body's immune system to target and eradicate cancer cells. This approach includes various modalities such as immune checkpoint inhibitors (ICIs)[4] and cancer vaccines,[5] each offering unique mechanisms to enhance immune responses against tumors. ICIs, for instance, have demonstrated remarkable efficacy in prolonging survival in patients with advanced cancers by blocking inhibitory signals that prevent T cells from attacking tumor cells. Similarly, adoptive cell therapy (ACT), especially CAR T-cell therapy, involves modifying a patient's T cells to improve their capacity to identify and eliminate cancer cells, showing significant success in hematological malignancies.[6] Despite these advancements, challenges remain, including immune-related adverse events (irAEs) and the complexity of the tumor microenvironment (TME), which can inhibit the effectiveness of immunotherapeutic agents. The heterogeneity of tumors along with immunosuppressive factors within the TME underscore the need for personalized treatment strategies and combination therapies to enhance the efficacy. Recent advancements in nanomedicine aim to address these challenges by optimizing the delivery of immunotherapeutic agents directly to immune cells involved in the anti-tumor response. This targeted approach not only boosts up the therapeutic index of immunotherapies but also opens avenues for combination therapies that synergize with existing immunotherapeutic strategies,

Department of Biological Sciences and Engineering, Indian Institute of Technology Gandhinagar, Palaj, Gujarat, 382355, India. E-mail: dhiraj.bhatia@iitgn.ac.in

† Both the authors contributed equally to this work.

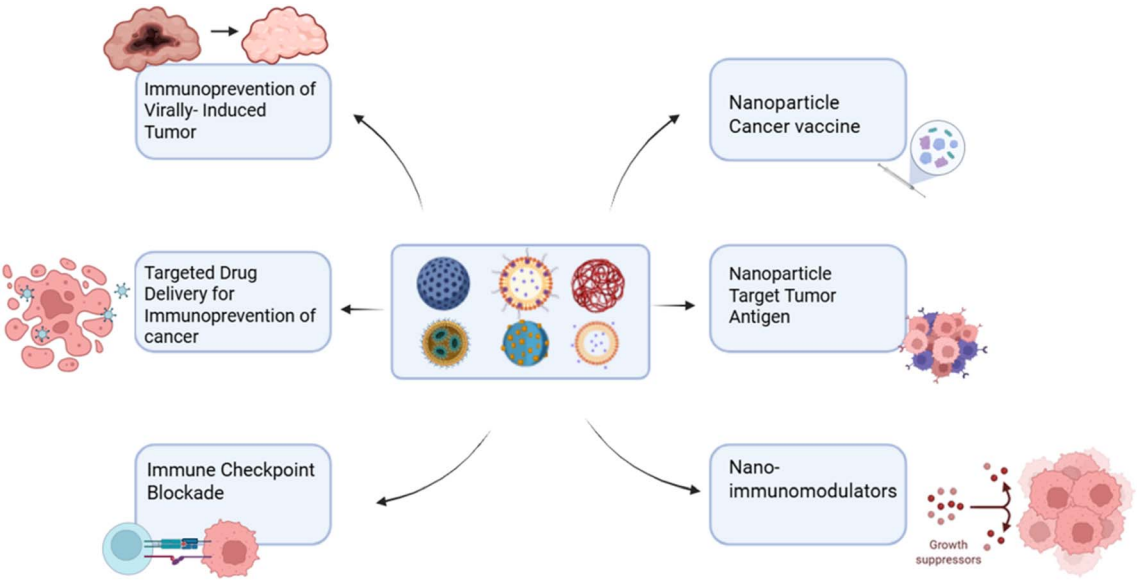

Fig. 1 Multifaceted advantages of nanoparticles in cancer therapy. (1) Immune prevention of virus-induced tumors, (2) nanoparticle-based cancer vaccines, (3) targeted delivery to tumor antigens, (4) modulation of the tumor microenvironment targeting immune cells, (5) checkpoint blockade inhibition, and (6) enhanced drug delivery for immunological prevention of cancer (figure made using Biorender).

potentially leading to improved patient outcomes. Various studies have reported that nanomedicine can significantly improve the efficacy of cancer immunotherapy by enhancing drug delivery, modulating immune responses, and overcoming barriers posed by the TME (Fig. 1).[7–9]

2. Role of each immune cell and its modification using nanoparticles

The immune system is a sophisticated network composed of cells, tissues, and organs that team up to protect the body against infections and diseases. Immune cells are the key players in this defense system, constantly patrolling the body for potential threats and mounting a response when necessary.[10] The immune system plays a crucial role in cancer immunotherapy, with various immune cell types contributing to the anti-tumor response. Nanoparticles have emerged as promising tools to modulate and enhance the function of these immune cells in the fight against cancer.[11,12]

2.1 Nanoparticles targeting T cells

T cells are central to cancer immunotherapy, as they can directly identify and eradicate tumor cells. Nanoparticles are known to activate and expand tumor-specific cells engineered to target and reprogram regulatory T cells (Tregs). These cells suppress anti-tumor immunity, thereby enhancing the overall T cell response.[13] The mode of action of T cells is further discussed in Fig. 2.

A certain application includes hybrid prodrug nanocarriers that co-deliver cisplatin and camptothecin which can stimulate the cGAS/STING pathway and induce DNA damage, leading to increased CD8+ T cell infiltration in the TME and improved immunotherapy outcomes in colorectal cancer.[14] Researchers developed a platinum(IV) prodrug, named "CPT-Pt(IV)", that incorporates both cisplatin and camptothecin (CPT). This prodrug can be activated by reactive oxygen species (ROS) within tumor cells, releasing both cisplatin and CPT. The hydrophobic nature of CPT-Pt(IV) allows it to self-assemble with a ROS-sensitive polymer (P1) and a lipid polymer (mPEG2k-DSPE) to form nanoparticles (NPs). These nanoparticles are capable of accumulating at the tumor site. Upon reaching the tumor, the NPs release cisplatin and CPT, leading to double DNA damage. This triggers the cGAS-STING pathway, promoting dendritic cell (DC) maturation and increasing the infiltration of CD8+ T cells into the tumor. This approach can potentially convert "immune cold tumors" & "immune hot tumors" enhancing tumor suppression through a combination of chemotherapy and immunotherapy in a mouse model of colorectal treatment.[14] Another strategy to speed up tumor suppression involves the use of prodrug nanocarriers derived from hyaluronic acid and adamantane-conjugated heterodimers of pyropheophorbide-a (PPa), cyclodextrin and JQ1, specifically targeting CD44-overexpressing pancreatic cancer cells, as described in Fig. 1. This approach combines phototherapy and immunotherapy to enhance T lymphocyte infiltration within the tumor. Additionally, JQ1 plays a critical role in suppressing phototherapy-induced immune evasion by downregulating c-Myc and programmed death ligand 1 (PD-L1), leading to significant tumor suppression.[15] The tLyp1 peptide-improved hybrid nanoparticles presented enhanced stability and effective targeting to Treg cells, and they improved the outcome of imatinib in downregulating Treg cell suppression by inhibition of STAT3 and STAT5 phosphorylation leading to a reduction in Treg cell numbers. There is an increase in CD8+ T cell infiltration within the tumor microenvironment (TME) which helps in combatting

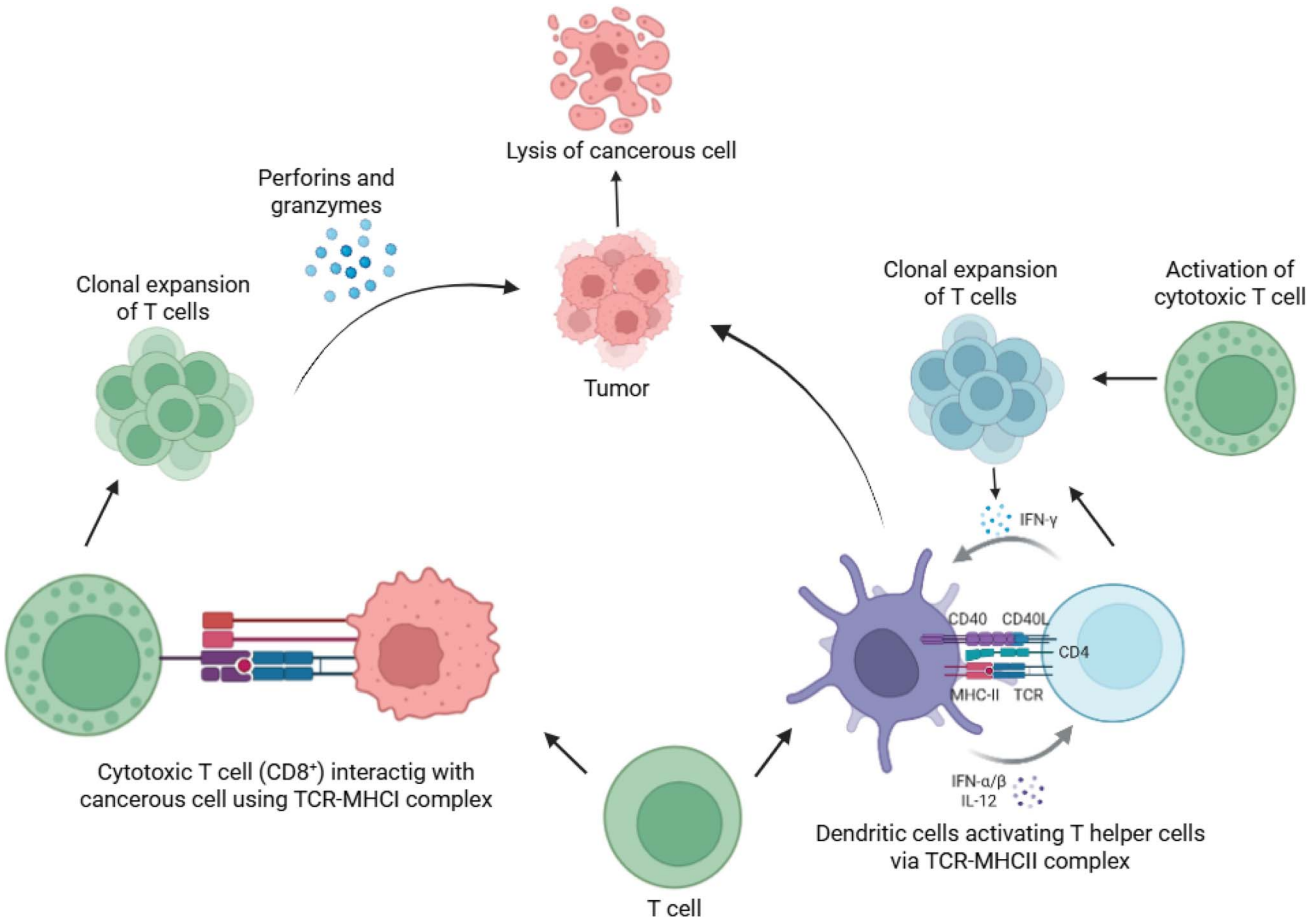

Fig. 2 Mode of action of T cells against cancerous cells. T cells are primarily of two types—cytotoxic T cells (CD8+ cells) and helper T cells (CD4+ cells). Cytotoxic T cells (CD8+ cells) identify and interact with cancerous cells *via* the TCR–MHC1 complex. This interaction leads to clonal expansion of cytotoxic T cells; they then release perforins and granzymes which will attack and lyse the cancerous cells. Whereas helper T cells interact with the antigen presenting cells like dendritic cells *via* the TCR–MHC2 complex, activating them. This activation leads to its clonal expansion, releasing IFN-gamma, which will recruit more dendritic cells and also activate cytotoxic T cells which will act on the cancerous cell altogether and lead to its lysis (image made using Biorender).

