Received: 12 October 2022 | Revised: 21 November 2022 | Accepted: 22 November 2022

DOI: 10.1002/wnan.1873

ADVANCED REVIEW

WIREs NANOMEDICINE AND NANOBIOTECHNOLOGY WILEY

Improved cancer immunotherapy strategies by nanomedicine

Shuai Guo[1] | **Jie Feng**[2] | **Zongheng Li**[1] | **Sugeun Yang**[3] | **Xiaozhong Qiu**[4] | **Yikai Xu**[2] | **Zheyu Shen**[1]

[1]School of Biomedical Engineering, Southern Medical University, Guangzhou, Guangdong, China

[2]Medical Imaging Center, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China

[3]Department of Biomedical Science, BK21 FOUR Program in Biomedical Science and Engineering, Inha University College of Medicine, Incheon, South Korea

[4]Guangdong Provincial Key Laboratory of Construction and Detection in Tissue Engineering, School of Basic Medical Sciences, Southern Medical University, Guangzhou, Guangdong, China

Correspondence
Jie Feng, Medical Imaging Center, Nanfang Hospital, Southern Medical University, 1023 Shatai South Road, Guangzhou, Guangdong 510515, China.
Email: fjnfyy@smu.edu.cn

Xiaozhong Qiu, Guangdong Provincial Key Laboratory of Construction and Detection in Tissue Engineering, School of Basic Medical Sciences, Southern Medical University, 1023 Shatai South Road, Guangzhou, Guangdong 510515, China.
Email: qqiuxzh@163.com

Yikai Xu, Medical Imaging Center, Nanfang Hospital, Southern Medical University, 1023 Shatai South Road, Guangzhou, Guangdong 510515, China.
Email: yikaivip@163.com

Abstract

Cancer immunotherapy agents fight cancer via immune system stimulation and have made significant advances in minimizing side effects and prolonging the survival of patients with solid tumors. However, major limitations still exist in cancer immunotherapy, including the inefficiency of immune response stimulation in specific cancer types, therapy resistance caused by the tumor microenvironment (TME), toxicities by the immune imbalance, and short lifetime of stimulator of interferon genes (STING) agonist. Recent advances in nanomedicine have shown significant potential in overcoming the obstacles of cancer immunotherapy. Several nanoscale agents have been reported for cancer immunotherapy, including nanoscale cancer vaccines impacting the STING pathway, nanomaterials reprogramming TME, nano-agents triggering immune response with immune checkpoint inhibitor synergy, ferroptosis-mediated and

Abbreviations: ACT, adoptive cell transfer; APC, antigen-presenting cell; ARG, arginine; CAR, chimeric antigen receptor; CCL22, chemotactic cytokines ligand 22; cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-3′,3′-cGAMP; CDN, cyclic dinucleotides; CDT, chemo-dynamic therapy; CLSM, confocal laser scanning microscopy; COX2, cyclooxygenase-2; CRISPR/Cas9, clustered regularly-interspaced short palindromic repeats/associated protein 9; CRT, calreticulin; CSF-1R, colony-stimulating factor 1 receptor; CT, computed tomography; CTL, cytotoxic lymphocyte; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; DAMP, danger-associated molecular pattern; DCs, dendritic cells; DHODH, dihydroorotate dehydrogenase; dsDNA, double-stranded DNA; ECM, extracellular matrix; ER, endoplasmic reticulum; FDA, Food and Drug Administration; FSP1, ferroptosis suppressor protein; GPX4, glutathione peroxidase 4; HMON, hollow mesoporous organosilica nanoparticles; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; IDO, indoleamine 2,3-dioxygenase; IgG, immunoglobulin G; IL, interleukin; iNOS, inducible nitric oxide synthase; IND, indoximod; INF, interferon; irAEs, immune-related adverse events; IRF, interferon regulatory factor; LPO, lipid peroxidation; LNPs, lipid nanoparticles; LPS, lipopolysaccharides; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; MTO, mitoxantrone; MRI, magnetic resonance imaging; NIR, near-infrared; NK, natural killer; NPs, nanoparticles; nMOF, nanoscale metal–organic framework; PA, photoacoustic; PBA, phenylbornic acid; PGE2, prostaglandin E2; PD-1/PD-L1, programmed cell death protein 1 pathway; PDT, photodynamic therapy; PTT, photothermal therapy; ROS, reactive oxygen species; STING, stimulator of interferon genes; TAA, tumor-associated antigen; TAMs, tumor-associated macrophages; TBK1, TANK binding kinase 1; TCR, T-cell receptor; TGF, transforming growth factor; Th, T helper; TIL, tumor-infiltrating T lymphocyte; TIME, tumor immune microenvironment; TLR, toll-like receptor; TME, tumor microenvironment; Tregs, regulatory T cells; VEGF, vascular endothelial growth factor.

Zheyu Shen, School of Biomedical Engineering, Southern Medical University, 1023 Shatai South Road, Guangzhou, Guangdong 510515, China.
Email: sz@smu.edu.cn

Funding information
Guangdong Provincial Natural Science Foundation of China, Grant/Award Number: 2021A1515010605; Guangzhou Key Research and Development Program of China, Grant/Award Number: 202103000094; Zhejiang Provincial Natural Science Foundation of China, Grant/Award Number: LR19E030001

Edited by: Xiangyang Shi, Associate Editor and Gregory M. Lanza, Co-Editor-in-Chief

indoleamine-2,3-dioxygenase immunosuppression-mediated cancer immunotherapy, and nanomedicine-meditated chimeric antigen receptor-T-cell therapy. Herein, we summarize the major advances and innovations in nanomedicine-based cancer immunotherapy, and outline the opportunities and challenges to integrate more advanced nanomaterials into cancer immunotherapy.

This article is categorized under:
Nanotechnology Approaches to Biology > Nanoscale Systems in Biology
Therapeutic Approaches and Drug Discovery > Nanomedicine for Oncologic Disease
Therapeutic Approaches and Drug Discovery > Emerging Technologies

KEYWORDS
cancer immunotherapy, chimeric antigen receptor-T cells, ferroptosis, immune checkpoints inhibitors, indoleamine-2,3-dioxygenase immuno-suppression, mRNA vaccines, nanomedicine, stimulator of interferon genes, tumor microenvironment

1 | INTRODUCTION

Cancer immunotherapy has been widely used in recent years due to its long-lasting immune response, noninvasive nature, and minimized side effects. It has shown great potential in conquering malignant tumors compared with conventional therapies such as surgical excision, chemotherapy, and radiotherapy. Agents of cancer immunotherapy have been used to activate or boost the immune response to kill cancer cells, and considered as a promising strategy for cancer treatment (Baxevanis et al., 2009; Chhabra & Kennedy, 2021; Helmy et al., 2013; Kruger et al., 2019; Schumacher & Schreiber, 2015; van den Bulk et al., 2018). Since the first marketed immunotherapy agent was approved by the US Food and Drug Administration (FDA) for hairy cell leukemia treatment in 1986 [i.e., cytokine interferon (INF)-α; Ahmed & Rai, 2003] many cancer immunotherapy agents have been developed. The major classes of immunotherapy agents could be used for generalized and personalized cancer immunotherapy. The former includes immune checkpoint inhibitors (ICIs; including PD1/PD-L1, CLTA-4; Darvin et al., 2018; Kim, Lee, et al., 2021; Li, Chan, et al., 2019; Sun et al., 2018; Thomas et al., 2018) cytokines (including IL-2, TGF-β1, IL-12, and IL-15; Berraondo et al., 2019; Chen & Mellman, 2013; Kim, Lee, et al., 2021; Nguyen et al., 2020) and immune cell depletion (Knuschke et al., 2016; Knutson & Disis, 2005; Matosevic, 2018; Mikelez-Alonso et al., 2021; Phung et al., 2020; Teng et al., 2015; Valipour et al., 2019; Yang, Li, et al., 2020) which enhance the overall immune system fitness by interfering with key mechanisms of immune regulatory. The latter includes the adoptive cell transfers therapies (e.g., chimeric antigen receptor (CAR)-T cells; Feins et al., 2019; Labanieh et al., 2018; Singh & Mcguirk, 2020) antibodies (nanobodies; Chanier & Chames, 2019; Chen et al., 2016, 2020; Kijanka et al., 2015) and antigen-specific vaccination (e.g., mRNA, peptides, and virus; Fiedler et al., 2016; Lanfermeijer et al., 2020; Tagliamonte et al., 2014; Yang et al., 2014) which guide the immune cells to the specific targets in patients.

However, the clinical reports in the last decades indicated that although immunotherapy shows significant improvement in tumor inhibition and patient survival, most patients still suffer from the inefficiency of immunotherapy, toxicities caused by enhanced immune response, and therapy resistance caused by TME or potential off-target effects (Sharma et al., 2017).

With the development of nanomedicine and an improved understanding of cancer immunotherapy mechanisms, a growing number of nanoscale cancer immunotherapy agents have been reported to overcome the obstacles mentioned above. Nanomedicine-mediated cancer immunotherapy exhibits significant potential, for example, implementing nanotechnology delivery to prevent the off-targeting problem, establishing the multifunctional nano-platform to enhance T-cell activation, and combining ICIs with nanomedicine to synergistically enhance the local therapy of cancer.

Herein, we provide a brief summary of the main principles, methods, and challenges of cancer immunotherapy. We then focus on novel nanomedicine-based cancer immunotherapy agents that overcome the obstacles and promote more opportunities. Our overarching goal is to provide insights for combining nanomedicine with cancer immunotherapy to improve the efficiency and safety of cancer immunotherapy and to finally improve patient clinical outcomes.

2 | CANCER IMMUNOTHERAPY

Although cancer immunotherapy has achieved clinical efficiency, it still faces several challenges in boosting efficiency and safety issues. Thus, research and development of novel cancer immunotherapy agents to overcome the obstacles appear to be particularly significant. Understanding how cancers interact with the immune system and how the therapeutic agents act on the TME is essential for the development of cancer immunotherapy agents.

2.1 | Principles of cancer immunotherapy

The immune system has the function of immune surveillance, defense, and regulation, playing the dual role of suppressing and promoting cancer progression. Evidence accumulated from animal models and patients indicates that the immune response recognizes and eliminates cancer cells by activating immune cells. Thus, understanding the immune cell classes and how they are activated is essential for the research and development of cancer immunotherapy agents (Sharma et al., 2017; van den Bulk et al., 2018; Willsmore et al., 2021; Yang, 2015).

The tumor immunoediting hypothesis includes three phases of the tumor-immune system interaction, that is, elimination, equilibrium, and escape. Elimination means killing cancer cells via innate and adaptive immune cells. Equilibrium is the period in which the immune system fails to kill some cancer cells in the elimination phase. Although a small number of tumor cells are alive despite monitoring by the immune system, they are not harmful and do not affect normal physiological functions. Once this equilibrium is broken, the tumor cells successfully "escape", and the immune system loses control of the tumor cell growth, resulting in their sustainable growth, affected by TME, with some tumor cells showing resistance (Teng et al., 2015).