cancer. These functionalized nanoparticles promote tumor suppression by enhancing the infiltration of dendritic cells, CD8+ T cells, and natural killer cells, while decreasing Treg and myeloid-derived suppressor cell (MDSC) populations.[16] Similarly, another study presents a lipid nanoparticle system, AntiCD3-LNP/CAR19 + shIL6, designed to simplify CAR-T cell production and reduce cytokine release syndrome (CRS). The nanoparticles, modified with a CD3 antibody and loaded with a plasmid encoding both anti-CD19 CAR and IL-6 shRNA, target and transfect T cells *in vivo*. This approach not only produces CAR-T cells directly in the body but also suppresses IL-6 to mitigate CRS. *In vivo* tests showed prolonged survival in leukemia model mice, with the lipid nanoparticle system exhibiting comparable anti-tumor efficacy to traditional *ex vivo* CAR-T cell preparations. This method enhances CAR-T therapy convenience and safety, facilitating its clinical application.[17,18]

2.2 Natural killer cells

Natural killer (NK) cells are one of the innate immune cells capable of directly identifying and destroying tumor cells. Certain nanoparticles can be used to deliver cytokines or other activating agents to stimulate NK cell function and enhance their cytotoxicity against tumor cells. Additionally, nanoparticles can be engineered to target and inhibit immunosuppressive factors in the tumor microenvironment, which can impair NK cell function.[19] Mature NK cells migrate from the bone marrow to peripheral tissues, where they execute cytotoxic functions against cancerous and virus-infected cells while interacting with other immune cells through cytokine secretion. Their infiltration into tumors correlates with improved prognosis in cancers like melanoma, renal cell carcinoma, liver tumors, and breast cancer. Enhancing the frequency, infiltration, and function of NK cells has been shown to improve cancer patient survival, highlighting their potential in immunotherapy (Fig. 3).[20,21]

NK cells, which belong to group I innate lymphoid cells, can rapidly target abnormal cells without prior sensitization and express the transcription factor T-bet along with Th1-related cytokines such as IFN-γ. CD16, also known as FcγRIII, is found on the surface of NK cells and mediates antibody-

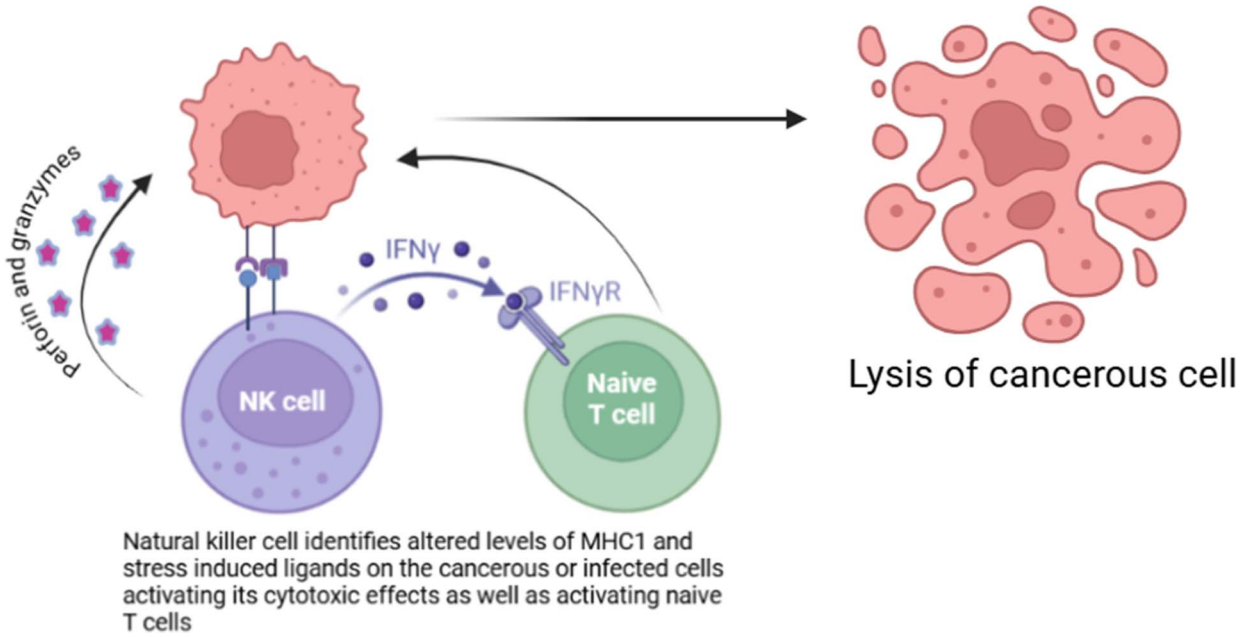

Fig. 3 Natural killer cell mode of action against cancer. Natural killer cells identify the altered levels of MHC1 and stress induced ligands like IFN-gamma in cancerous cells and thus activate naïve T cells and secreting lytic granules like perforins and granzymes, leading to lysis of the cancerous cells (figure made using Biorender).

dependent cellular cytotoxicity.[22–24] Self-assembled selenopeptide nanoparticles have been developed to enhance tumor chemoimmunotherapy by activating natural killer (NK) cells through their oxidative metabolites. This study introduces self-assembled selenopeptide nanoparticles designed to enhance chemoimmunotherapy for cancer treatment. The nanoparticle leverages the oxidative metabolite of selenopeptides to activate natural killer (NK) cells. It has a tumor-targeting motif, which is an enzyme-responsive cleavable linker, and a selenoamino acid tail that is sensitive to reactive oxygen species (ROS), enabling controlled drug release and NK cell activation. The selenopeptide nanoparticle delivers doxorubicin (DOX) to solid tumors, where ROS triggers both the release of the drug and the activation of NK cells, creating a synergistic effect between chemotherapy and immunotherapy. This dual-action approach improves antitumor efficacy by enhancing drug accumulation, penetration, and controlled release at the tumor site. *In vivo* and *in vitro* results demonstrate that this combination therapy

Table 1 Comparative overview of trispecific NK cell nanoengagers: components, targets, and therapeutic efficacy. This table presents the outcomes of different treatment strategies combining EGFR-targeted nanoparticles, immune modulators, and chemotherapy. The α-EGFR/α-CD16/α-4-1BB EPI NPs showed the best tumor growth inhibition (TGI), demonstrating that simultaneous delivery of chemotherapeutics and immune activators significantly enhances therapeutic efficacy. EGFR targeting is essential for NK cell-mediated tumor recognition and response, especially in EGFR-expressing tumors[26,27]

Sr. no.	Treatment combination	Tumor model	Tumor growth inhibition (TGI)	Key findings
1	α-EGFR/α-CD16/α-4-1BB EPI nanoparticles (NPs)	A431	84%	Best therapeutic outcome with significant tumor suppression and survival benefit
2	α-EGFR/α-CD16/α-4-1BB NPs + free EPI	A431	64%	Moderate tumor reduction: Combination of therapy showed some benefit, but less effective than targeted NPs
3	α-EGFR/α-CD16/α-4-1BB NPs + free α-EGFR	A431	49%	Tumor inhibition observed, but less effective compared to the targeted treatment with EPI
4	α-EGFR/α-CD16/α-4-1BB EPI NPs	MB468	84%	Strong anticancer response with enhanced tumor targeting and immune system activation
5	α-EGFR/α-CD16/α-4-1BB NPs	HT29	66%	Moderate tumor inhibition with EGFR targeting playing a crucial role in NK cell activation
6	α-EGFR/α-CD16/α-4-1BB EPI NPs	HT29	84%	High level of tumor suppression due to targeted drug delivery to EGFR-overexpressing tumors
7	α-CD16/α-4-1BB NPs + free α-EGFR	HT29	No significant TGI	No impact on EGFR-negative tumors; NK cells unable to target tumors effectively

significantly improves the antitumor activity.[25] Recruitment of NK cells has always been difficult; however, Kin Man Au *et al.* demonstrated that effective NK cell activation can be achieved by the spatiotemporal coactivation of CD16 and 4-1BB stimulatory molecules on NK cells with nanoengagers, and the nanoengagers are more effective than free antibodies. They conjugated anti-mouse CD16 antibodies to polyethylene glycol-poly(lactic-*co*-glycolic acid) (PEG-PLGA) nanoparticles, along with anti-mouse 4-1BB and anti-human EGFR antibodies. This resulted in tri-specific PEG-PLGA nanoparticles that effectively activated NK cells by simultaneously stimulating CD16 and 4-1BB molecules on NK cells. The nanoengagers were tested in various treatment combinations, including free EPI, EGFR-targeted EPI nanoparticles (α-EGFR EPI NPs), and combinations with immune agonistic antibodies (α-CD16/α-4-1BB). The results showed that the most effective treatment was the combination of α-EGFR/α-CD16/α-4-1BB EPI NPs, which significantly inhibited tumor growth and prolonged the survival in mouse models of colorectal and breast cancer. This treatment enhanced tumor targeting and NK cell activation, showing synergistic effects between chemotherapy and immunotherapy. These nanoparticles enhanced the recruitment of NK cells to EGFR-positive tumor cells.[26] Their interactions with other immune cells, through cytokine secretion and chemokine release, position NK cells as potent effectors against cancer, infectious diseases, and chronic inflammation. Furthermore, increased NK cell infiltration into the tumor microenvironment correlates with better prognoses in various cancers, including melanoma, renal cell carcinoma, liver tumors, and breast cancer (Table 1).

2.3 Myeloid cells

Myeloid-derived suppressor cells (MDSCs) are a diverse group of immature myeloid cells known for their ability to suppress anti-tumor immune responses. They play a significant role in the tumor microenvironment (TME) by promoting immunosuppression, which hinders the effectiveness of cancer immunotherapy. Nanomedicine has emerged as a promising strategy to target and modulate MDSCs, enhancing anti-tumor immunity. Nanoparticles can be used to target and deplete MDSCs or reprogram them into more pro-inflammatory phenotypes, thereby reducing their immunosuppressive effects and enhancing anti-tumor immunity. Additionally, the ability of nanomedicines to improve the pharmacokinetics and biodistribution of therapeutic agents allows for more effective targeting of MDSCs within tumors, potentially leading to improved patient outcomes.[28,29] A novel cancer therapy was developed by coating iron oxide magnetic nanoparticles (MNPs) with membranes derived from myeloid-derived suppressor cells (MDSCs), resulting in MNPs@MDSCs, which significantly enhance tumor targeting compared to red blood cell-coated or naked MNPs. This approach utilizes the natural tumor-homing properties of MDSCs, allowing precise tumor accumulation. Once in the tumor microenvironment, MNPs@MDSCs act as photothermal therapy (PTT) agents, induce immunogenic cell death (ICD) and trigger the release of danger-associated molecular patterns (DAMPs) to activate immune responses. Additionally, these nanoparticles reprogram tumor-associated macrophages (TAMs) from a pro-tumor to an anti-tumor phenotype and reduce the tumor's metabolic activity, collectively leading to enhanced tumor destruction and improved immune system activation.[30] The MNPs@MDSCs exhibit excellent biocompatibility and favorable pharmacokinetics, making them a promising candidate for integrated cancer imaging and treatment. In another approach, a light-triggered sequential drug delivery system, the rapid release of sunitinib not only aids in antiangiogenic therapy but also plays a crucial role in targeting myeloid-derived suppressor cells (MDSCs). By inhibiting MDSCs, the system helps to reverse the immunosuppressive environment typically created by tumors. This reduction in MDSCs enhances the immune response against the tumor, thereby improving the overall effectiveness of the chemotherapy delivered by the doxorubicin-loaded nanoparticles. This strategy effectively combines immunomodulation with targeted chemotherapy for better cancer treatment outcomes.[31] In the tumor microenvironment, the NLRP3 inflammasome drives the production of interleukin-1β (IL-1β), promoting tumor growth and immune suppression. This study demonstrated that 30 nm gold nanoparticles (Au NPs) disrupt the NLRP3 inflammasome in bone marrow-derived macrophages by preventing the NLRP3–NEK7 interaction, a process mediated by reactive oxygen species (ROS). Density functional theory (DFT) calculations revealed the mechanism behind the superior ROS scavenging abilities of Au NPs. When Au NPs were combined with H6, a peptide targeting MDSCs, they effectively reduced IL-1β production and decreased the MDSC population in the tumor microenvironment. This led to enhanced T cell activation and improved the efficacy of immunotherapy in both PD-1 sensitive and resistant mouse tumors.[32] Overall, the integration of nanomedicine in modulating MDSCs represents a novel approach to overcoming the challenges posed by the immunosuppressive TME, thereby enhancing the efficacy of cancer immunotherapy and offering new avenues for treatment strategies. This innovative approach underscores the potential of nanotechnology to revolutionize cancer treatment by specifically targeting key immune regulators within the TME.

2.4 Neutrophils

Neutrophils, the most abundant white blood cells in the body, are emerging as a promising target for cancer immunotherapy using nanomedicines. As the first responders to inflammation, neutrophils can be harnessed to deliver nanoparticle-based therapies directly to tumor sites (Fig. 4). Nanotechnology offers new strategies to modulate neutrophil function and exploit their unique properties for more effective cancer treatment.[33] A study developed engineered bacterial membrane biomimetic nanoparticles, Angiopep-2 *E. coli* membrane (ANG-2 EM@PPC), for targeted drug delivery in glioma therapy. These nanoparticles were fabricated using bacterial membranes expressing Angiopep-2 for enhanced brain-targeting capability. Cellular studies demonstrated that ANG-2 EM@PPC efficiently hitchhikes on activated neutrophils, altering their death

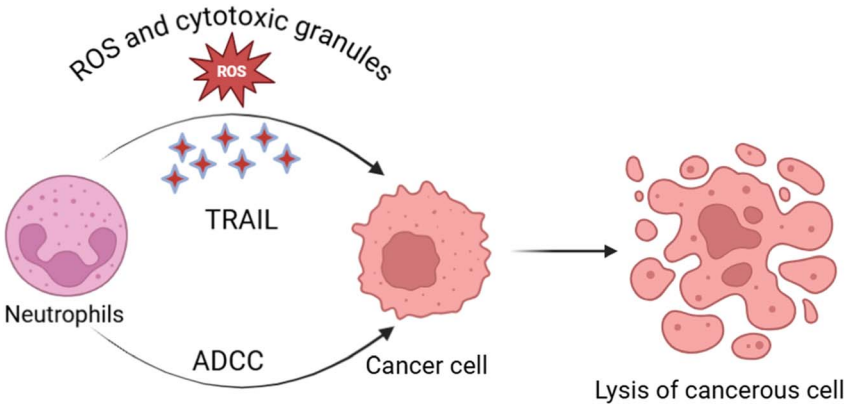

Fig. 4 Neutrophil mode of action against cancer. Neutrophils can kill tumor cells by releasing reactive oxygen species (ROS) and proteolytic enzymes, such as matrix metalloproteinase-9 (MMP-9), which degrade the extracellular matrix, facilitating immune cell infiltration and tumor cell destruction. Neutrophils also release tumor necrosis factor (TNF) of which one is Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL), that induces apoptosis selectively in cancer cells while sparing most normal cells. Neutrophils also mediate ADCC by binding to antibody-opsonized cancer cells *via* Fcγ receptors, especially FcγRIIa. This interaction triggers neutrophils to kill the target cells primarily through a process called trogocytosis (figure made using Biorender).

pathway from NETosis to apoptosis, thus facilitating their uptake in the tumor microenvironment. *In vivo* experiments in glioma-bearing mice revealed that ANG-2 EM@PPC nanoparticles effectively crossed the blood–brain barrier, accumulated in brain tumors, and significantly improved anti-glioma efficacy compared to control formulations while showing no systemic toxicity.[34] Another study shows that the lipid metabolism-related gene enoyl-CoA δ-isomerase 2 (ECI2) acts as a tumor suppressor in colorectal cancer (CRC) and is negatively associated with poor prognosis in CRC patients. Mechanistically, ECI2 reduces ether lipid-mediated interleukin 8 (IL-8) expression, which in turn decreases neutrophil recruitment and the formation of neutrophil extracellular traps (NETs), thereby contributing to the suppression of CRC. Specifically, ECI2 inhibits ether lipid synthesis in CRC cells by preventing the peroxisomal localization of alkylglycerone phosphate synthase (AGPS), the key enzyme in ether lipid production.[35]

Another study illustrates that modifying the tumor microenvironment through photosensitization (PS) enhances the delivery of nanoparticles (NPs) by promoting neutrophil infiltration. The researchers created a drug delivery system using NPs coated with anti-CD11b antibodies (NPs-CD11b) to specifically target activated neutrophils. Intravital microscopy revealed that neutrophil infiltration, triggered by PS, facilitates the delivery of NPs-CD11b to the tumor, as the depletion of neutrophils systemically completely prevented NP accumulation in the tumor. Notably, neutrophil uptake of these NPs did not hinder their activation or migration. In mouse models of cancer, combining tumor PS with photothermal therapy using anti-CD11b antibody-conjugated gold nanorods (GNRs-CD11b) resulted in enhanced tumor treatment.[36] A stealth nanovehicle, utilizing neutrophil camouflage, has been designed to target the tumor's immunosuppressive microenvironment and enhance immunotherapy by inducing pyroptosis. This system includes anti-CD11b and IR820-conjugated bovine serum albumin nanoparticles loaded with decitabine. The neutrophil camouflage enables efficient tumor targeting by leveraging neutrophils' natural attraction to tumors. IR820 acts as a tracking molecule for precise delivery. Upon release, decitabine increases gasdermin E levels, and laser activation of caspase-3 triggers pyroptosis, enhancing the immune response. In a triple-negative breast cancer model, this strategy not only strengthens tumor immunotherapy but also establishes a strong immune memory to prevent lung metastasis. Fig. 5 shows various approaches involving immune cells to target cancer cells.[37] There are various advances in the feild of cell modulation using nanoparticles as shown in Table 2.

3. Design strategies of nanoparticles

3.1 Different shapes of nanoparticles

In recent years, nanotechnology has played a pivotal role in advancing cancer immunotherapy by addressing several challenges associated with traditional treatments. One of the key strategies involves size and shape optimization of nanoparticles, which significantly affects their accumulation at tumor sites. The shape of particulate drug carries has been identified as a key parameter in determining their biological outcomes. Along with traditional spherical nanoparticles in research, which come with certain limitations, a group of researchers introduced a non-spherical nanodisk drug delivery system which is designed to improve tumor targeting and drug retention for prostate cancer treatment to address the limitations of conventional spherical nanoparticles and chemotherapy-induced toxicity. The nanodisks are modified with the CR(NMe)EKA peptide, which specifically binds to extracellular matrix fibronectin and its complexes. It enhances tumor vessel and stroma targeting. This modification significantly improves drug accumulation at tumor sites compared to conventional nanospheres. When loaded with paclitaxel, the

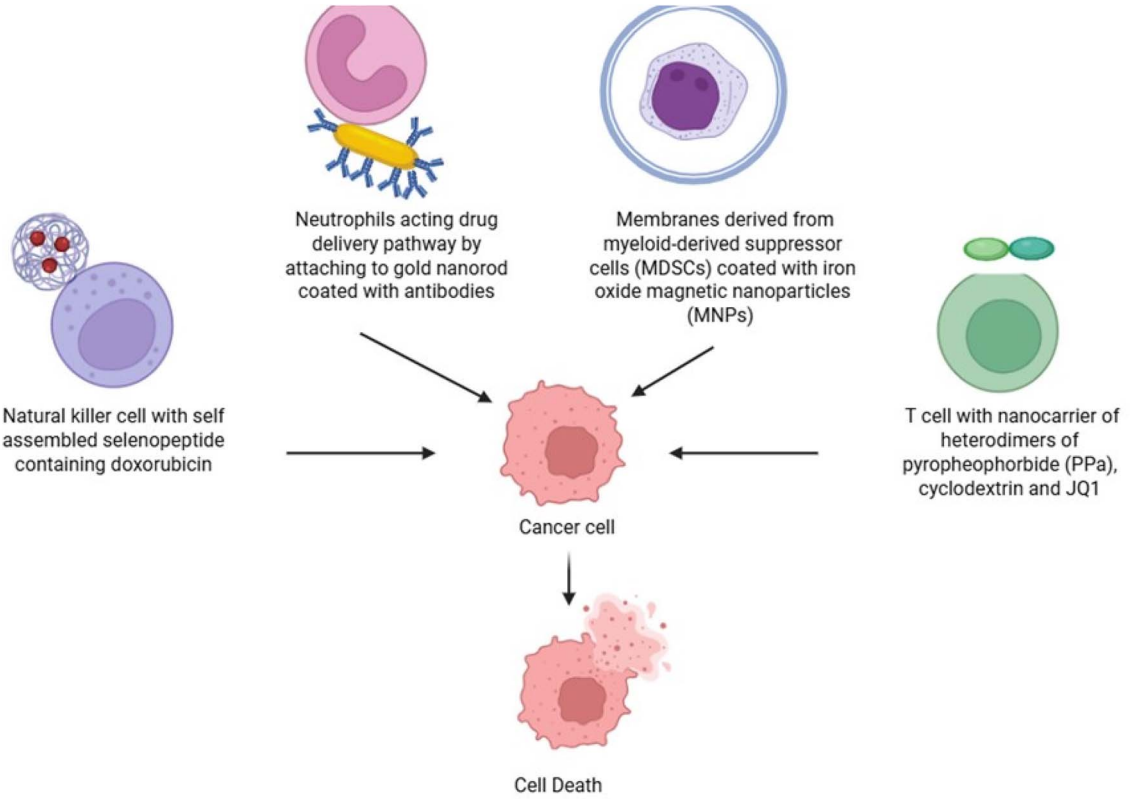

Fig. 5 Various approaches to target cancer cells. (1) Self assembled selenopeptide containing doxorubicin attached to a natural killer cell. (2) Gold nanorods coated with antibodies which are attached to neutrophils. (3) Membranes derived from myeloid derived suppressor cells coated with iron oxide nanoparticles. (4) Heterodimer of pyropheophorbide, cyclodextrin and JQ1 attached to T cells (figure made using Biorender).

targeted nanodisks demonstrate superior antitumor efficacy over free paclitaxel, unmodified nanodisks, and nanospheres, likely due to their enhanced tissue penetration and retention.[42] Another novel nanovaccine system with nanodisks has been developed to enhance anti-tumor T cell responses against tumors expressing HPV-16 E6/E7 antigens and melanoma-specific neoantigens by improving antigen presentation and immune activation. The system utilizes nanodisks to efficiently deliver tumor antigens and stimulate a strong adaptive immune response. When administered subcutaneously, nanodisks loaded with the HPV-16 E7 antigen are taken up by antigen-presenting cells (APCs), such as dendritic cells (DCs), which then migrate to lymph nodes and present the antigens *via* major histocompatibility complex (MHC) molecules to CD8+ T cells. This results in a 32% E7-specific CD8+ T cell response, a 29-fold improvement over soluble peptide vaccines. The activated cytotoxic T lymphocytes (CTLs) infiltrate the tumor microenvironment, leading to the destruction of HPV16 E6/E7-expressing TC-1 tumors in mucosal sites, including the lungs, inner lip, and intravaginal tissues. Compared to a live listeria vaccine combined with anti-PD-1 IgG, the nanodisc plus anti-PD-1 therapy shows similar T cell activation and tumor control by preventing T cell exhaustion.[43] A conventional anthracycline chemotherapeutic drug, such as doxorubicin (Dox), works by intercalating into DNA, disrupting its function. Utilizing DNA nanotechnology, few researchers hypothesized that they could optimize the delivery of Dox to human breast cancer cells by customizing DNA nanostructures. They tested two DNA origami structures on three breast cancer cell lines (MDA-MB-231, MDA-MB-468, and MCF-7), which were designed with varying degrees of global twist to affect the DNA helix relaxation. This tuning allowed them to control drug encapsulation efficiency, release rate, and increase cytotoxicity compared to free Dox. Flow cytometry analysis showed enhanced apoptosis and increased internalization of the drug, suggesting that DNA origami-based delivery systems improve Dox efficacy by controlling release kinetics and promoting cancer cell death.[44]

3.2 Types of nanoparticles

The choice of material composition is also vital, with liposomes, lipid nanoparticles (LNPs), polymeric nanoparticles (PNPs), and inorganic nanoparticles offering distinct advantages in terms of biocompatibility and drug loading capacity. These materials can be tailored to deliver drugs, antigens, or immune modulators effectively, enhancing the immune response against tumors. The table below presents various nanomaterial-based approaches for enhancing cancer immunotherapy by targeting specific immune cells—natural killer cells, myeloid-derived suppressor cells, and neutrophils. These strategies demonstrate innovative ways to enhance immune responses and improve cancer treatment outcomes (Table 3).