Cancer immunotherapy has gained significant bench-to-bedside success in the last 50 years by focusing on T lymphocyte cell regulation, which stresses the importance of $CD8^+$ T cells in tumor cell destruction and secretion of cytokines. When dendritic cells (DCs) activate T cells via cross-presenting exogenous antigens in the lymph node with major histocompatibility complex (MHC) molecules, T lymphocytes differentiate to T effector cells (Teffs) that kill cancer cells and memory T cells that inhibit cancer cell metastasis and recurrence (Fu & Jiang, 2018; Lees, 2020; Teng et al., 2015; Waldman et al., 2020). Also, immune checkpoint inhibitors (ICIs), such as PD-1/L1 and CTLA-4, are commonly used for suppressing cancer progression. By blocking the immune checkpoints, Teffs are upregulated by the enhanced recognition of cancer cells (Figure 1a,b; Teng et al., 2015).

TME, defined as the external and internal environment of a tumor, includes the function, structure, and metabolism of the tumor tissues and resident immune cells. TME plays a key role in determining cancer initiation, metastasis, and drug resistance. Therefore, understanding to effectively activate immune cells in TME is a key factor for the research and development of cancer immunotherapy agents. The angiogenic endothelial cells and vascular pericytes in the biological barrier prevent immune cell penetration into the tumor site. In addition, TME affects immune cells (Cheng et al., 2020), as shown in Figure 2 and discussed as follows.

Tumor-associated macrophages (TAMs) play a crucial role in antitumor treatments and are abundant in tumor location. TAMs include M1 and M2 phenotypes with polarization. M1 macrophages are known as the pro-inflammatory macrophages with secretion of IL-1β and TNF-α, which attack tumor cells. Usually, their differentiation is suppressed in TME, but could be reversed by lipopolysaccharides (LPS) and INF-γ secretion. The M2 phenotype macrophages are the main population of TAMs, leading to cancer progression and metastasis, which is known as the anti-inflammatory macrophages with secretion of IL-10, transforming growth factor-β (TGF-β), and arginase 1 (Arg1). The M2 macrophages can be further divided into subtypes, including M2a macrophages, which exhibit functions of anti-inflammatory and tissue remodeling; M2b macrophages, which exhibit functions of T helper (Th) activation and immunoregulation, leading to the promoting of tumor progression; M2c macrophages, which present functions of phagocytosis of apoptotic cells, immunosuppression and tissue remodeling; M2d macrophages, which promote angiogenesis and tumor progression. To effectively suppress cancers and further prevent the metastasis, reversal of TAMs polarization in TME is necessary (Funes et al., 2018; Pan et al., 2020; Wang, Ma, et al., 2021).

DCs present antigens to T cells by MHC molecules. In TME, the anti-inflammatory factors impede the monocytes normal differentiation into DCs and enhance the immature regulatory DCs transformation, which further inhibits T-cell function by secreting TGF-β. To promote $CD8^+$ T cells formation, the DCs antigen-presenting to T cells is proposed to be enhanced by cancer immunotherapy agents (Teng et al., 2015).

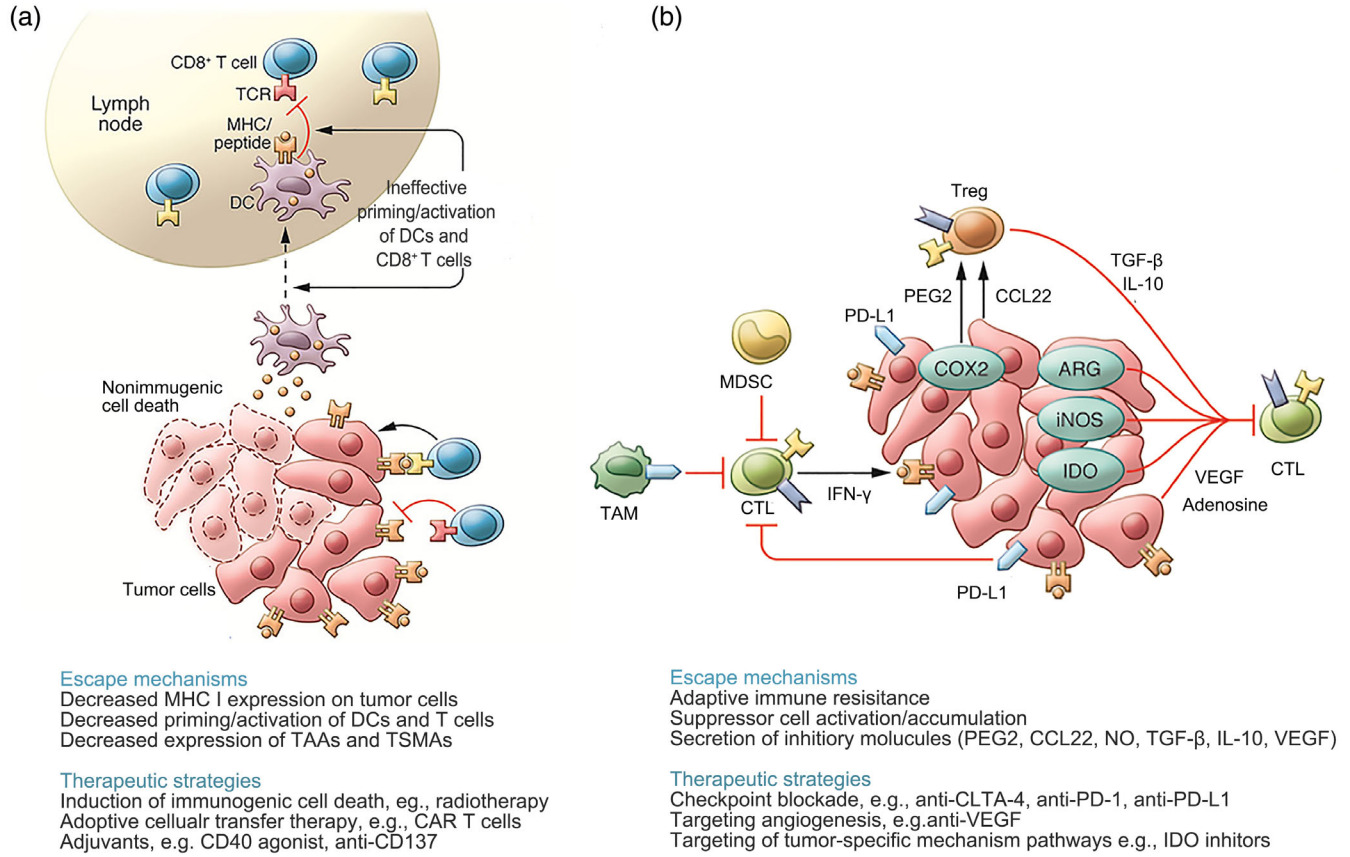


FIGURE 1 Cancer immunotherapeutic options: T-cell activation (a) and ICI synergy (b). Reproduced with permission from Teng et al. (2015), Copyright 2021, American Society for Clinical Investigation (ASCI)

Natural killer (NK) cells show significant immune surveillance in cancer progression and are an attractive candidate for cancer immunotherapy. However, NK cell-mediated cancer immunotherapy is still not fully developed for the clinic (Becker et al., 2016; Valipour et al., 2019). To obtain satisfactory outcomes of NK cell-mediated cancer immunotherapy, the focus is on disrupting TME barriers (Kim, Kim, et al., 2021; Matosevic, 2018; Mikelez-Alonso et al., 2021; Phung et al., 2020; Yang, Li, et al., 2020).

Thymus-dependent lymphocytes (i.e., T cells) are the major component of lymphocytes with targeted cell killing, assisting or inhibiting the antibody production from B cells, and resisting specific antigens and mitogens. Also, the cytokines secreted by T cells fight against cancer progression. T cells can be classified according to the function and surface markers. Teffs, such as $CD8^+$ T cells, play a crucial role in cancer immunotherapy by their ability to attack tumor cells. Regulatory T cells (Tregs) are abundant in tumor tissues due to chemo-attracting and differentiating into Tregs subpopulations in TME, which restrains the number of Teffs. T helper (Th) cells play the role of intermediator that proliferate and diffuse to activate other types of immune cells. Memory T cells are responsible for the secondary immune response, which can inhibit the cancer recurrence and metastasis (Knuschke et al., 2016; Knutson & Disis, 2005; Nakamura & Harashima, 2017; Teng et al., 2015; Thommen & Schumacher, 2018; Waldman et al., 2020). Development of cancer immunotherapy agents to correct homeostatic regulatory defects and regenerate therapeutic Teffs is critical in cancer immunotherapy. Moreover, taking advantage of Th and memory T cells to mediate a robust and long-lasting immune response is essential in cancer immunotherapy.

Recently, the tumor immune microenvironment (TIME) defined as the immunological components of the tumors has drawn wide attention, which determines the progress of tumor (Cassim & Pouyssegur, 2019; Fu et al., 2021). Scientists have been focusing on developing of strategies for re-modulation of the TIME, for example, boosting of the DCs to enhance the cross-priming of T cells, polarization of the microphages to promote the CTL profiling, or stimulation of the NK cells activation. Thus, for efficient boosting of the immune system to fight cancer, nanomedicine was introduced to address the penetration problems of immune cells and reprogram them in TME.