Table 2 Advances in immune cell modulation using nanoparticles

Immune cell	Method	Material/nanoparticles used	Mechanism	References
T cells	Hyaluronic acid nanocarriers	Derived from hyaluronic acid, adamantane-conjugated heterodimers of PPa, cyclodextrin, and JQ1	Targets CD44-overexpressing cells, combines phototherapy and immunotherapy to enhance T lymphocyte infiltration	38
T cells	CPT-Pt(IV) nanoparticles	Platinum(IV) prodrug with ROS-sensitive polymer (P1) and mPEG2k-DSPE	Releases cisplatin and camptothecin, triggering the cGAS-STING pathway to enhance CD8+ T cell infiltration	14
T cells	tLyp1 peptide-modified nanoparticles	Hybrid nanoparticles targeting Treg cells	Enhances the imatinib effect by downregulating Treg cells, increasing CD8+ T cell infiltration	18
T cells	AntiCD3-LNP/CAR19 + shIL6 lipid nanoparticles	Modified with CD3 antibody and loaded with anti-CD19 CAR and IL-6 shRNA plasmids	Produces CAR-T cells *in vivo* and suppresses IL-6 to mitigate CRS	17
NK cells	Selenopeptide nanoparticles	Self-assembled selenopeptide with an enzyme-responsive linker and a selenoamino acid tail	Activates NK cells *via* oxidative metabolites, delivers doxorubicin to tumors, enhancing chemotherapy and immunotherapy synergy	25
NK cells	Tri-specific PEG-PLGA nanoparticles	Conjugated with anti-CD16, anti-4-1BB, and anti-EGFR antibodies	Simultaneously stimulates CD16 and 4-1BB on NK cells, enhancing activation and recruitment to EGFR-positive tumor cells	26
MDSCs	MNP@MDSCs	Iron oxide magnetic nanoparticles coated with MDSC membranes	Enhances tumor targeting, induces immunogenic cell death, and reprograms tumor-associated macrophages	39
MDSCs	Light-triggered nanoparticles	Doxorubicin-loaded nanoparticles with rapid sunitinib release	Inhibits MDSCs, reverses immunosuppression, and enhances chemotherapy efficacy	30
MDSCs	Gold nanoparticles (Au NPs)	30 nm Au NPs combined with H6 peptide targeting MDSCs	Disrupts NLRP3 inflammasome, reduces IL-1β production, and decreases MDSC population	31
Neutrophils	ANG-2 EM@PPC nanoparticles	Bacterial membrane biomimetic nanoparticles hitchhiking on neutrophils	Alters the neutrophil death pathway, facilitating tumor uptake and improving glioma treatment	33
Neutrophils	NPs-CD11b and albumin nanoparticles	Nanoparticles coated with anti-CD11b antibodies and albumin NPs with TA99 antibody for neutrophil recruitment	Targets activated neutrophils, enhancing NP delivery to tumors *via* photosensitization, enhances tumor accumulation of NPs *via* neutrophils, improving photodynamic therapy efficacy	40 and 41
Neutrophils	Stealth nanovehicles	Neutrophil-camouflaged nanoparticles with decitabine and IR820 E	Induces pyroptosis, enhancing tumor immunotherapy and preventing metastasis	37

4. Photoimmunotherapy

Photoimmunotherapy is an innovative approach in cancer treatment that combines the principles of immunotherapy with light-activated nanoparticles to enhance the therapeutic efficacy. By utilizing nanoparticles that can target tumor cells and deliver photosensitizers, this technique enables localized activation through light exposure, generating reactive oxygen species and heat that directly kill cancer cells while simultaneously stimulating the immune response. This dual action not only promotes tumor destruction but also primes the immune system to attack metastases, potentially leading to a broader anti-tumor effect. Recently, a novel nanocomposite was developed using an aluminum-based metal–organic framework (Al-MOF), combined with indocyanine green (ICG) for imaging, an αCD47 antibody to target the CD47 protein that inhibits phagocytosis, and the TLR7/8 agonist resiquimod (R848). Activated by an 808 nm laser, the nanocomposites exhibited photothermal effects, releasing their cargo and generating reactive oxygen species (ROS) within the tumor microenvironment. This strategy shifted immunosuppressive M2 macrophages to the immune-stimulatory M1 phenotype, enhanced dendritic cell (DC) maturation, and activated T-cells for strong anti-tumor immunity. *In vivo* imaging confirmed specific αCD47-CD47 binding, showing potential for early cancer detection and therapeutic modulation of the tumor microenvironment.[55] Similarly, phototherapy (PT) induces immunogenic cell death (ICD), leading to the release of tumor-specific antigens (TSAs) and damage-associated molecular patterns (DAMPs). This process enhances the tumor microenvironment's immunogenicity by promoting dendritic cell (DC) maturation and increasing the levels of pro-inflammatory cytokines like IL-2, IL-6, IL-12, IFN-γ, and TNF-α. The immunostimulatory effects of PT strengthen anti-tumor immunity beyond what immunotherapy alone can achieve. While immunotherapy can initiate an immune response at the tumor site, it often falls short in completely eradicating primary tumors (Fig. 6).[56,57]

Table 3 Nanotechnology-based approaches in cancer immunotherapy. This table presents various nanomaterial-based approaches for enhancing cancer immunotherapy by targeting specific immune cells—natural killer cells, myeloid-derived suppressor cells, and neutrophils. These strategies demonstrate innovative ways to enhance immune responses and improve cancer treatment outcomes

Disease	Nanomaterial used	Methods	Mechanism	Immune cells	References
Lung cancer	Cationic liposomes (DOTAP + cholesterol)	Lipoplexes complexed with plasmid DNA encoding TUCS2, injected intravenously in Kras-mutant mice	TUCS2 upregulation triggered proinflammatory cytokines and the IL-15 pathway, increasing NK cells	NK cells	45 and 46
Lung cancer	Fe_3O_4@PDA NP-labeled NK cells	Fe_3O_4 NPs were prepared by the thermal decomposition method and emulsified to add Fe_3O_4 NPs	Fe_3O_4@PDA NP-labeled NK cells significantly inhibited tumor growth and reduced the apoptosis of A549 cancer cells	NK cells	47
Lymphoma (EG07-OVA)	Gemcitabine-encapsulated lipid nanocapsules	Subcutaneous injection of fluorescence dye-tagged gemcitabine nanocapsules into tumor-bearing mice	MDSC depletion at the tumor and spleen, enhancing cytotoxic T cell proliferation	MDSCs	48
Breast cancer	Aptamer-modified PEGylated liposomes with doxorubicin	IV injection of T1 aptamer-conjugated liposomes targeting MDSCs in a tumor microenvironment	MDSC depletion in blood, the spleen, and tumors, reversing immune suppression and activating CD8+ T cells	MDSCs	49
Melanoma (B16F10)	Mesoporous silica nanoparticles coated with lipids, carrying all-trans retinoic acid, IL-2, and doxorubicin	IV administration of multidrug-loaded nanoparticles into tumor-bearing mice	MDSC differentiation into antitumor immune cells (mature DCs, macrophages, and granulocytes), increasing tumor-specific immune response	MDSCs	50
Melanoma	Photosensitizer-loaded albumin nanoparticles + TA99 antibody	IV injection of pyropheophorbide-a-loaded albumin nanoparticles + TA99 antibody, followed by laser irradiation (660 nm)	Albumin nanoparticles bind to neutrophils *via* FcγRIII, TA99 recruits neutrophils to tumor *via* ADCC, and photodynamic therapy enhances tumor suppression	Neutrophils	51
Carcinoma	Gold nanorods (GNRs) coated with anti-CD11b antibody	Photosensitization (PS), photothermal therapy, intravital microscopy, and neutrophil depletion	PS triggers neutrophil infiltration; NPs target neutrophils; neutrophils deliver NPs into tumors, enhancing tumor treatment	Neutrophils	52
Glioma	Paclitaxel-containing liposomes inside neutrophils	*Ex vivo* neutrophil loading with paclitaxel-liposomes, IV injection, and inflammation at the operative site guide neutrophils to tumors	Operative-site inflammation induces proinflammatory cytokines (IL-10 and CXCL1), enhancing neutrophil infiltration and drug delivery	Neutrophils	33
Lung cancer	Pixantrone-loaded liposomes decorated with poly(sialic acid)-octadecylamine	IV injection of poly(sialic acid)-modified liposomes, targeting L-selection on neutrophils	Poly(sialic acid) binds L-selectin on neutrophils, enhancing uptake and tumor homing, leading to improved anticancer effect	Neutrophils	53
Melanoma and colorectal cancer	CpG ODN-modified HDL nanodiscs	Subcutaneous injection of CpG ODN-loaded HDL nanodiscs conjugated with neoantigen peptides	CpG ODN binds TLR-9 to DCs, enhancing antigen presentation and cytotoxic T cell activation, boosting vaccine efficacy	DCs	54

A new approach for detecting and treating microscopic tumors to prevent recurrence is by fluorescence-guided intervention that can enhance standard therapies. This study integrates targeted photo-activable multi-agent liposomes (TPMAL) with fluorescence-guided intervention and laser endoscopy (ML7710) to advance photoimmunotherapy. TPMAL

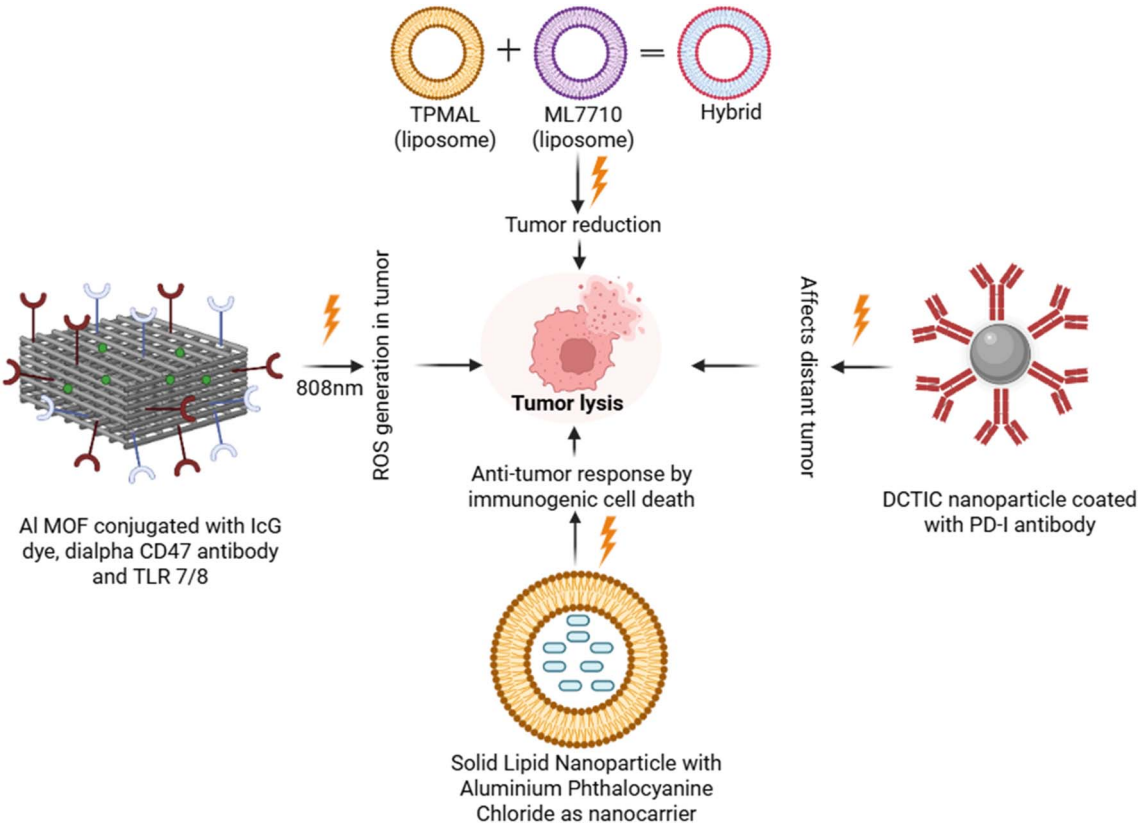

Fig. 6 Current applications of photodynamic therapy (PDT) across four distinct methods. (1) Aluminum-based motifs conjugated with ICG, Dialpha CD7 antibodies, and TLR 7/8, which, upon PDT treatment at 808 nm, generate ROS in tumors. (2) Hybrid liposomes that enhance drug delivery and reduce tumors effectively when subjected to PDT. (3) DCT nanoparticles coated with PD1 antibodies, which target and impact distant tumors following PDT application. (4) Solid lipid nanoparticles serving as nanocarriers that, when treated with PDT, elicit anti-tumor responses through immunogenic cell death (figure made using Biorender).

combine nanoliposome chemotherapy with fluorophores and photosensitizer immunoconjugates, while ML7710, linked to Modulight Cloud, enables real-time monitoring and analysis. In peritoneal carcinomatosis mouse models, TPMAL improved drug delivery to metastases by 14-fold, and ML7710 facilitated effective fluorescence-guided drug delivery and light dosimetry, leading to reduced treatment variability and enhanced tumor control without additional side effects.[58] Few researchers designed an aggregation-induced emission (AIE)-active compounds using acceptor engineering, leading to the development of DCTIC, a molecule with optimal phototheranostic properties (refer to Fig. 3). DCTIC was formulated into dual-targeted nanoparticles (NPs) for tumors and mitochondria, enabling effective trimodal imaging and synergized photodynamic/photothermal cancer immunotherapy with PD-1 antibodies. Thus, it not only eradicated primary tumors but also inhibited the growth of distant tumors.[59] Cancer cell membrane-coated nanoparticles (CCMV/LTNPs) were designed to enhance therapeutic efficacy by integrating photodynamic therapy (PDT), a TLR7 agonist, and tumor antigens. These biomimetic nanoparticles specifically target and kill tumor cells *via* PDT while simultaneously boosting host antitumor immune responses through the immune adjuvant and tumor antigens derived from the cancer cell membrane, effectively addressing residual tumor cells. While photodynamic therapy (PDT) faces challenges like limited photosensitizer activity in aqueous environments and poor bioavailability.[60] To address these, a new photosensitizer system, SLN-AlPc, was developed, showing enhanced therapeutic efficacy. *In vitro* studies demonstrated that light-activated Solid Lipid Nanoparticles with Aluminum Phthalocyanine chloride (SLN-AlPc) increased reactive oxygen species (ROS) production in murine melanoma B16–F10 cells and influenced dendritic cell (DC) activation. PDT-induced cell death was associated with damage-associated molecular pattern (DAMP) exposure and autophagosome formation. Furthermore, DCs exposed to PDT-treated cells exhibited immune activation, marked by morphological changes, increased the expression of MHCII, CD86, and CD80, and elevated the production of IL-12 and IFN-γ, indicating a shift towards an antitumor immune response. These findings suggest that SLN-AlPc could significantly enhance PDT efficacy by inducing immunogenic cell death (ICD) and activating DCs.

Circulating tumor cells (CTCs) are key indicators for monitoring tumor progression and prognosis, but capturing them with high sensitivity and purity remains challenging. Researchers address these challenges by developing biomimetic magnetic nanoparticles (NPs) coated with hybrid membranes (HM) derived from fused human breast cancer cell membranes

(TMs) and leukocyte membranes (WMs). The TM component enhances target specificity, improving capture efficiency, while the WM reduces interference from white blood cells, increasing capture purity. Additionally, using an innovative inverted microfluidic chip with polymer photonic crystals, the system amplifies 808 nm excitation light, enabling effective photothermal and photodynamic inactivation of captured CTCs, potentially hindering tumor metastasis.[61] A novel cancer treatment strategy combining photothermal therapy with immune-enhancing nanoparticles and checkpoint-blockade immunotherapy, aiming to eliminate primary tumors, prevent metastasis, and offer protection against relapse, has been designed. The nanoparticles, consisting of indocyanine green (ICG) and imiquimod (R837), are co-encapsulated in poly(lactic-*co*-glycolic acid) (PLGA), ICG serves as a photothermal agent which is activated by near-infrared (NIR) laser light to induce localized tumor ablation. The ablation generates tumor-associated antigens, which trigger an immune response. R837, a Toll-like receptor-7 (TLR-7) agonist, acts as an immune adjuvant, enhancing the immune response against the tumor. The combination of these nanoparticles with checkpoint blockade therapy, using anti-CTLA4 antibodies, further strengthens the immune response by inhibiting the negative regulatory effects of CTLA4 on T-cell activation. The mechanism involves photothermal tumor destruction, antigen release, immune activation *via* R837, and checkpoint blockade to maintain immune efficacy.[62] Another key study in photothermal therapy introduces dopamine–melanin colloidal nanospheres (Dpa–melanin CNSs) as an innovative photothermal therapy (PTT) agent for cancer treatment. These nanoparticles are synthesized through the oxidation and self-polymerization of dopamine in a water–ethanol–ammonia mixture which results in biocompatible and biodegradable nanospheres with controllable sizes. Due to their small size (~70 nm), they remain in circulation for an extended period and accumulate in tumors *via* the enhanced permeability and retention (EPR) effect. Upon near-infrared (NIR) laser irradiation, Dpa–melanin CNSs efficiently convert light into heat, achieving a high photothermal conversion efficiency of 40%, which leads to localized tumor cell apoptosis and necrosis while minimizing damage to the surrounding healthy tissues.[63] A study has developed polydopamine-coated aluminium oxide (Al_2O_3) nanoparticles as an efficient photothermal therapy (PTT) agent for cancer. These nanoparticles exhibit strong photothermal conversion upon near-infrared (NIR) laser irradiation to effectively generate localized heat to ablate tumor cells. To enhance the immune response, they were combined with a CpG adjuvant which acts as an immunostimulant by activating Toll-like receptor 9 (TLR9) on antigen-presenting cells, such as dendritic cells. This combination therapy not only destroyed primary melanoma tumors but also triggered immunogenic cell death (ICD) which led to the release of tumor-associated antigens. The released antigens were taken up by dendritic cells which promote their maturation and stimulate the proliferation of cytotoxic T lymphocytes (CTLs). The activated immune system recognized and attacked residual tumor cells and distant metastases, preventing recurrence.[64] Similarly, gold nanostars (pAuNSs) have also been explored as an effective photothermal therapy (PTT) agent in combination with cancer immunotherapy. These nanoparticles efficiently absorb near-infrared (NIR) laser light, converting it into heat that selectively destroys tumor cells while minimizing damage to healthy tissues. The tumor cell destruction triggers the release of tumor-associated antigens, which enhances immune recognition. To further amplify the immune response, the treatment is combined with dendritic cell-based immunotherapy and anti-PD-L1 checkpoint blockade. Dendritic cells process the released tumor antigens and activate cytotoxic T lymphocytes (CTLs), leading to a systemic anti-tumor immune response. Meanwhile, PD-L1 blockade prevents immune suppression, allowing T cells to effectively attack both primary and distant metastatic tumors.[65] Chemoimmunotherapy, a widely used approach to treat cancer was further developed with multifunctional nanoplatforms like immunotherapy and photothermal therapy (PTT) to enhance cancer treatment efficacy. These nanoplatforms co-deliver chemotherapeutic agents like docetaxel, immunomodulators such as cynomorium songaricum polysaccharide, and photothermal agents like green tea polyphenol–iron complexes. Upon administration, the nanoparticles accumulate in tumors *via* the enhanced permeability and retention (EPR) effect, where they facilitate immunogenic cell death (ICD) induced by chemotherapy. The dying cancer cells release tumor-associated antigens and damage-associated molecular patterns (DAMPs), which activate dendritic cells and promote the recruitment of cytotoxic T lymphocytes (CTLs). Simultaneously, near-infrared (NIR) laser irradiation triggers the photothermal effect, further destroying tumor cells while boosting antigen presentation and immune activation.[66]

Apart from photoimmunotherapy, there are other combined immunotherapies for enhanced cancer treatment. One of them is sonodynamic therapy (SDT), which has emerged as a promising non-invasive treatment approach in recent years. This technique harnesses the power of ultrasound waves to activate specific compounds known as sonosensitizers which in turn generate reactive oxygen species (ROS). These highly reactive molecules induce oxidative stress in nearby cells, ultimately leading to targeted cell damage or death, particularly useful in cancer therapy.[67,68] A study explored using a glutamate–tyrosine copolymer as a nanoparticle which would degrade in the presence of cathepsin B. This polymer carries hematoporphyrin which later forms a sonosensitiser, leading to cell death. They observed that cathepsin B levels correlated with the cellular uptake of the molecule in the cell. After examination in various pancreatic cancer cell lines and immunocompetent models, they observed that the overall acoustic energy delivered per unit area plays a more critical role, rather than the ultrasound (US) intensity alone.[69] Another study explored hollow mesoporous manganese dioxide as a carrier for poly(allylamine hydrochloride), providing MRI-based therapy guidance. They were subsequently loaded with indocyanine green (ICG), which is released into the tumor microenvironment and helps in both imaging and treatment. Upon release, ICG performs multiple functions: (1) it facilitates oxygen (O_2) generation, (2) enhances the tumor's sensitivity to photodynamic therapy (PDT), and (3)

depletes intracellular glutathione (GSH), thereby elevating oxidative stress within the tumor cells, and (4) accumulation of it in the cells exerts PDT as well as PTT effect. Hence, it has a multimodal effect of photodynamic therapy, photothermal therapy, chemodynamic therapy all at once. Under near-infrared light, the treatment showed strong anti-tumor effects and good biocompatibility. This study developed a smart, biomimetic nanoparticle system that responds to the tumor environment, improves oxygen levels, and effectively delivers ICG. It offers a promising, cost-effective approach for combined phototherapy and chemodynamic therapy in cervical cancer.[70] Researchers have developed small iron–platinum nanoparticles that address tumor hypoxia and enhance sonodynamic therapy. These particles break down hydrogen peroxide in tumors to release oxygen, improving the low-oxygen environment. Under ultrasound, they generate singlet oxygen, effectively killing cancer cells. Tested on breast cancer cells, the nanoparticles showed strong anti-tumor effects and good safety, offering a promising approach to more effective cancer treatment.[71]

5. Therapeutic cancer vaccines

The integration of nanotechnology into cancer immunotherapy represents a groundbreaking advancement in the fight against cancer. Therapeutic cancer vaccines have received renewed interest over the past decade, driven by advances in our understanding of tumour-associated antigens, the natural immune response, and the emergence of innovative antigen delivery technologies, all contributing to more effective vaccine development.[72] By harnessing the unique properties of nanomaterials, researchers aim to overcome existing barriers in cancer treatment, including the need for specificity and reduced systemic toxicity. To address this, multiple approaches are designed, one of which is a nanovaccine with functional grippers, specifically maleimide-modified Pluronic F127-chitosan nanoparticles encapsulating astragalus polysaccharide (AMNPs). These nanoparticles capture tumor antigens post-cryoablation, target lymph nodes, activate dendritic cells, and modulate T cell differentiation, breaking the immunosuppressive environment. In a Lewis lung cancer model, AMNPs significantly regress primary tumors, inhibit untreated tumor growth, and improve survival rates, offering a promising approach for personalized cancer immunotherapy.[73] Another *in situ* nanovaccine based on the cationic peptide DP7-C with cholesterol modification is designed for cancer immunotherapy. It promotes tumor cell death, antigen presentation, and relieves immune suppression, effectively targeting primary tumors in CT26 and B16F10 models. The nanovaccine contains a cocktail of small interfering RNAs (siRNAs) and immunologic adjuvant CpG ODNs and exhibits a synergistic effect in the cancer treatment. This nanovaccine converts cold tumors into hot tumors and enhances the response to anti-PD-1 therapy by modulating the tumor microenvironment, offering a versatile approach for developing cancer nanovaccines (Fig. 7).[74] Tumosomes are immunomodulatory nanoliposomes designed to mimic pathogen-like biochemical characteristics, enhancing antitumor immunity by turning tumors into personalized vaccines. They are synthesized by integrating tumor cell membrane proteins (serving as tumor-specific antigens) with lipid-based adjuvants, such as monophosphoryl lipid A (MPLA), which provides a danger signal, and dimethyldioctadecylammonium (DDA), which enhances cellular uptake. These components improve antigenicity and immune activation by stimulating innate immune receptors, including TLRs, NOD, inflammasomes, and STING pathways, in lymph nodes and the spleen. Upon image-guided intralymphatic injection, tumosomes efficiently deliver tumor antigens and immunostimulatory signals, promoting a long-term adaptive immune response, boosting cytotoxic T cell activation, and