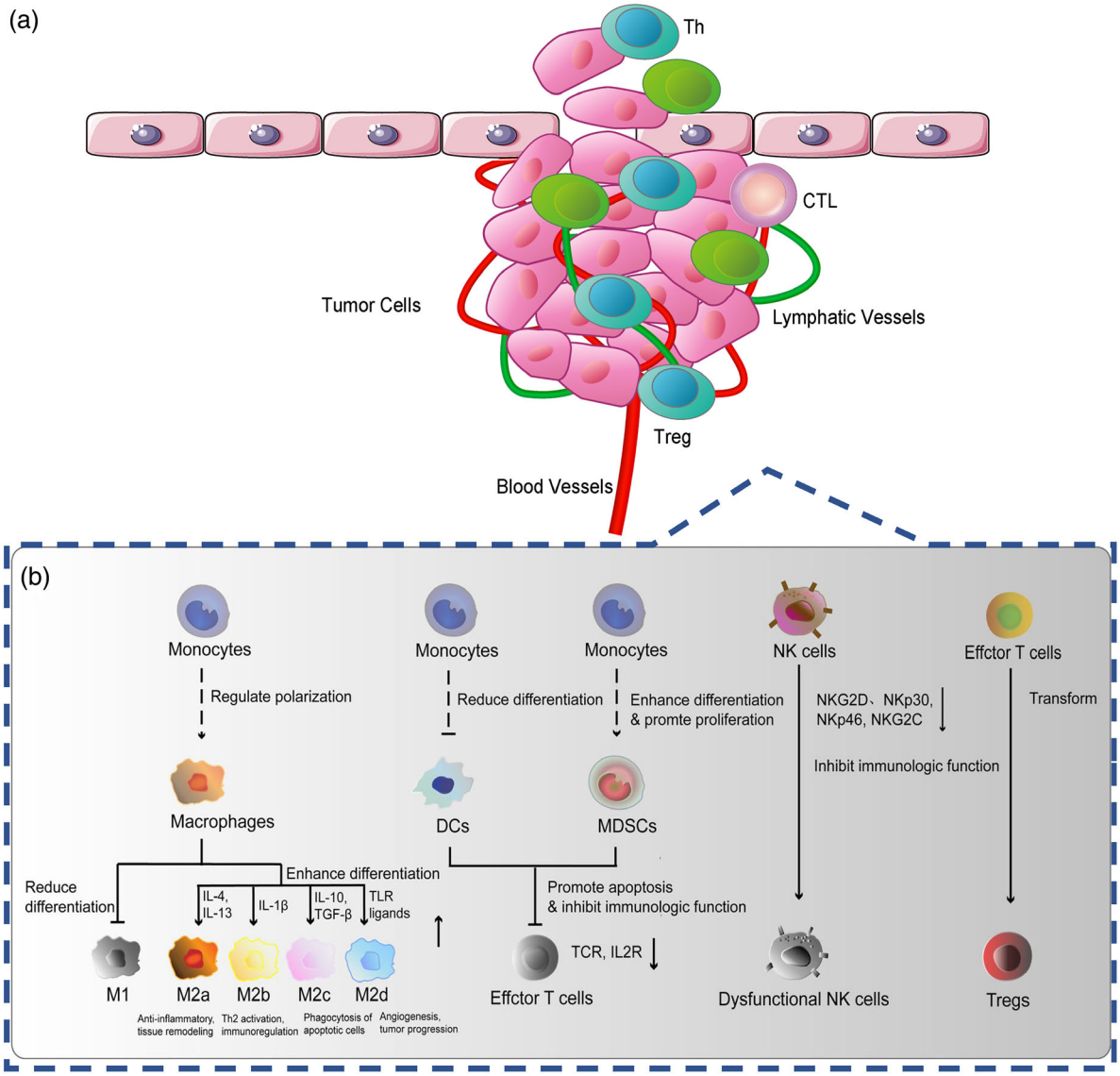


FIGURE 2 (a) Components of TME; (b) illustration of immune cell dysfunctions in TME, including enhanced differentiation of macrophages to M2 rather than M1 phenotype; DCs differentiation from monocytes is reduced while that of MDSCs is enhanced, which is disadvantageous to T-cell activation; NK cells are defunctionalized by cytokines, including NKG2D, NKP30, NKp46, and NKG2C and T cells differentiate to T_{regs} rather than T_{effs}. Reproduced with permission from Cheng et al. (2020), Copyright 2020, John Wiley and Sons

2.2 | Cancer immunotherapy classes

This review article discusses nanomedicine-based cancer immunotherapy focusing on four classes (Riley et al., 2019; Yang, 2015). In this section, we provide a brief overview of each class and highlight its major advantages and limitations, which need to be addressed to develop advanced nanomedicines.

ICIs are the most widely used and investigated cancer immunotherapy. The most commonly used ICIs are PD-1/L1 and CTLA-4. The antibodies of ICIs evade the interaction of cancer cells with T cells to prevent immune escape. So far, more than 10 ICIs have been approved for clinical use, and there are ongoing clinical trials using ICIs. Nevertheless, the clinical impact of ICIs is limited, including side effects and inefficient immune response in some types of cancer (Lavacchi et al., 2020; Li, Chan, et al., 2019; Pérez-Ruiz et al., 2020).

Cytokines are the first class of cancer immunotherapy to be introduced into the clinic. INF-α recombination therapies were approved in 1986 and directly stimulate the immune system by cytokine injection. However, the application of cytokine treatment is limited due to the drawbacks, such as short half-life and over-activation of T cells

(Abastado, 2012; Berraondo et al., 2019; Kim, Lee, et al., 2021; Nguyen et al., 2020; Showalter et al., 2017; Signore et al., 2003; Tan et al., 2018).

CAR-T cells have attracted much attention following FDA approval. In this strategy, T cells are collected from patients to express CAR through genetic engineering, which specifically binds to the corresponding antigen presented on the surface of tumors. Cancer immunotherapy with CAR T cells have advantages in immune stimulation (Labanieh et al., 2018; Pérez-Ruiz et al., 2020; Singh & Mcguirk, 2020). However, recently, the outcomes of CAR-T-cell clinical trials indicated that the toxicity from T cells is unpredictable (Brudno & Kochenderfer, 2019; Schubert et al., 2021; Yu et al., 2019).

Cancer vaccines utilize tumor-associated antigens (TAAs) to stimulate the immune system against cancer with prolonged effects and consist of DCs-based and nucleic acid-based (e.g., mRNA) vaccines (Osipov et al., 2019). The DCs-based vaccines are the most widely investigated cancer vaccines based on cells, for which DCs are collected from patients and engineered to express TAAs for T-cell activation (Rojas-Sepúlveda et al., 2018; Sabado et al., 2017; Santos & Butterfield, 2018). The nucleic acid vaccines (e.g., DNA or RNA-based vaccines) depend on the delivery of exogenous DNA or RNA to target cells. Typically, the DNA or RNA is taken up by antigen-presenting cells (APCs) and presented to T cells. However, the clinical trials of nuclei acids always face failure caused by the low-efficiency delivery of DNA or RNA (Kijanka et al., 2015; Pardi et al., 2018; Sahin et al., 2020). Therefore, to expand the clinical application of cancer vaccines, there is an urgent need for novel technologies in cancer immunotherapy to eliminate toxicity from T cells and enhance the delivery efficiency of nucleic acids. Moreover, a growing number of cancer vaccines are using neoantigens produced by chemotherapy, phototherapy (PTT), or chemo-dynamic therapy (CDT), etc., as discussed below in Section 3.2.

Although the major classes of cancer immunotherapy have achieved significant advances in recent years, limitations, including side effects, insufficient immune cell boosting, short lifetime, potential toxicity, and low delivery efficiency, still impede their application in the clinic.

2.3 | Obstacles in cancer immunotherapy

Although cancer immunotherapy has been proven to be a validated and critically important approach for cancer treatment, we list here 10 obstacles that impede its further application in the clinic: (1) determination of the tumor immunity's major drivers; (2) establishment of the human immunity models for preclinical study; (3) comprehension of immune environment of tumors in specific organs; (4) identification of the immunoescape drivers on the level of molecules and cells; (5) elucidation of the synthetic immunity's advantages and disadvantages compared with endogenous one; (6) effectiveness evaluation of early clinical study on cancer immunotherapy; (7) evaluation of the influence of steroids and immunosuppression on tumor immunotherapy and autoimmune toxicity; (8) maximization of personalized strategies based on complex biomarkers; (9) development of the advanced regulative end-points in tumor immunotherapy; (10) optimization of the long term rate of survivors based on combined multidrug tumor immunotherapy protocols (Hegde & Chen, 2020).

Nanomedicine was introduced in cancer immunotherapy to overcome the obstacles mentioned above. The nanomedicine-mediated improvements of cancer immunotherapy include (1) improved site-specific delivery and bioavailability by nanocarriers; (2) enhanced anti-tumor response by T-cell boosting, such as the STING activation nanoparticles or vaccines; (3) reduced toxic side effects, such as nanomedicine-mediated engineered CAR-T-cell therapy; (4) overcoming physical barriers and TME suppression by reprogramming of the TME or indoleamine-2,-3-dioxygenase (IDO) inhibition; (5) enhancing the targetability of immune cells by STING pathway activation (Bockamp et al., 2020; Brouillard et al., 2021; Chong et al., 2020; Huang et al., 2019; Liu, An, et al., 2020; Mi et al., 2019; Mikelez-Alonso et al., 2020; Nakamura & Harashima, 2017; Sau et al., 2018; Shao et al., 2015).

3 | NANOMEDICINE-MEDIATED CANCER IMMUNOTHERAPY

The cancer-immunity cycle summarized by Martin et al. includes the following seven phases, as shown in Figure 3 (Martin et al., 2020). (1) Release of cancer cell antigens, including TAAs and tumor-specific antigens (TSA); (2) cancer antigen presenting by APCs, which include B cells, DCs, and macrophages, can uptake and process antigens to T cells; (3) initiation and activation of T cells, in which T cells are activated by further differentiating to Teffs under cross-presentation of DCs; (4) trafficking of T cells from lymph nodes to tumors; (5) tumor infiltration of T cells; (6) tumor

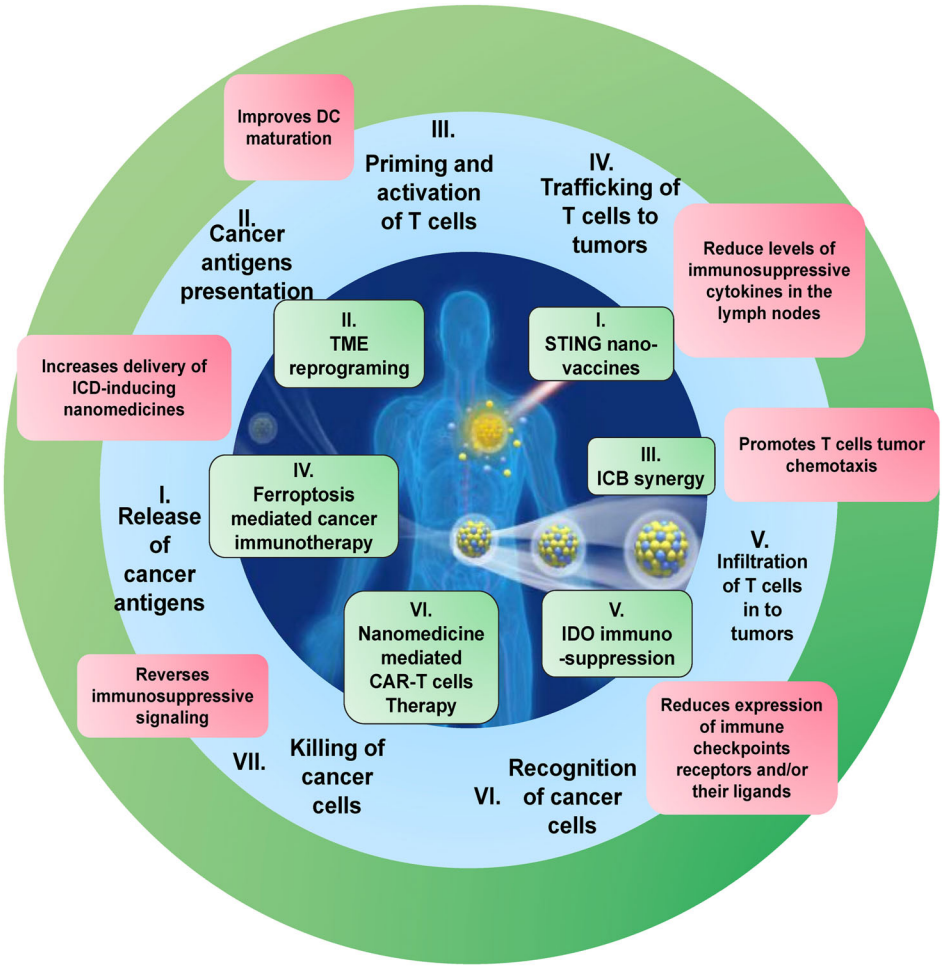


FIGURE 3 Cancer immunity cycle responsiveness to cancer immunotherapeutic nanomedicine. Four classes of cancer immunotherapeutic agents: STING nano-vaccines, nanomedicines involved in TME reprogramming, nanomedicines with ICI synergy, and nanomedicines for ferroptosis-meditated cancer immunotherapy. This figure is originally created by the authors

cell recognition of T cells; (7) tumor cell killing by T cells. Numerous nanomedicine-based cancer immunotherapy agents have been designed based on the cancer-immunity cycle.