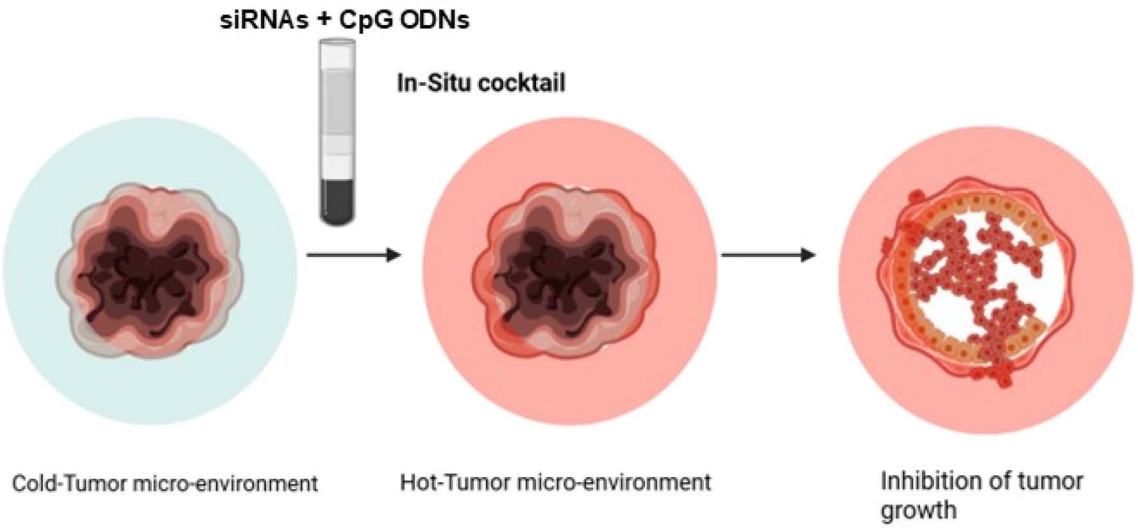

Fig. 7 Cold-to-hot tumor transformation by nanovaccine. Transformation of a cold tumor microenvironment into a hot one and enhanced tumor growth inhibition when treated *in situ* with a vaccine. The nanovaccine facilitates siRNA delivery, induces tumor cell apoptosis, and promotes dendritic cell maturation (image made using Biorender).

suppressing tumor growth. Tumosome treatment significantly prolongs survival rates in tumor-bearing mice and can be combined with immune checkpoint inhibitors to prevent T cell exhaustion in the immunosuppressive tumor microenvironment.[75]

Personalized cancer vaccination using nanomaterials shows significant promise for cancer immunotherapy. In this study, a nanochaperone (PBA-nChap) is designed to capture tumor-associated antigens (TAAs) *in situ*, enhancing cancer immunotherapy. PBA-nChap efficiently captures TAAs, protects them from degradation, and transports them to antigen-presenting cells to promote cross-presentation. Intratumor injection of PBA-nChap combined with pretreatment *via* photodynamic therapy (PDT) boosts the immune response and demonstrates strong antitumor effects. Additionally, a nanovaccine created by co-culturing PBA-nChap with tumor cell fragments from surgically resected primary tumors *in vitro*, when used with immune checkpoint blockade (ICB) therapy, effectively prevents tumor recurrence and metastasis post-surgery.[76] A novel nanovaccine for immunotherapy consists of R837-loaded poly(lactic-*co*-glycolic acid) coated with a calreticulin (CRT)-expressed cancer cell membrane antigen. The complete antigen array is obtained by inducing immunogenic cell death *in vitro*, which avoids severe systemic toxicity associated with *in vivo* chemotherapy. This nanovaccine co-delivers the adjuvant R837 and Luc-4T1 membrane antigen, triggering a personalized immune response against the tumor. The calreticulin on the nanovaccine's surface promotes the active uptake by dendritic cells, enhancing the antitumor effect and activating immune memory cells for long-term protection.[77] Efficient vaccine delivery to dendritic cells (DCs) is crucial for inducing strong immune responses in cancer immunotherapy. Traditional nanovaccine strategies focus on receptor-mediated endocytosis, often overlooking the role of macropinocytosis in antigen uptake. Songlei Zhou *et al.* developed a biomimetic nanovaccine (R837-αOVA-ApoE3-HNP) composed of a PLGA core encapsulating the adjuvant imiquimod (R837), a phospholipid membrane carrying the antigen peptide (αOVA), and apolipoprotein E3 (ApoE3) to enhance micropinocytosis-mediated uptake by DCs. This nanovaccine significantly increased antigen internalization, DC maturation, and antigen presentation, leading to robust T cell responses and effective tumor inhibition in combination with αPD-1 therapy.[78] Due to inefficient uptake by dendritic cells (DCs), a dual-scale mesoporous silica vaccine, combining mesoporous silica microrods (MSRs) with mesoporous silica nanoparticles (MSNs), was proposed. Upon injection, MSRs form a 3D macroporous scaffold that recruits DCs through chemokine release. The recruited DCs then internalize antigen- and Toll-like receptor 9 agonist-loaded MSNs within the scaffold, leading to potent activation of antigen-presenting DCs. This dual-scale vaccine significantly enhances antigen-specific T cell responses and melanoma inhibition, outperforming single-component vaccines, and shows synergy with immune checkpoint inhibitors in tumor-bearing mice.[79] To enhance the effectiveness of protein subunit vaccines, a study investigates the use of pH-responsive, endosomolytic polymer nanoparticles. These nanoparticles were originally designed for RNA delivery, composed of amphiphilic diblock copolymers. The core block is ampholytic, and the corona block is polycationic with thiol-reactive pyridyl disulfide groups, which enable the dual delivery of both antigens (ovalbumin) and immunostimulatory CpG oligodeoxynucleotides (CpG ODN). The mechanism involves the nanoparticles forming 23 nm particles that encapsulate both the protein antigen (ovalbumin) and the CpG ODN. Upon administration, the pH-responsive nanoparticles are taken up by immune cells *via* endocytosis. The acidic environment in endosomes triggers the endosomolytic properties of the nanoparticles, causing them to rupture and release the encapsulated antigens and CpG ODN into the cytoplasm. This disruption facilitates antigen processing and enhances antigen cross-presentation, a key process for activating CD8+ T cells. The study shows that when these nanoparticles are used for vaccination, they significantly improve both CD8+ T cell responses (*e.g.*, IFN-γ+ CD8+ T cells) and CD4+ T cell (Th1) responses, compared to free antigens or a physical mixture of antigens and adjuvants. The dual-delivery system also results in a balanced antibody response (IgG1/IgG2c), further enhancing the vaccine's effectiveness. Additionally, intradermal delivery of these nanoparticles further boosts immune responses, especially CD8+ T cell activation. Overall, the mechanism of pH-responsive, endosomolytic nanoparticles involves improved antigen processing, cross-presentation, and a robust immune response, positioning them as a promising delivery platform for protein subunit vaccines.[80] Another group of researchers introduced a carbon nanoparticles–Fe(II) complex (CNSI–Fe) that efficiently delivers Fe to tumor cells, inhibiting tumor growth with minimal toxicity in H22 tumor-bearing mice. Intratumoral injection of CNSI–Fe significantly increased Fe levels in tumors, inducing oxidative stress and effectively inhibiting tumor growth, comparable to cisplatin. Due to its low Fe accumulation in other tissues, CNSI–Fe showed low systemic toxicity, suggesting its potential for cancer therapy through "off-label" use to benefit patients immediately (Fig. 7).[81]

6. Tumor modification

Over the past few decades, considerable efforts have been devoted to enhancing the delivery of nanotherapeutics to solid tumors, and nanomedicines mark a significant advancement in cancer immunotherapy by enabling precise delivery of therapeutic agents directly to tumors.[82] Through the use of nanoparticles, these treatments boost the immune response against cancer cells while reducing harm to healthy tissues.[83] One of the recent and significant findings is BiTEs (bispecific T cell engagers), which are engineered proteins featuring two antigen-binding sites linked by a short sequence or shared Fc domain. One site targets a tumor-associated antigen (TAA), while the other binds to a T cell activator, like the CD3 molecule on the T cell receptor (TCR) complex. This dual binding triggers T cell activation and formation of immune synapses, leading to tumor cell destruction. BiTEs can be adapted to target various TAAs, broadening their potential application in cancer therapy.[84] Another study introduces a novel approach using biological

nanoparticles derived from *Escherichia coli*'s outer membrane vesicles (OMVs) to trigger ferroptosis and stimulate immune responses. These OMVs, functionalized with ferrous ions and loaded with a STING agonist (OMV/SaFeFA), exhibit peroxidase-like activity that induces lipid peroxidation in tumor cells. The system is designed for pH-responsive release and tumor targeting, providing effective tumor-specific therapy with minimal side effects. In colon tumor-bearing mouse models, OMV/SaFeFA significantly enhanced antitumor responses and extended survival, with no observed acute toxicity, highlighting its potential for future clinical use.[85] Another research suggested TME-responsive nanoparticles, which were developed to boost antitumor immunity and prevent immune escape by codelivering an interleukin-12 (IL-12) gene and a colony-stimulating factor-1 receptor (CSF-1R) inhibitor (PLX3397). The nanoparticles' design includes disulfide bonds for reduction sensitivity and cRGD peptides for tumor targeting. This strategy aims to enhance local immune responses by expressing IL-12 while modulating tumor-associated macrophages (TAMs) by inhibiting CSF-1/CSF-1R signaling. The nanoparticles effectively reprogrammed the TME by activating T cells, repolarizing TAMs, reducing myeloid-derived suppressor cells (MDSCs), and promoting dendritic cell maturation. These changes led to significant tumor suppression and inhibited metastasis. Single-cell analysis revealed alterations in cell infiltration, transcriptional profiles, signaling, and interactions within the TME, highlighting the potential of this combinatorial immunotherapy using immunomodulatory nanoparticles.[86]