We reviewed the advances in nanomedicine-based cancer immunotherapy agents that have successfully achieved prolonged immune effect, low immune toxicity, and high targeting accuracy (Zhang, Wang, et al., 2020) and summarized six significant classes of nanomedicine, modulating the cancer immunity cycle (Figure 3). (1) Nanoscale cancer vaccines with functions in STING pathway that promotes T cells activation by secreting INF-β; (2) nanomedicines involving TME reprogramming, which enhances TAA delivery, modulates M1 and M2 phenotypes of macrophages in TME and boosts DCs presentation to T cells; (3) synergy between nanomedicines and ICIs, inducing T-cell upregulation by strengthening recognition of tumor cells; (4) ferroptosis-mediated cancer immunotherapy, innovatively combining ferroptosis and cancer immunotherapy to achieve immune-modulation and enhanced programmed cell death; (5) IDO immunosuppression-mediated cancer immunotherapy; (6) nanomedicine-mediated CAR-T-cell engineering; (7) NK cells augmented cancer immunotherapy mediated by nanomedicine; and (8) mRNA vaccines mediated cancer immunotherapy by nanomedicine, and so forth, as summarized in Table 1.

3.1 | Nanoscale cancer vaccines with functions on STING pathway

Recently, cancer immunotherapeutic agents related to activation of cGAS (cyclic GMP-AMP synthase)-STING pathway has drawn attention for its efficient targeting and effectiveness in cancer therapy. The mechanism could be generalized:

TABLE 1 Strategies of improving cancer immunotherapy by nanomedicine

Strategy	NPs	Composition or method	Function	References
Nanoscale cancer vaccines with functions on STING pathway	A synthetic cancer nano-vaccine platform	Co-loading the STING (stimulator of interferon genes) agonist cGAMP (cyclic GMP-3′,3′-cGAMP) and peptide neoantigens into pH-responsive endosomolytic polymersomes	Immunogenic cancer cells for efficiently promoting CD 8^+ T cells stimulation	(Shae et al., 2020)
	SN38 polymeric nanoparticles (NPs)	SN38 polymer	Enhancing the targeting accuracy of SN38 to cancer cells and providing a long-lasting effect of the cGAS (cyclic GMP-AMP synthase)-STING (stimulator of interferon genes) pathway	(Zhao et al., 2021)
	PC 7A (NPs)	OVA antigen and a synthetic pH-sensitive polymer	Prolong the initiation of the immune system by STING oligomerization and condensation driven by PC 7A through polyvalent interactions	(Li et al., 2021)
TME reprogramming by nanomedicines	Single-crystal Fe (NPs)	Single-crystal Fe and polymers	Reactive oxygen species (ROS) inducing of immunogenic cell death (ICD) of cancer cells, which promotes DCs maturation and T cells presentation with robust T cells boosting	(Liang et al., 2021).
	Virus-like particles (VLP)	A chemically modified VLP called bacteriophage Qβ and Dye for near-infrared (NIR) absorption	PTT (photothermal therapy) inducing ICD of cancer cells, activating T cells to suppress cancer cells by Teffs, and preventing metastasis by memory T cells	(Shahrivarkevishahi et al., 2021)
	Nanoplatform for PTT and PDT (photodynamic therapy)	Pardaxin (FAL) peptides, hollow gold nanospheres (FAL-ICG-HAuNS) with conjugation of indocyanine green (ICG), and liposomes of hemoglobin (FAL-Hb lipo)	Synergistic ICD-associated immunogenicity by ROS generated via endoplasmic reticulum (ER) stress	(Li, Chan, et al., 2019)
	Nano metal–organic framework (nMOF)	Cu-porphyrin	Evoking ICD-induced robust T cells activated by PDT under NIR light irradiation, CDT (chemo-dynamic therapy) with Fenton-like reaction of Cu^{2+}, and synergistic PD-L1 blocking, enlarged the effectiveness of PDT/CDT to suppress distant tumors	(Ni et al., 2019)

TABLE 1 (Continued)

Strategy	NPs	Composition or method	Function	References
Nanomedicine-triggered immune response with ICI synergy	Engineered platelets combination of anti-PD-L1	Engineered platelets coating with anti-PD-L1	Selective and temporal controlling and releasing of cancer immunotherapeutic agents in nano-vesicles and efficient recruitment of immune cells for tumor inhibition	(Wang, Li, et al., 2021)
	PTT genome-editing	Delivering of CRISPR/Cas9 for PD-L1 targeting using gold nanodots	Improvement of DCs presentation to T cells and promoted cytotoxic T lymphocyte (CLT) infiltration into tumors	(Tang et al., 2021)
	Engineered immunosuppressive NPs	Coating of anti-PD-L1, that is, MSC-PD-L1^{+} NPs	Manage and reduce immune-related adverse events (irAEs) in normal cells and tissues caused by the toxicity of T cells activation	(Shen et al., 2021)
Ferroptosis-mediated Cancer Immunotherapy	–	–	Enhancement of the lipid peroxidation (LPO) accumulation by CD8^{+} T cells boosting	–
IDO immunosuppression-mediated cancer immunotherapy	Chemo-immuno synergistic platform	Loading of the anthraquinone chemotherapeutic agent mitoxantrone (MTO) into liposomes, followed by the addition of indoximod (IND)	The immunotherapy response was significantly improved by the IDO immunosuppression	(Mei et al., 2020)
Nanomedicine-meditated chimeric antigen receptor (CAR)-T-cell therapy	Ionizable lipid nanoparticles (LNPs)	Delivery of mRNA into T cells	Inducing of expression of CAR at levels comparable to electroporation with limited toxicity.	(Billingsley et al., 2020)
NK cells augmented cancer immunotherapy mediated by nanomedicine	Liposomes	Delivery of the TGF (transforming growth factor)-β siRNA into NK cells	Downregulation of the expression of TGF-β in TME	(Xu et al., 2014)
	Chitosan-based NPs	Delivery of the dsNKG2D-IL-21 gene to TME	The penetration of the NK cells and T cells are largely enhanced by the increased IL (interleukin) level as induced by the NPs	(Tan et al., 2017)
	Immunoglobulin G (IgG)/phenylbornic acid (PBA)	Delivery of the IgG to tumor location to active NK cells	In situ activation of NK cells with enhancement of tumor-infiltrating as boosted by IgG.	(Zheng et al., 2019)
mRNA vaccines mediated cancer immunotherapy by nanomedicine	mRNA NPs	Ovalbumin-coded mRNA and a palmitic acid-modified TLR7/8 agonist R848 (C16-R848) as the core and the lipid-PEG as the shell	Enhancing the delivery efficiency of mRNA vaccines	(Islam et al., 2021)

in the bone marrow-derived primary dendritic cells (BMDCs), the dimerized cGAMP (cyclic GMP-3′,3′-cGAMP) known for cGAS sensing of DNA in the cytoplasm, or agonists, for example, cyclic dinucleotides (CDN), recruit the TANK binding kinase 1 (TBK1) proteins. Subsequently, TBK1 phosphorylates and stimulates the interferon regulatory factor-3 (IRF-3), defined as TBK1-IRF 3 pathway activation. As illustrated in Figure 4, through the endoplasmic reticulum (ER) to Golgi trafficking, phosphorylated IRF 3 enters BMDCs nuclei releasing INF-I and further activating T cells and generating $CD8^+$ T cells (Jiang et al., 2020; Luo et al., 2017; Wang et al., 2020; Zou et al., 2021). However, the use of STING pathway agonist is still limited due to insufficient boosting of the immune response, short lifetime, and high cost, hindering its broad clinical application (Hoong et al., 2020). A growing number of advanced nanomedicine-based cancer immunotherapy agents involving STING pathway activation have been reported that overcome the obstacles of STING vaccines (Dane et al., 2022; Li, Mirlekar, et al., 2022; Li, Khorsandi, et al., 2022; Wang, Bergholz, et al., 2022).

Shae et al. reported the delivery of a synthetic cancer nano-vaccine platform, nanoSTING-vax, to immunogenic cancer cells for efficiently promoting CD 8^+ T cells stimulation (Shae et al., 2020). Co-loading of the STING agonist cGAMP and peptide neoantigens into pH-responsive endosomolytic polymersomes (Figure 5a) promoted their co-delivery to the cytosol. Consequently, via endosomal escape, the cytosolic antigen processing promotes MHC class I presentation, and cytosolic cGAMP activation of the STING pathway elicited inflammatory cytokine (e.g., INF-α/β, IL-12, TNF-α) production and CD 8^+ T-cell differentiation (Shae et al., 2020).

Zhao et al. performed in vivo screening of DNA-targeting chemo-agents and found SN38 (7-ethyl-10-hydroxycamptothecin) to be the most potent drug to induce STING pathway stimulation in BMDCs (Zhao et al., 2021). SN38 causes DNA damage and subsequent leakage of DNA fragments in cancer cells that are delivered to BMDCs by exosomes and activate the cGAS-STING pathway. Furthermore, SN38 polymeric nanoparticles have long blood circulation and TME-specific degradation, enhancing the targeting accuracy of SN38 to cancer cells and providing a long-lasting effect of the cGAS-STING pathway. Thus, the immune system could be effectively boosted by the prolonged anti-tumor effect of SN38 polymeric nano-STING agonist (Figure 5b; Zhao et al., 2021).

Another simplified nano-vaccine was reported by Li et al. (2021). The PC 7A nanoparticles, a long-lasting STING agonist, are composed of the OVA antigen and a synthetic pH-sensitive polymer poly-(ethylene oxide)-β-poly (methyl methacrylate) (PEG-PMMA). The nano-vaccine generated a robust T-cell response with highly accurate delivery of tumor antigens from DCs into lymph nodes. Furthermore, this advanced STING vaccine provided prolonged initiation of the immune system by STING oligomerization and condensation driven by PC 7A through polyvalent interactions, as examined by the confocal laser scanning microscopy (CLSM) figures in Figure 5c-i. The efficiency of STING activation was correlated with PC 7A valency as shown in Figure 5c-ii (Li et al., 2021).

Since cancer antigen-specific $CD8^+$ T cells are critical in the anti-cancer immune response to kill cancer cells and suppress cancer metastasis and recurrence, T cells activation and tumor infiltration are crucial in developing strategies of cancer immunotherapy enhancement by nanomedicine (Liang et al., 2021).

We have summarized the major classes of the STING agonist-mediated by nanomedicine in Figure 4, including (a) the small molecule chemotherapy agents such as DOX and SN38, which generate DNA fragments to stimulate the cGAS-STING pathway (Zhao et al., 2021); (b) CDNs (cyclic dinucleotides), which stimulate the cGAS-STING pathway by recruiting TBK1 proteins (Shae et al., 2020); (c) SR-717 (Zou et al., 2021), Mn^{2+} and Zn^{2+} (Wang et al., 2020) can enhance cGAMP activity; (d) PC 7A can enhance STING protein the activity by polyvalent combinations (Li et al., 2021).

Overall, the nanoscale cancer vaccines affecting the STING pathway show significant potential T-cell activation, leading to $CD8^+$ T cells differentiation. However, STING agonists with a prolonged lifetime and sufficient STING pathway activation that show potential to be utilized in the clinic are still inadequate. Thus, the development of STING agonists requires further efforts to offer new therapeutic opportunities in cancer immunotherapy.

3.2 | TME reprogramming by nanomedicines

Recently, nanoparticles inducing immunogenic cell death (ICD) were applied in TME (He, Ni, et al., 2020; Li et al., 2021; Shae et al., 2020; Zhao et al., 2021; Zhu et al., 2020) to imitate anti-tumor immune response, which include secretion and expression of cytokines, activation and redistribution of immune effector cells, and transformation of memory T cells from Teffs. Nanoparticles with PTT functions generate heating effect at tumor locations (Chang et al., 2021; Shahrivarkevishahi et al., 2021; Zhang, Zhang, et al., 2020; Zhou et al., 2021) photodynamic therapy (PDT), producing singlet oxygen (Li, Yang, et al., 2019; Showalter et al., 2017; Yang, Zhang, et al., 2020; Zhang & Li, 2018), or

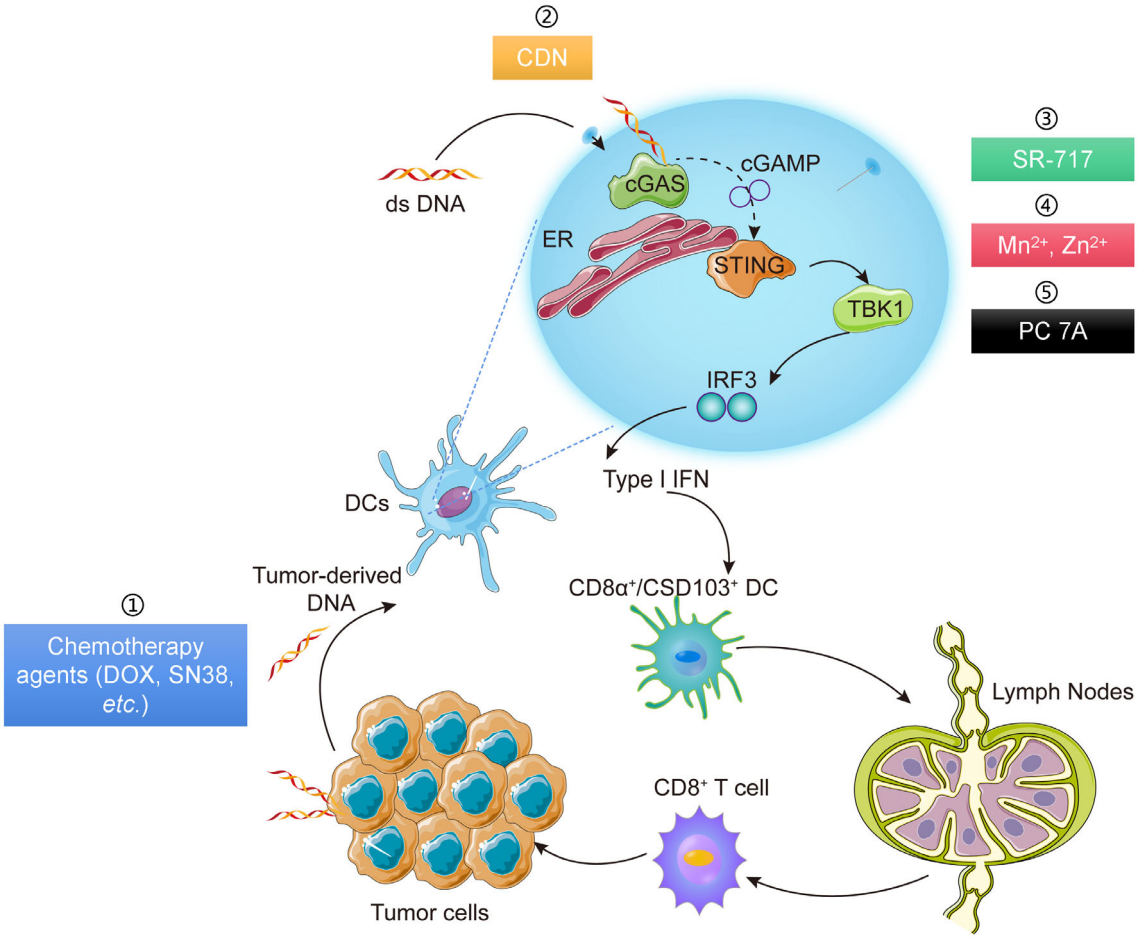


FIGURE 4 STING pathway with activation of dsDNA or STING agonists: IRF-3 induced INF-I releasing and triggering of T cells with further differentiation of $CD8^+$ T cells to kill cancer cells. This figure is originally created by the authors

CDT generating reactive oxygen species (ROS) induced by Fenton reaction (Fe^{2+} and Fe^{3+})/Fenton-like reaction (e.g., Mn^{2+}, Cu^{2+}; Jiang et al., 2021; Kong et al., 2021; Li, Lai, et al., 2022; Li & Rong, 2020; Liu, Zhen, et al., 2020; Ni et al., 2019; Wang, Xu, et al., 2021) can lead to ICD of cancer cells. Furthermore, fragments of dead cancer cells can enhance DCs maturation, presenting TAAs to T cells, promoting the generation of $CD8^+$ T cells, and secretion of INF-γ to kill cancer cells. The differentiated memory T cells impede the cancer cell metastasis and suppress remote tumor formation. Exemplified as single-crystal Fe nanoparticles for ferroptosis and immunotherapy of cancer, the Fe^0-generated ROS in TEM causes sufficient ferroptosis. Simultaneously, ROS-induced ICD promotes DCs maturation and T-cell presentation with robust T-cell boosting (Figure 6; Liang et al., 2021).

As reported by Shahrivarkevishahi et al., virus-like particles (VLPs) were designed and applied as multiple functional nanocarriers by mimicking the architecture of viruses. Figure 7. shows that VLPs serve as a specific functionalization and immunization platform by dye conjugation for near-infrared (NIR) absorption of PTT, inducing ICD of cancer cells, activating T cells to suppress cancer cells by Teffs, and preventing metastasis by memory T cells (Shahrivarkevishahi et al., 2021).

Also, a double endoplasmic reticulum (ER)-targeting strategy to realize PDT and PTT was reported for cancer immunotherapy that produced synergistic ICD-associated immunogenicity by ROS generated via ER stress. This novel nanoplatform included pardaxin (FAL) peptides, hollow gold nanospheres (FAL-ICG-HAuNS) with conjugation of indocyanine green (ICG), and liposomes of hemoglobin (FAL-Hb lipo). Under the exposure to NIR light irradiation, calreticulin (CRT) generated by PTT and PDT acted as an "eat me" signal to stimulate antigen-presentation of DCs to T cells, leading to various immune response, such as proliferation of $CD8^+$ T cells and secretion of cytotoxic cytokines, which significantly enhanced cancer immunotherapy (Figure 8a; Li, Yang, et al., 2019).

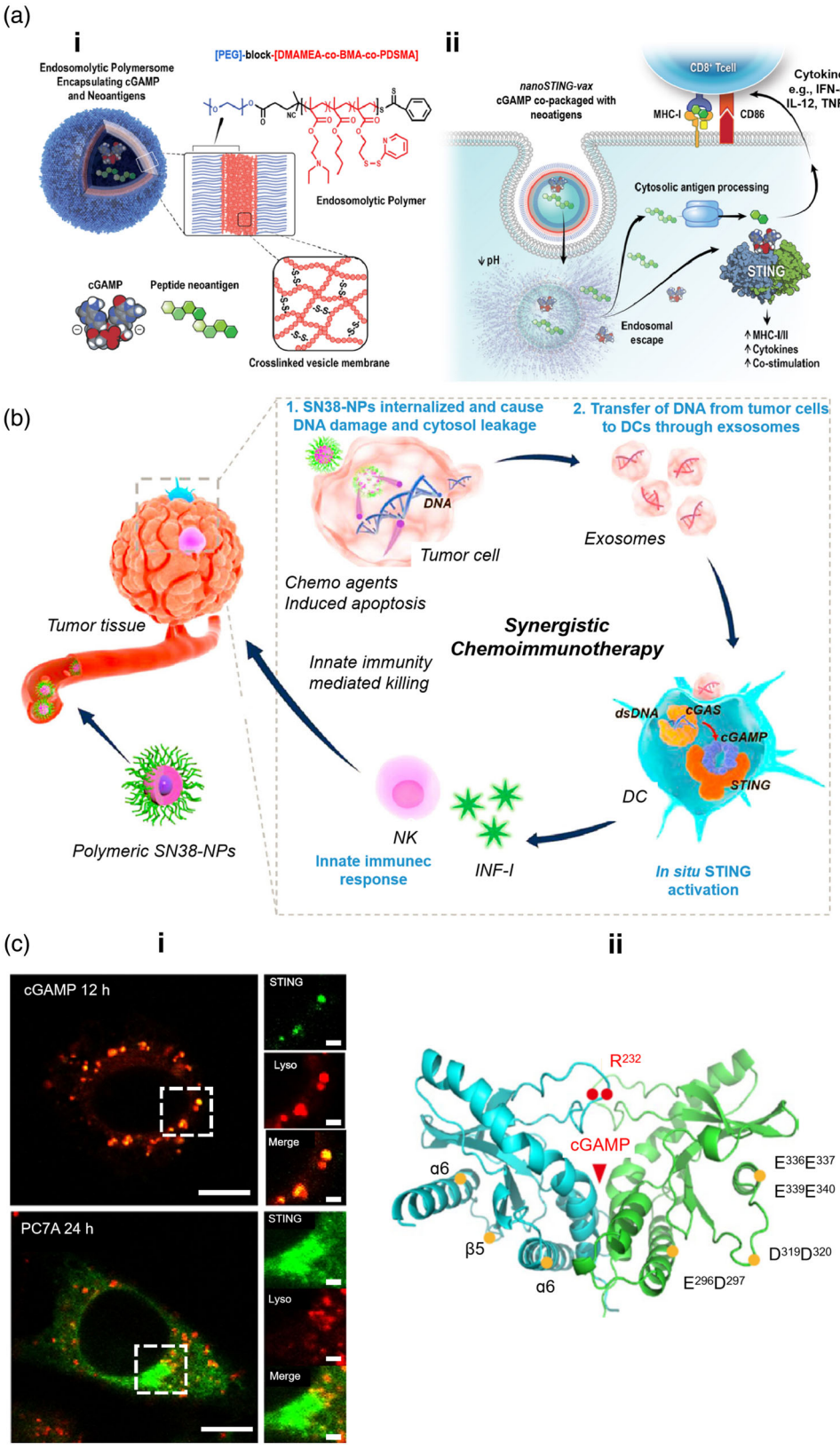


FIGURE 5 Nano-vaccines involving STING activation: (a) NanoSING-vax, a nanoplatform for dual-delivery of peptides antigens and cyclic dinucleotides STING agonist. Reproduced with permission from (Shae et al., 2020, Copyright 2020, American chemistry society. (b) Polymeric SN38 for cancer chemoimmunotherapy with in situ activation of the STING pathway. Reproduced with permission from Zhao et al. (2021), Copyright 2021, Elsevier. (c) PC 7A, the polyvalent STING agonist triggering STING by polyvalent interaction and correlated with the PC 7A valency with prolonged activation effects. Reproduced with permission from Li et al. (2021), Copyright 2021, Springer Nature