Another study developed an ATP-triggered, pH-sensitive nanomaterial, HCPT@ZIF-90-PEG-FA, for targeted drug delivery and treatment of colorectal cancer. The system efficiently loaded 10-hydroxycamptothecin (HCPT) with a drug loading of 22.3% and demonstrated enhanced therapeutic efficacy due to active targeting with FA and dual-responsive drug release. The nanomaterial significantly inhibited cancer cell proliferation by blocking DNA synthesis, and *in vivo* experiments confirmed its effectiveness in eradicating tumors, suggesting it as a promising strategy for colorectal cancer treatment.[87] Recently, a study investigated the antitumor effects of beta-D-glucose-reduced silver nanoparticles (AgNPs-G) in a murine model of triple-negative breast cancer (TNBC). AgNPs-G demonstrated significant antitumoral activity, reducing the expression of PCNA, IDO, and GAL-3, while increasing caspase-3 expression. The treatment also remodeled the tumor microenvironment by boosting memory T cells and innate effector cells, decreasing CD4+ and regulatory T cells, and elevating TNF-α, IFN-γ, and IL-6 levels. These findings suggest that AgNPs-G not only inhibit tumor growth but also effectively modulate the immune response in TNBC.[88] Alkaliptosis is a pH-dependent form of cell death with potential for tumor suppression, but its regulation is not fully understood. Researchers identified an itchy E3 ubiquitin protein ligase (ITCH) as a key inhibitor of alkaliptosis in human pancreatic ductal adenocarcinoma (PDAC) cells. Reduced ITCH expression enhances alkaliptosis by increasing JTC801-induced cell death and growth inhibition, while ITCH overexpression counteracts these effects. Mechanistically, ITCH inhibition leads to decreased ubiquitination of large tumor suppressor kinase 1 (LATS1), reducing Yes1-associated transcriptional regulator (YAP1)-dependent activation of solute carrier family 16 member 1 (SLC16A1), which inhibits alkaliptosis. Lower ITCH levels are also linked to improved survival in PDAC patients, highlighting ITCH's role in modulating alkaliptosis and its potential for targeted therapy.[89] Tumor-associated macrophages (TAMs) play a crucial but poorly understood role in prostate cancer (PCa). In a study, PCa growth was significantly suppressed in mice with macrophage-specific Ubc9 deficiency compared to wild-type controls, partly due to an enhanced CD8+ T cell response. STAT4, a key UBC9-mediated SUMOylation target at lysine 350 (K350), was identified as central to this process. Mutation of STAT4 (K350R) boosted its nuclear stability, promoting proinflammatory macrophage activation. The UBC9 inhibitor 2-D08 enhanced TAMs' antitumor effects and increased PD-1 expression on CD8+ T cells, showing synergy with immune checkpoint blockade therapy.[90]

7. Surface modification

The modification of immune cell surfaces is a pivotal area of research in nanomedicine, particularly for enhancing therapeutic efficacy in cancer immunotherapy. This approach involves the strategic alteration of immune cell surfaces to improve their functionality, targeting precision, and interaction with therapeutic agents.[83] By employing various surface modification techniques, researchers aim to create immune cells that can more effectively recognize and attack tumor cells, thereby amplifying the body's natural immune response against cancer. Recent advancements in synthetic chemistry and nanotechnology have facilitated the development of sophisticated strategies for modifying immune cell surfaces.[83] Adoptive T cell therapy has emerged as a revolutionary immunotherapy for treating cancer *via* surface modification. CRISPR/Cas9-based genome editing offers targeted therapy for cervical cancer by focusing on HPV oncogenes. To enable this, a pH-responsive hybrid nanovector was developed to co-deliver Cas9 mRNA and gRNAs targeting E6 or E7 oncogenes. The nanovector, made from acetalated cyclic oligosaccharide (ACD) and low molecular weight polyethyleneimine, forms ACD nanoparticles (ACD NPs) that effectively load Cas9 mRNA and gRNAs. In HeLa cells, ACD NPs showed high transfection efficiency with low toxicity, leading to precise genome editing of E6 and E7 oncogenes with minimal off-target effects. *In vivo*, E6/ACD NPs and E7/ACD NPs demonstrated significant antitumor effects and improved CD8+ T cell survival by reversing the immunosuppressive microenvironment, enhancing outcomes when combined with adoptive T-cell transfer.[91] Chen X. *et al.* suggested a strategy to develop and anchor aPD1-formed nanogels onto T cells using bioorthogonal click chemistry before adoptive transfer. This allows for the co-existence of aPD1 with ACT T cells and responsive drug release, significantly enhancing treatment efficacy in murine solid tumor models. The tumor weight in the group treated with cell-surface anchored aPD1 was reduced to 18% of that in the group treated with free aPD1 and T cells.[92] Similarly, Li X. *et al.* developed a strategy to load T cells with

SHP099, an allosteric SHP2 inhibitor, to boost their therapeutic effectiveness. By remotely loading SHP099 into lipid nanoparticles modified with triarginine motifs, SHP099 nanocrystals formed inside the vesicles, achieving high loading efficiency and prolonged retention within the T cells. These SHP099-loaded T cells sustained PD-1/PD-L1 pathway inhibition and enhanced cytolytic activity. In a mouse model, these tumor-homing T cells showed better tumor accumulation than systemically administered nanoparticles. In established solid tumors, SHP099-loaded T cells led to complete tumor eradication and durable immune memory, effectively blocking the PD-1/PD-L1 pathway. This approach highlights the potential of combining T cell therapy with SHP2 inhibition and suggests the lipid nanocrystal platform as a versatile method for loading T cells with immunomodulatory drugs.[93]

Natural killer (NK) cell infusion shows promise in cancer therapy, but its efficacy is hindered by the acidic tumor microenvironment (TME) and neutrophil extracellular traps (NETs). Recently, polymer hydrogels have gained attention in combination therapies due to their ability to load and release therapeutic agents with high bioavailability and minimal systemic toxicity. They developed a dual pH-responsive hydrogel containing a tumor acidity neutralizer (mesoporous bioactive glass nanoparticles) and NET lyase (DNase I) to enhance NK cell infusion and prevent post-resection hepatocellular carcinoma (HCC) recurrence. This biocompatible hydrogel forms an adhesive gel at the surgical site, rapidly achieving hemostasis. It neutralizes tumor acidity, reduces infiltration of immunosuppressive cells, and releases DNase I in response to pH changes, degrading NETs. The combined approach significantly boosts NK cell efficacy, preventing HCC recurrence without systemic toxicity.[94] Artificial antigen-presenting cells (aAPCs) show significant potential in overcoming the limitations of current T-cell activation methods, such as low expansion rates and limited efficacy. Gold nanoparticles (AuNPs) are ideal for nanoscale aAPCs due to their biocompatibility, simple synthesis, and adaptable surface chemistry. Esmaeili F. *et al.* developed spiky AuNPs with branched geometries to enhance the activation of primary human T-cells. The unique structure of these spiky AuNPs improves biomolecule loading and T-cell activation by enabling multivalent binding of costimulatory ligands and receptors. Compared to traditional systems, spiky AuNPs achieve superior polyclonal T-cell expansion, sustained cytokine production, and generate highly functional T-cells with reduced exhaustion. Spiky AuNPs also demonstrated effective activation and expansion of CD19 CAR-T cells, showing increased cytotoxicity against target cells with fewer effector cells than Dynabeads.[95] Nanoparticle-based cancer immunotherapy has shown promising therapeutic potential in clinical settings, primarily using nanoparticles as delivery vehicles but often overlooking their potential to directly modulate immune responses, because solid tumors present a challenging microenvironment with a dense extracellular matrix, poor vascularization, and physical stromal barriers that significantly limit the penetration and distribution of nanoparticles. These factors reduce their ability to effectively reach and engage immune cells within the tumor, and many nanoparticles aren't designed to specifically target just one type of immune cell, which means they can end up interacting with the wrong cells. Nanoparticles can elicit complex and sometimes contradictory immune responses that vary with nanoparticle type, dosage, and cellular context.[82,96,97]

Inspired by the endogenous endoplasmic reticulum (ER) stress caused by unfolded/misfolded proteins, a study presents a rationally designed immunogenic cell death (ICD) inducer named NanoICD, a nanoparticle engineered for ER targeting and retention. By carefully controlling the surface composition and properties, NanoICD effectively accumulates in the ER, induces ER stress, and activates ICD-associated immune responses. Furthermore, NanoICD is generally applicable to various proteins and enzymes to enhance immunomodulatory capacity. This is exemplified by encapsulating catalase (CAT) to obtain NanoICD/CAT, which effectively alleviates the immunosuppressive tumor microenvironment and induces robust antitumor immune responses in 4T1-bearing mice. This work demonstrates the potential of engineered nanostructures to autonomously regulate biological processes, providing valuable insights into the development of advanced nanomedicines for cancer treatment.[28] Another study developed a nanodrug delivery system for bladder cancer (BCa) using poly(ε-caprolactone)-*block*-methoxy poly(ethylene glycol) PCL-MPEG and poly(ε-caprolactone)-*block*-poly(ethylene glycol)-aldehyde PCL-PEG-CHO to create micelles (PP) that encapsulate the water-insoluble compound astragaloside IV (PPA). The surface aldehyde groups on PPA reacted with the amino groups of the aPD-L1 antibody, enabling its attachment to the micelles. The resulting PPA@aPD-L1 complex effectively delivered both astragaloside IV and aPD-L1 antibody to BCa cells, enhancing drug stability, tumor targeting, and retention time. This approach significantly prolonged the survival and reduced the tumor volume in BCa-bearing mice by inhibiting NF-κB and STAT3 signaling pathways, increasing IFN-γ, and decreasing IL-10 levels, which modulated T cell infiltration in tumors.[9]

Nanozymes based on metal ions such as Fe^{2+}, Mn^{2+}, and Cu^{+} can catalyze tumor endogenous H_2O_2 to generate toxic hydroxyl radicals ($^{\bullet}OH$) through chemodynamic therapy (CDT), enhancing tumor immunogenicity. For example, MnOx nanospikes have been designed to intrinsically induce immune responses *via* CDT, significantly improving the therapeutic efficacy against primary, distant, and metastatic tumors. Additionally, CDT-mediated catalase-like activity generates molecular oxygen, promoting 1O2 production through PDT or SDT. Multifunctional nanozymes like $CoFe_2O_4$ nanoflowers achieve cascade catalysis of ROS generation, combining CDT and SDT to amplify oxidative stress and effectively trigger immunogenic cell death (ICD), thereby boosting antitumor immunity.[31] Chemodynamic therapy (CDT) utilizes reactive oxygen species (ROS) to destroy cancer cells but is often limited by the tumor's antioxidant defenses. Most approaches focus on either boosting ROS production or weakening the tumor's antioxidant capacity. In contrast, they developed a mild yet effective nanodrug with minimal side effects. This system employs Au@Pt nanozymes attached to a bacterial surface (Bac-Au@Pt) for targeted CDT. Bacteria's tumor-targeting ability combined with the acidic

Table 4 Surface-modified immune cells and their applications

Sr. no.	Type of cell	Nanoparticles	Results	References
1	HeLa cells	ACD nanoparticles	Reduction in toxicity, minimal side effects, and antitumour effect	91
2	T cells	aPD1 nanogel	Responsive drug release, 18% reduction in tumor weight, and enhanced efficacy	92
3	T cells	SHP009 inhibitor loaded into lipid nanoparticles modified with triarginine motifs	Tumor eradication and blocking the programmed death 1 pathway	93
4	Natural killer cells	Mesoporous glass NPs	Reduced toxicity, increased NK cell efficacy, and neutralized tumor acidity	94
5	T Cells	Spiky AuNPs	Increased cytokine production, cytotoxicity, and T cell functionality	95
6	Bacterial cell membrane	Au–Pt NPs	Reduction in tumor cells without affecting healthy cells and precise ROS delivery	31

environment-sensitive catalytic properties of the Au@Pt nanozyme allows precise ROS delivery to cancer cells. Additionally, interferon-gamma released by T cells selectively reduces intracellular reductants in tumor cells without affecting healthy cells. As a result, a low dose of Bac-Au@Pt achieves strong anticancer efficacy while remaining non-toxic to normal cells, even in the acidic environment.[32] Platinum B(II)[97] drugs, commonly used as first-line anticancer agents, often face limitations due to side effects and drug resistance. To address these challenges, a stimuli-responsive nanovehicle was developed using octahedral platinum(IV) prodrug loaded onto upconversion nanoparticles (UCNPs). This system integrates an octadecyl aliphatic chain and a histone deacetylase inhibitor to enhance the therapeutic effects of cisplatin. Coated with DSPE-PEG2000 and RGD peptides for tumor specificity, the nanoparticles (UCNP/Pt(IV)-RGD) can be activated by up-conversion luminescence and glutathione, enabling controlled release of the drug and showing high antitumor efficiency and imaging capabilities in both *in vitro* and *in vivo* studies.[99] The recent advancements in the applications of surface modified immune cells are discussed below in Table 4.