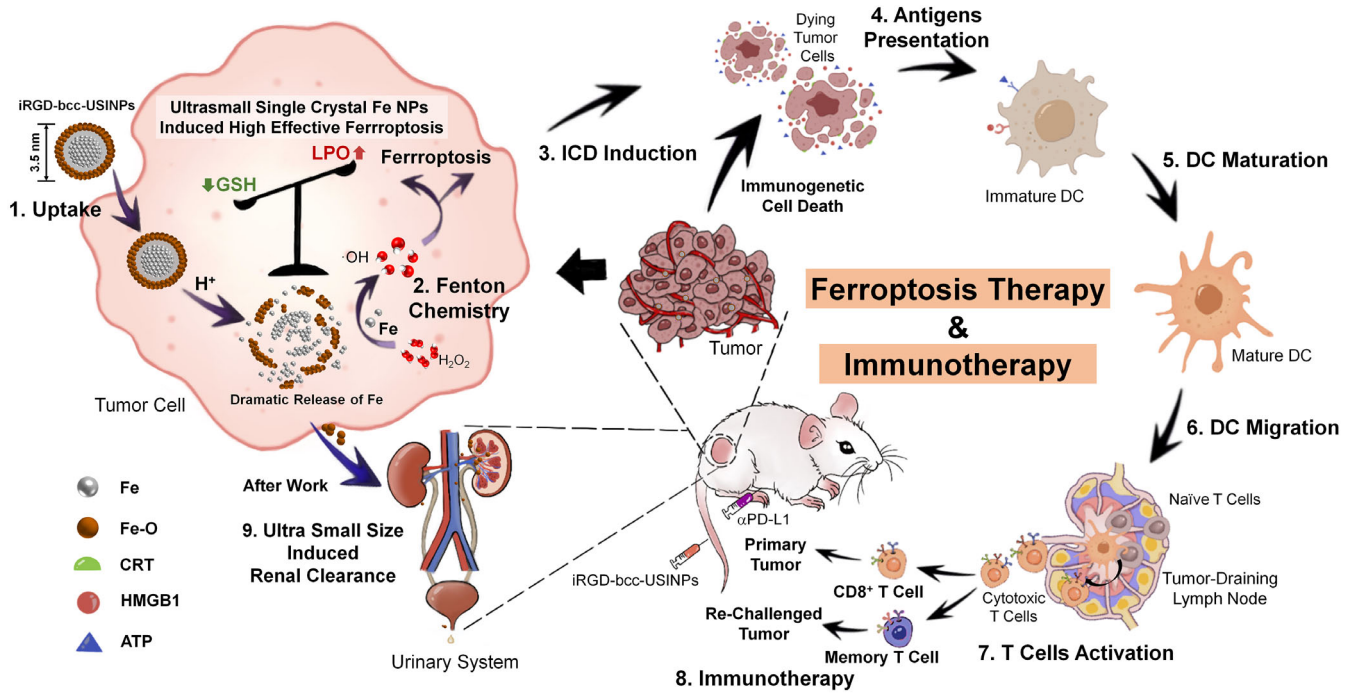


FIGURE 6 Nanomedicine-based cancer immunotherapy involving TME reprogramming by CDT-induced ICD, TAA delivery enhancement of DCs and cross-presentation to T cells, and inducing robust T-cell activation. Reproduced with permission from Liang et al. (2021), Copyright 2021, American Chemical Society

In order to realize synergistic therapy of light-triggered PDT and hormone-triggered CDT, Ni et al. reported a nano metal–organic framework (nMOF) based on Cu-porphyrin. This nanoplatform, as shown in Figure 8b, by evoking ICD-induced robust T cells activated by PDT under NIR light irradiation, CDT with Fenton-like reaction of Cu^{2+}, and synergistic PD-L1 blocking, enlarged the effectiveness of PDT/CDT to suppress distant tumors based on abscopal effects in mouse tumor models (Ni et al., 2019). The Cu-porphyrin-nMOFs were TME responsive, generating robust ROS at the tumor site but not in somatic cells. Moreover, the nanoparticles accumulated at tumor locations via the EPR effect. Therefore, the Cu-porphyrin-nMOF can perform promising anti-tumor effects without side effects.

Overall, the above-mentioned nanomaterials with PTT or CDT functions induce TME reprogramming by ICD-induced immune response, which can overcome cancer immunotherapy resistance. However, cold tumors with few immune cell infiltrations cannot be effectively suppressed by ICD-induced immune response. Another consideration is the effect of ICD-induced specific immune cell subpopulations, such as expression of immunosuppressive molecules PD-1/L1. Thus, improved strategies for converting cold tumors to hot tumors combined with ICIs synergy are necessary (Han et al., 2019; Kruger et al., 2019; Long et al., 2019; Shen et al., 2021; Tang et al., 2021; Wang, Li, et al., 2021).

3.3 | Nanomedicine-triggered immune response with ICI synergy

ICI therapy has consistently shown remarkable cancer immunotherapy outcomes in the clinic and is considered the gold standard for developing new cancer immunotherapy agents. Among them, anti-PD-1/L1 and anti-CTLA-4 are the most commonly used antibodies for boosting T cells immunity (Figure 9; Willsmore et al., 2021). However, ICIs still have the limitations of low response rates in some solid tumors and unpredictable toxicities (Cha et al., 2019; Darvin et al., 2018; Kruger et al., 2019; Lavacchi et al., 2020; Li, Chan, et al., 2019; Long et al., 2019; Pérez-Ruiz et al., 2020; Sun et al., 2018; Thomas et al., 2018). Thus, novel nanoplatforms synergistic with ICIs have been developed to efficiently activate T cells (Chen et al., 2016; Han et al., 2019; Li et al., 2023; Shen et al., 2021; Wang, Li, et al., 2021).

As reported by Wang et al., a novel nanocarrier has been developed for cancer immunotherapy using engineered platelets, which achieved selective and temporal control and release of cancer immunotherapeutic agents in nano-

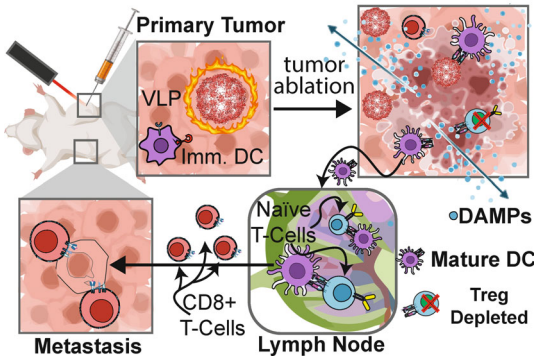


FIGURE 7 Illustration of cancer immunotherapy by virus-like particles (VLPs) and its effect induced by PTT under NIR irradiation, which stimulates $CD8^+$ T-cell activation for cancer cell suppression and metastasis inhibition. Reproduced with permission from Shahrivarkevishahi et al. (2021), Copyright 2021, American Chemical Society

vesicles and efficient recruitment of immune cells for tumor inhibition. Additionally, anti-PD-L1 enhanced the CAR-T-cell therapy by T cells upregulation with enhanced tumor cell recognition (Figure 10; Wang, Li, et al., 2021).

Besides, as reported by Tang et al., a PTT genome-editing strategy was designed to improve ICI therapy by CRISPR/Cas9-mediated PD-L1 disruption and mild-hyperthermia-induced ICD activation by delivering CRISPR/Cas9 for PD-L1 targeting using gold nanodots. The strategy helped improve DCs presentation to T cells and promoted CLT infiltration into tumors. Thus, the immunosuppressive TME was reprogrammed (Figure 11a; Tang et al., 2021).

As reported by Shen et al., the engineered immunosuppressive nanoparticles with a coating of anti-PD-L1, that is, MSC-PD-$L1^+$ NPs, could potentially manage and reduce immune-related adverse events (irAEs) in normal cells and tissues caused by the toxicity of T cells activation (Figure 11b). This novel strategy showed potential to manage different tumor immunotherapy-related irAEs in clinical applications (Shen et al., 2021).

The ICI synergistic nanomedicine has shown significant potential in cancer immunotherapy due to the robust boosting of T cells. However, side effects of the ICIs therapy are of serious concern. Recently, several studies have reported irAEs affecting every organ system. Excessive activation without control is defined as immune imbalance, leading to damage and inflammation of normal tissues. Therefore, advanced nanomedicines shall focus on reducing the side effects of ICIs to broaden the clinical application.

3.4 | Ferroptosis-mediated cancer immunotherapy

Ferroptosis is a new type of programmed cell death, as defined by Stockwell et al. in 2012. It is iron-dependent, and genetically, biochemically, and morphologically distinct from necrosis, apoptosis, and autophagy. Glutathione peroxidase 4 (GPX4) has been shown to be a critical factor in ferroptosis modulation that reduces the accumulation of lipid peroxidation (LPO; Chen et al., 2021; Dixon et al., 2012; Du et al., 2022; He, Liu, et al., 2020; Hu et al., 2021; Jiang et al., 2015; Liu et al., 2018; Miotto et al., 2020; Tang et al., 2021; Wang et al., 2019; Wang, Zhang, et al., 2022; Xu et al., 2021). Strategies of ferroptosis in TME, which generates ROS by Fenton or Fenton-like reaction, or downregulates GPX4 to induce peroxidation of cancer cell membranes leading to ferroptosis of cancer cells, have been widely used in the design of cancer ferroptosis therapy agents (Du et al., 2022; Hou et al., 2020; Liu et al., 2018; Shen, Song, et al., 2018; Xu et al., 2021; Yang & Stockwell, 2016). The ferroptosis suppressor protein (FSP1), another ferroptosis defense system and a pivotal component of the CoQ antioxidant system (nonmitochondrial), works parallelly with the GPX4 pathway based on canonical glutathione (Bersuker et al., 2019). Besides, dihydroorotate dehydrogenase (DHODH) was reported as a novel target in cancer, which works parallelly to GPX4 in mitochondria to suppress ferroptosis in the inner membrane of mitochondria through reduction of ubiquinol (Mao et al., 2021). Furthermore, ferroptosis could be potentially utilized in the research and development of cancer immunotherapy agents.