8. Metal organic frameworks

To make cancer treatments work better and reduce unwanted side effects, scientists are designing special tiny delivery systems that can carry drugs exactly where and when they are needed. Integrating various biological membranes with metal–organic frameworks (MOFs) has emerged as a powerful strategy to enhance targeted delivery, immune modulation, and overall therapeutic efficacy while minimizing systemic toxicity.[100] MOFs are a mixture of metal ions and organic molecules which gives them a strong but flexible cage-like structure with a lot of empty space inside perfect for holding drugs. Their design can be adjusted easily, and they can respond to stimuli like heat, pH, or light, so the drug can be released in a smart and controlled way exactly at the tumor site.[101,102] Researchers developed a cobalt-based MOF loaded with anethole trithione and coated it with a macrophage membrane to improve tumor targeting and reduce immune clearance. In another study, they designed a similar macrophage-coated MOF system (PCMM NPs) combining polypyrrole (PPy) for photothermal therapy and cantharidin (CTD) as the drug. Upon irradiation, PPy generates heat, accelerating the release of CTD and iron ions, which trigger a Fenton reaction by reacting with hydrogen peroxide to produce cytotoxic hydroxyl radicals. CTD also inhibits the tumor's heat shock response, enhancing sensitivity to photothermal therapy.[103] Like macrophages, a neutrophil membrane-coated nanoplatform is designed, which integrates silver nanoparticles (AgNPs), a porphyrinic metal–organic framework (PCN), and the neutrophil membrane (NM). This design allows for precise, inflammation-targeted drug delivery. Under near-infrared (NIR) light, the PCN generates singlet oxygen ($^1O_2$), which activates the AgNPs to release cytotoxic Ag^+ ions. This light-triggered release system ensures controlled therapeutic action with minimal side effects, making it a promising approach for safe and effective cancer treatment.[104,105] With nanotechnology, several types of "nanocarriers" (small containers) have been created. Metal–organic frameworks (MOFs), constructed using different metal ions exhibit distinct physicochemical and biological properties that make them valuable in cancer immunotherapy. Zirconium (Zr)-based MOFs are known for their exceptional stability due to Zr^{4+} forming Zr_6 clusters that create rigid frameworks like UiO-66, originally made using terephthalic acid. UiO-66 is thermally and chemically stable and can be functionalized, *e.g.*, with amine groups to create UiO-66-NH_2, enhancing biocompatibility for drug delivery and immunotherapy.[106,107] Zr^{4+} also promotes dendritic cell maturation and T cell activation, acting like an adjuvant, and can generate ROS under X-ray irradiation for photodynamic therapy (PDT). Examples like MOF-CpG-DMXAA and SNPs@Zr-MOF-RB improve immune response and modulate the tumor microenvironment. Similarly, Cui *et al.* developed a neutrophil-inspired ferric porphyrin-based MOF sensitive to glutathione, loaded with porcine pancreatic elastase (PPE) and coated with a neutrophil membrane. At the tumor site, the MOF releases PPE, which mimics neutrophils by triggering histone H1 release to selectively kill cancer cells. Simultaneously, laser-activated MOFs produce singlet oxygen, causing DNA breaks and

promoting histone H1 translocation, thereby triggering adaptive immune responses to suppress both primary and metastatic tumors.[108,109] Other metals like manganese-based MOFs (Mn-MOFs) show ability to activate the cGAS-STING pathway, triggering the release of type I interferons and inflammatory cytokines that promote dendritic cell maturation and cytotoxic T lymphocyte (CTL) infiltration. These immune responses transform immunologically "cold" tumors into "hot" ones. Mn^{2+} ions also possess photothermal conversion and Fenton reaction capabilities.[110] Aluminum-based MOFs (Al-MOFs) have immune-adjuvant properties. Al^{3+} salts are known to enhance antigen-presenting cell (APC) recruitment and T cell activation. MOFs such as MIL-100(Al) and Al-TCPP have demonstrated ROS-generating abilities despite aluminum's non-redox nature.[111] Their high porosity, large surface area, and customizability make them ideal candidates for targeted drug delivery and controlled release systems; however, MOFs offer advantages like high loading capacities and controlled release, but their potential toxicity needs thorough investigation as toxicity, biocompatibility and long-term effects remain risks.

9. AI/ML in cancer immunotherapy

Artificial intelligence (AI) and machine learning (ML) are transforming cancer immunotherapy by helping doctors better predict how individual patients will respond to treatment. By analyzing complex data like clinical records, molecular profiles, and medical images, these technologies make it possible to tailor treatments to each person's unique situation. This shift toward more personalized and effective immunotherapy is leading to better outcomes for many cancer patients.[112–115] A study by A. Prelaj *et al.* presents the development of an eXplainable machine learning model (XAI) to predict immunotherapy outcomes in patients with advanced non-small cell lung cancer (NSCLC). Using real-world data from 480 patients treated either with immunotherapy alone or in combination with chemotherapy, five machine learning models were evaluated across six clinical endpoints. CatBoost demonstrated the highest accuracy, particularly for 6-month overall survival and time to treatment failure. SHAP analysis identified the neutrophil-to-lymphocyte ratio as the most influential predictor, with additional contributions from performance status, PD-L1 expression, treatment line, and combination therapy. The findings highlight a transparent and data-driven tool to support clinical decision-making in NSCLC immunotherapy.[116] Another study presents a novel approach to optimizing treatment pathways for early-stage breast cancer, specifically Ductal Carcinoma *In Situ* (DCIS), which accounts for 35% of non-invasive cases. By modeling treatment decisions as a Markov Decision Process (MDP) and applying deep reinforcement learning, the authors aim to improve clinical decision-making without relying on often-incomplete patient records. Instead, they leverage NCCN guidelines and expert input from Moffitt Cancer Center to build a reliable, guideline-driven simulation. This work stands out for the perspectives on treatment path optimization and insights into AI-driven cancer care.[117]

Another study explores a robust multi-omics and AI-driven approach to identify therapeutic targets in pancreatic ductal adenocarcinoma (PDAC), a cancer with extremely poor prognosis. Integrating genomics, spatial transcriptomics, proteomics, and ceRNA analysis with deep learning-based QSAR modeling, the study identifies TNFRSF10A (TRAILR1) as a potential target, notably overexpressed in immune-excluded tumor regions. Using the SELFormer model and virtual screening, the authors repurpose FDA-approved drugs temsirolimus, ergotamine, and capivasertib which show strong binding affinity and stability in molecular dynamics simulations. It highlights the strategy for targeting PDAC's resistant tumor niches through AI-guided drug repurposing.[118] Another study introduces a novel, unsupervised AI/ML approach for identifying whole-genome biomarkers in neuroblastoma (NBL), a cancer with highly variable outcomes. Unlike conventional models reliant on clinical staging and MYCN amplification, this method analyzes small, noisy, multi-omic datasets using algorithms inspired by quantum mechanics. From just 101 patients, two label-free, sex-agnostic biomarkers were identified that outperformed standard indicators, with a Cox hazard ratio of 4.0 ($P = 2.3 \times 10^{-5}$). Validation in an independent 419-patient cohort confirmed their accuracy (73–80% concordance) and generalizability across platforms. The biomarkers also revealed novel disease mechanisms, supporting their potential for personalized NBL treatment.[119]

10. Challenges

Nanomedicine presents several disadvantages when applied to cancer immunotherapy. One significant challenge is the complexity and heterogeneity of tumors, which can limit the effectiveness of nanoparticle-based therapies. Tumors often exhibit variability in their genetic and phenotypic characteristics, immune infiltration, and response to therapies, making it difficult for a single nanomedicine approach to be universally effective.[120] Additionally, there is an incomplete understanding of nano–bio interactions, which complicates the design of nanoparticles that can effectively target and engage the immune system without causing adverse effects. Potential toxicity and immunogenicity of certain nanomaterials can also pose risks, as some nanoparticles may elicit unwanted immune responses or have inherent toxicity.[120] Furthermore, the rapid clearance of nanoparticles from the body can lead to poor pharmacokinetics, limiting their therapeutic impact. Furthermore, manufacturing challenges, including ensuring consistent quality and scalability of nanomedicines, also present barriers to their widespread clinical application. Lastly, the high costs associated with developing and producing nanomedicines can restrict access to many patients, raising concerns about the affordability and sustainability of these innovative therapies in the healthcare system.[120] Targeting and delivery present other hurdles. For nanoparticles to work best, they must bypass natural biological barriers and specifically accumulate in tumor tissues. Achieving this level of control is still a technological and a biological challenge, with issues of off-target effects and unpredictable distribution remaining central concerns.[121]

Immunological complications can also arise. These include unwanted immune or hematological reactions, such as allergies, immune suppression, or unexpected toxicities, all of which can complicate clinical translation and require thorough long-term safety studies.[122] Another few advanced smart delivery systems are transforming how nanomedicines work. Scientists are engineering nanoparticles that respond to specific cues from the tumor microenvironment like acidic pH, enzymes, or even external stimuli such as light to release drugs exactly where they are needed.[96] Developing nanomedicines for clinical translation and commercialization requires overcoming significant hurdles in chemistry, manufacturing, and quality control. Some nanomaterials may have inherent toxicity or induce unwanted immune responses. Certain types of nanoparticles, such as iron oxide nanoparticles, have been associated with anaphylactic reactions, endotoxin contamination, and other immunological complications. Nanoparticles may have difficulty penetrating solid tumors and achieving a homogeneous distribution within the tumor microenvironment. Furthermore, the dense extracellular matrix and high interstitial fluid pressure in tumors can hinder nanoparticle extravasation and accumulation. Nanoparticles are often rapidly cleared from the body by the reticuloendothelial system, leading to poor pharmacokinetics and limited tumor exposure. This can limit the therapeutic impact of nano-immunotherapies. The development and manufacturing of nanomedicines can be costly and complex, which may limit their accessibility and scalability for widespread clinical use. Despite these challenges, ongoing research and technological advancements are aimed at overcoming the limitations of nanomedicine in cancer immunotherapy. Strategies such as optimizing nanoparticle design, improving tumor penetration, and enhancing nano–bio interactions hold promise for realizing the full potential of nano-immunotherapy in the future.[123,124]

11. Future aspects

Combining nanomedicines with other cancer immunotherapies like checkpoint inhibitors, therapeutic vaccines, and adoptive cell transfer could lead to synergistic effects and improved outcomes. Nanoparticles can be engineered to deliver multiple immunomodulatory agents simultaneously to potentiate the anti-tumor immune response.[125,126] Researchers are making rapid progress in developing advanced, stimuli-responsive delivery systems, such as nanoparticles that release their payloads in response to tumor-specific signals like acidity or enzymes. The use of light-responsive nanomedicines is also growing, especially for enhancing the effectiveness of immune checkpoint blockade therapies. Another area of advancement is the integration of mRNA-loaded nanoparticles, which can train the immune system to better recognize and attack tumors.[127] The immunosuppressive nature of the tumor microenvironment (TME) remains a major obstacle to effective cancer immunotherapy. Nanomedicines can be designed to reprogram the TME by delivering immunostimulatory agents, inhibiting immunosuppressive pathways, or enhancing immune cell infiltration and function within the tumor.[7,128] As our understanding of tumor heterogeneity and individual immune profiles advances, personalized nano-immunotherapies tailored to a patient's specific tumor antigens and immune status could lead to more effective and durable responses. Nanoparticles can be customized for each patient to optimize the delivery of personalized immunotherapies.[125,129] Nanoparticles can help overcome key delivery barriers that limit the efficacy of many immunotherapies, such as poor solubility, short half-life, and off-target effects. Nano-formulations can improve pharmacokinetics, enable targeted delivery to tumors or lymph nodes, and enhance stability and bioavailability of immunotherapeutic agents.[126,128] The design of personalized nanomedicines leverage tumor biomarkers to customize treatment for individual patients. This precision approach aiming to optimize the immune response against cancer cells while minimizing damage to healthy tissues can be a potential healthcare advantage.[130] Most successes with cancer immunotherapy so far have been in hematological malignancies and melanoma. Applying nano-immunotherapies to treat solid tumors, which present additional challenges like the dense extracellular matrix and immunosuppressive stroma, could significantly expand the impact of this approach.[7,129]

Conflicts of interest

The authors declare no conflict of interest.

Data availability

This is a review article. No new data were produced in this work.

Acknowledgements

We thank all the members of SG and DB labs for reading the manuscript and for their valuable feedback. The work in host labs was funded by GSBTM, Gujcost-DST, SERB-ANRF and STARS-MoES, GoI and CCRH.

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