Nanomedicines mediating ferroptosis always generate ICD-induced immune response triggered by ROS. Also, ferroptosis in cancer cells is under the surveillance of the immune system. $CD8^+$ T cells downregulate SLC3A2 and SLC7A11 subunits of system X_c^- by secreting INF-γ, which suppresses the bioactivity of system X_c^-, a glutamate-cystine antiporter which exporting glutamate and importing cystine. The inhibition of system X_c^- leads to insufficient

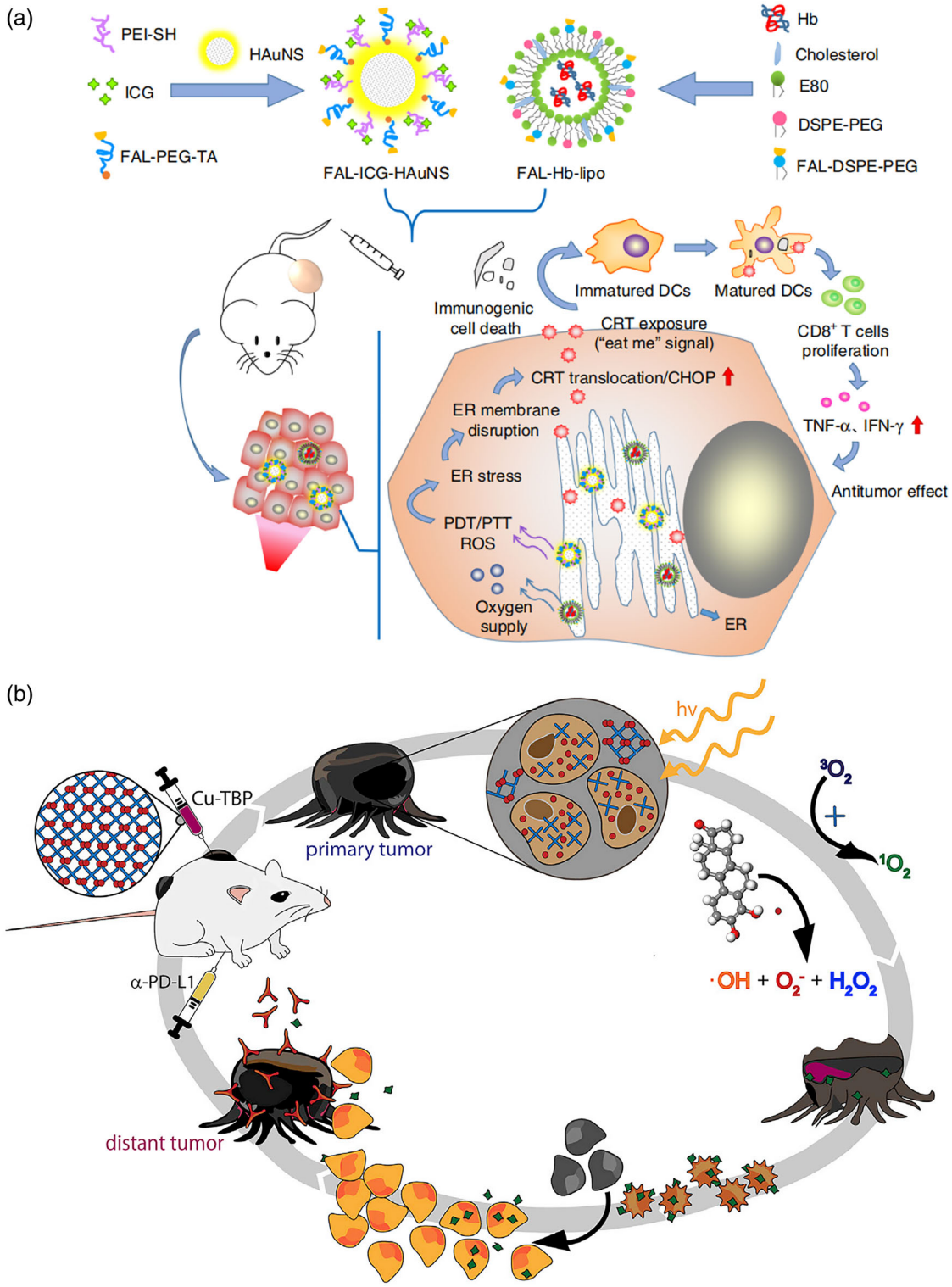


FIGURE 8 (a) Double ER-targeting nanoplatform, FAL-Hb-lipo to realize PDT, and PTT for cancer immunotherapy, resulting in synergistic ICD-associated immunogenicity by ROS produced via ER stress. Reproduced with permission from Li, Yang, et al. (2019), Copyright 2019, Nature Publishing Groups. (b) Cu-porphyrin nanoscale metal–organic framework (nMOF) to mediate synergistic hormone-triggered CDT and light-triggered PDT with PD-L1 blockage for cancer immunotherapy. Reproduced with permission from Ni et al. (2019), Copyright 2019, Elsevier

cystine transportation into cancer cells and inadequate cysteine conversion. Since cysteine is indispensable in glutathione production, the depletion of cysteine causes downregulation of GPX 4 due to glutathione lacking, further leading to cancer cells death by LPO accumulation on the cell membrane (Figure 12; Yang & Stockwell, 2016). Thus, ferroptosis is

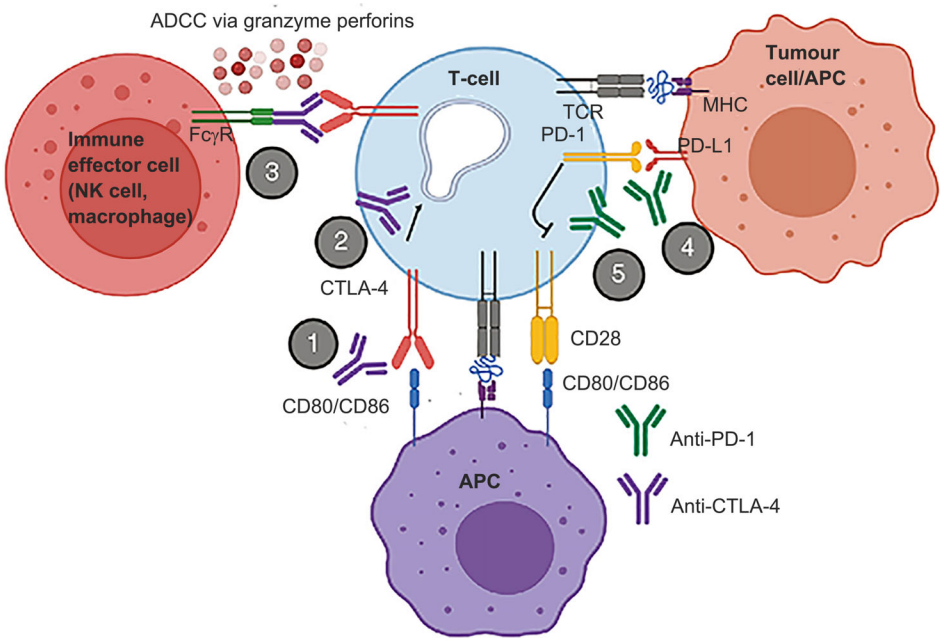


FIGURE 9 Nanomedicines involving ICI synergy in cancer immunotherapy, including blocking of PD-1/L1 and CTLA-4 immune checkpoints of T cells to enhance the T-cell recognition of cancer cells. Reproduced with permission from Willsmore et al. (2021), Copyright 2021, John Wiley and Sons

considered one of the novel cancer immunotherapy candidates with remarkable crosstalk between immune and tumor cells, representing a good perspective for the research and development of novel cancer immunotherapy agents.

3.5 | IDO immunosuppression-mediated cancer immunotherapy

Indoleamine-2,3-dioxygenase (IDO) is an enzyme of speed limit, which metabolizes the tryptophan (an essential amino acid) into downstream kynurenines. Suppression of IDO could predominantly inhibit metabolic activity, impeding immune cell inhibition or T-cell death. Thus, inhibition of IDO is a pivotal area of cancer immunotherapy, especially in nanomedicine-meditated IDO immunotherapy due to the advantages of targetability and limited side effects of the IDO inhibitor-conjugated nanoparticles (Zhai et al., 2020).

Mei et al. reported a multiple functional nanoplatform of chemo-immuno synergistic cancer therapy consisting of a liposomal carrier for codelivery of ICD stimulus plus an inhibitor of IDO. It was prepared by loading the anthraquinone chemotherapeutic agent mitoxantrone (MTO) into liposomes, followed by the addition of indoximod (IND), the pre-drug of IDO inhibition in the lipid layer. The CT 26 colorectal cancer model demonstrated the generation of a robust immune response, characterized by ICD makers. Furthermore, the immunotherapy response was significantly improved by the codelivery of IND (Mei et al., 2020). Thus, IDO immunosuppression-mediated cancer immunotherapy is considered a novel approach to efficiently stimulate the immune system and fight cancer.

3.6 | Nanomedicine-meditated CAR-T-cell therapy

CAR-T-cell therapy relies on manipulating patient T cells to create personalized cancer immunotherapy. The viral delivery vectors, however, result in serious side effects. The messenger RNA has been developed for inducing transient CAR expression, avoiding the side effects caused by viral vectors. However, electroporation is required for T-cell mRNA delivery, which is also toxic. To overcome these obstacles, Billingsley et al. reported the use of ionizable lipid nanoparticles (LNPs) to deliver in vitro mRNA into human T cells. The multi-functional nanoplatform could induce expression of CAR at levels comparable to electroporation with limited toxicity (Billingsley et al., 2020). Thus,

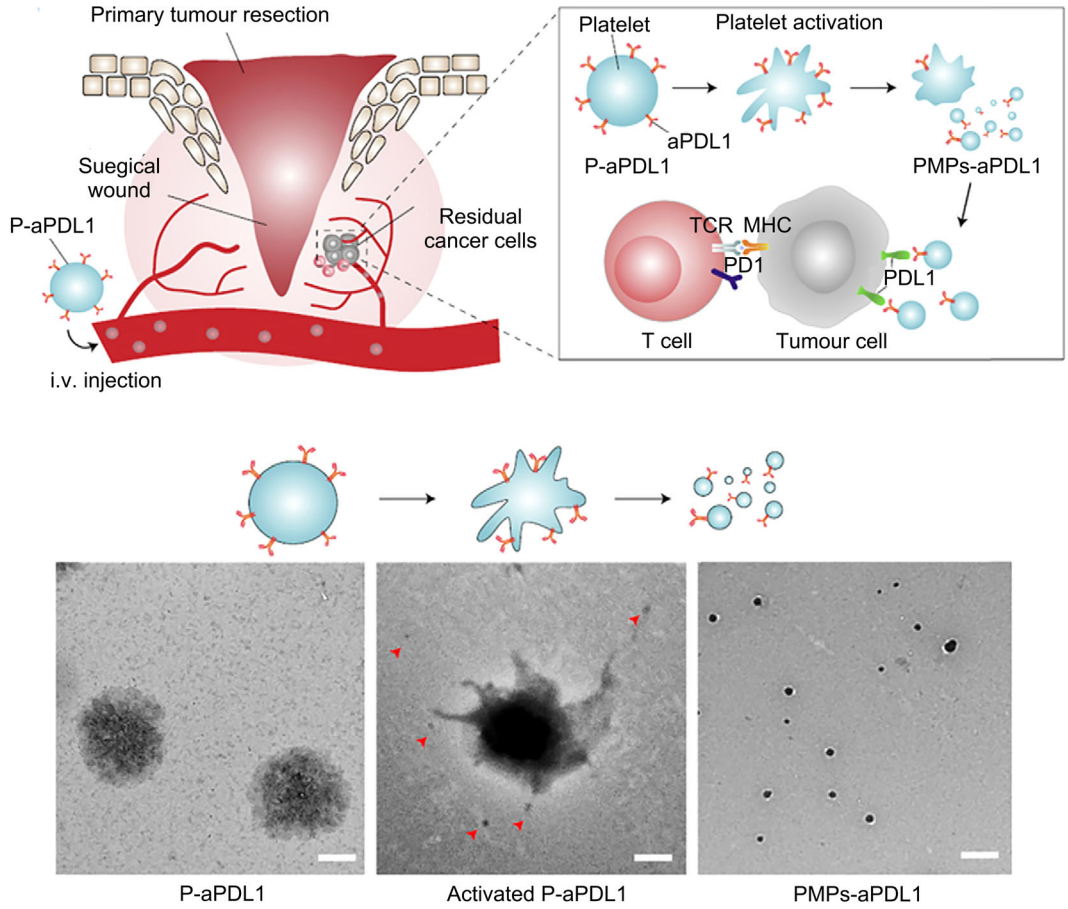


FIGURE 10 Schematic illustration of engineered platelets with PD-1/L1 blockage: Engineered platelet-assisted tumor immunotherapy serving as vehicles for ICI therapy and enhancers for CAR-T-cell therapy. Reproduced with permission from Wang, Li, et al. (2021), Copyright 2021, Elsevier

introducing nanomedicine to prevent the potential toxicity of the CAR-T cells shows significant potential in overcoming the obstacles of CAR-T therapy.

3.7 | NK cells augmented cancer immunotherapy mediated by nanomedicine

NK cells play a significant role in initiating cancer immunotherapy with suppression of the cancer cells metastases. However, the capability of NK cells penetration into the solid tumor is uncertain due to the immune-invasion factors, which influences the antitumor efficiency. Nanomedicine has been developed to boost NK cells functions for cancer immunotherapy (Guillerey, 2020). The strategies could be generalized as (a) immune suppression conversion of TME for the NK cells mediated by nanomedicine, such as delivery of the TGF-β siRNA by liposomes, which successfully downregulate the expression of TGF-β in TME (Xu et al., 2014); (b) enhancement of the NK cells penetration into the solid tumors, for example, the delivery of the dsNKG2D-IL-21 gene to TME by chitosan-based NPs, leading to the increase section of IL-21, and the enhanced penetration of NK cells and T cells (Tan et al., 2017); (c) the nanoengagers are utilized to promote the tumor-NK cells interaction, for example, the reported nanoparticles with Immunoglobulin G (IgG) as the core and phenylbornic acid (PBA) as the shell were utilized for in situ activation of NK cells with enhancement of tumor-infiltrating as boosted by the IgG (Zheng et al., 2019). The above-mentioned strategies significantly improve the NK cells therapy by nanomedicine (Guillerey, 2020). Therefore, the NK cells-based cancer immunotherapy is promising.

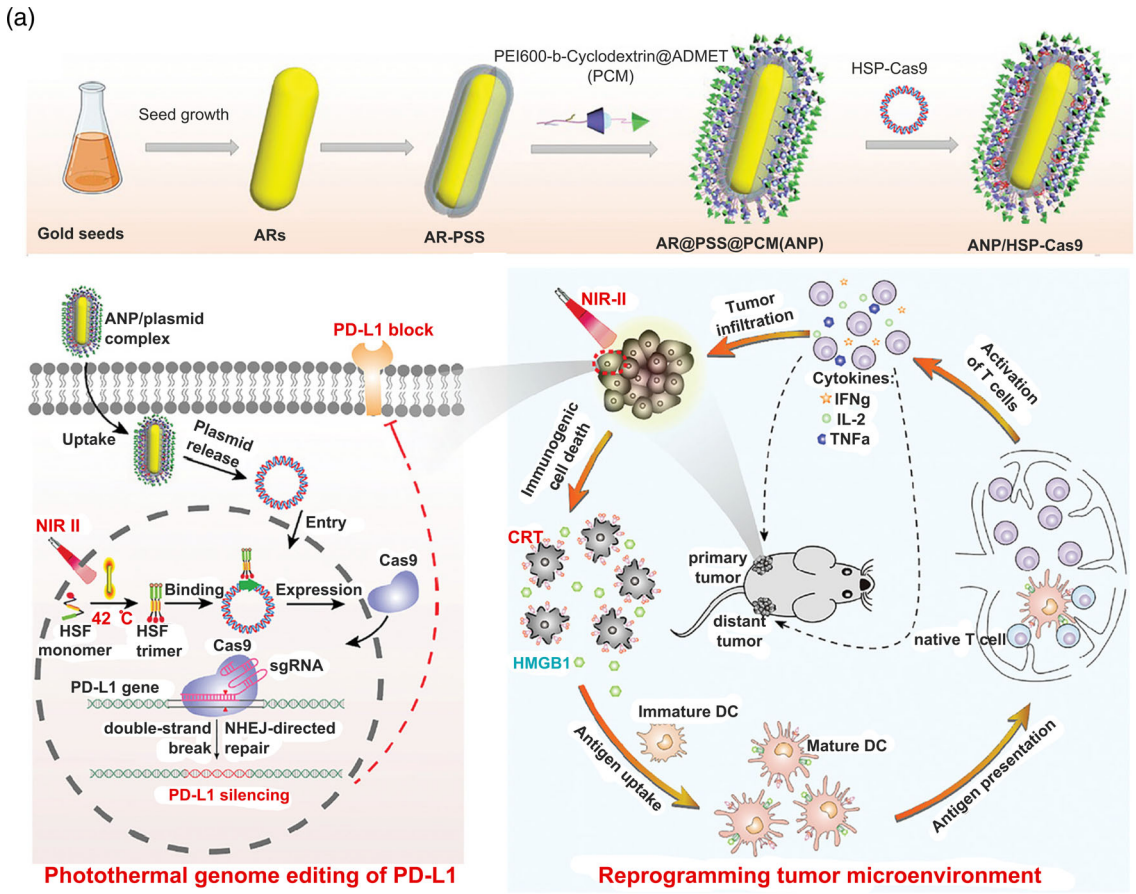


FIGURE 11 (a) Schematic illustration of the photothermal genome-editing strategy to improve ICI therapy by CRISPR/Cas9-mediated disruption of PD-L1 and mild hyperthermia-induced activation of immunogenic cell death (ICD); reproduced with permission from Tang et al. (2021), Copyright 2021, Wiley. (b) Schematic illustration of the engineered immunosuppressive nanoparticles with anti-PD-L1 coating, which shows the potential of managing and reducing irAEs. Reproduced with permission from Shen et al. (2021), Copyright 2021, American Chemical Society

3.8 | mRNA vaccines mediated cancer immunotherapy by nanomedicine

The mRNA vaccines have shown great potential in boosting of robust T cells response in cancer immunotherapy. However, the delivery efficiency of mRNA vaccines has always limited the antitumor efficacy. The strategies utilizing NPs as the carrier can enhance the mRNA delivery efficiency in tumor tissues. For example, a mRNA vaccine NPs was constructed with ovalbumin-coded mRNA and a palmitic acid-modified TLR7/8 agonist R848 (C16-R848) as the core and the lipid-PEG as the shell. The mRNA NPs remarkably improved antitumor efficiency due to the enhanced transfection

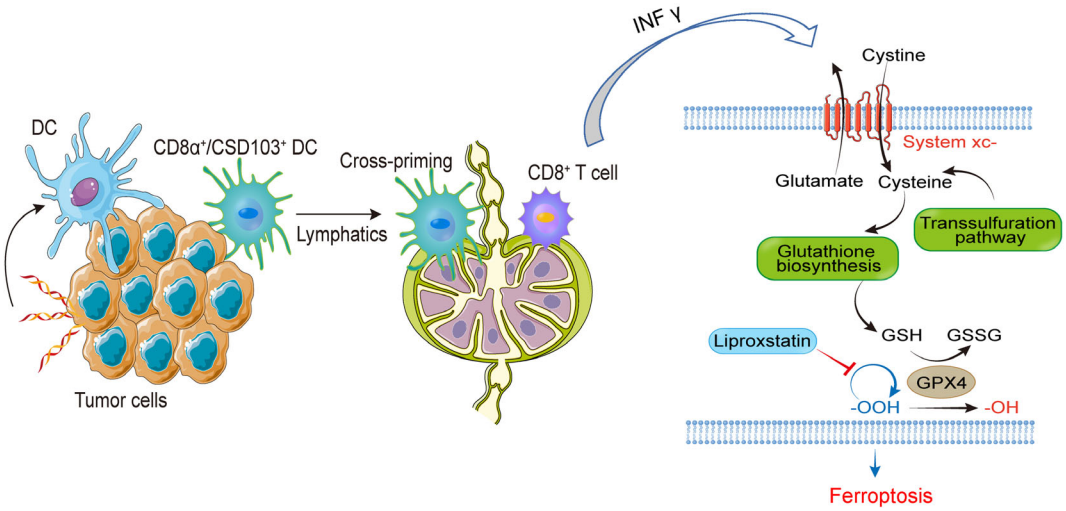


FIGURE 12 Ferroptosis-mediated cancer immunotherapy: Mechanism of ferroptosis induced by ROS and under modulation of GPX4; $CD8^+$ T cells accelerating ferroptosis by INF-γ secretion. This figure is originally created by the authors

efficacy (Islam et al., 2021). Therefore, nanomedicine can be utilized to enhance the efficiency of mRNA vaccines delivery for cancer immunotherapy.

4 | CONCLUSIONS AND FUTURE PROSPECTS

In summary, we summarized the advances in cancer immunotherapy as well as highlighted significant obstacles in the field. The strategies to improve nanomedicine-based cancer immunotherapy have been discussed, including triggering the immune system to kill cancer cells and enhancing nanomedicine-mediated delivery of immune cells at the tumor site. Also, we have discussed other perspectives of nanomedicine-based cancer immunotherapy agents, such as cancer immunotherapy by nanomedicines inducing ferroptosis.

Since the INF-α approval by FDA in 1986, cancer immunotherapy has been widely used in the clinic and focuses on immune system activation to destroy cancer cells. Various cancer immunotherapy agents (e.g., antibodies of PD-1/L1 and CTLA-4) have been developed and marketed and have achieved significant advances in patient survival and solid tumor inhibition.

Moreover, with the rapid development of nanotechnology, strategies for developing nanomedicine-based cancer immunotherapy agents have been promoted. Given the advances in nanomedicine-based cancer immunotherapy, the crossing of the two disciplines is expected to generate tremendous momentum for the improvement of cancer therapies. Nanomedicine-based cancer immunotherapy agents have provided strategies with more traceability, favorable immune response, and reduced toxicity. Additionally, with the rapid development of the imaging technology development, the cancer therapy is realizing visual monitoring by magnetic resonance imaging (MRI), computed tomography (CT), photoacoustic (PA) imaging, and so forth (Gaikwad et al., 2018; Shen, Liu, et al., 2018; Xiao et al., 2023; Yang, Zhou, et al., 2020).

Although cancer immunotherapy agents have been extensively studied and broadly implemented, efficiently boosting immune cells and overcoming therapy resistance caused by the TME appear to be significant challenges hindering the advancement of the immunotherapy approach. Targeting the immune cells in a solid tumor is difficult due to the immunosuppressive TME, compressed vasculature, and dense tissues present in the tumor location, impeding T-cell infiltration. Future research and development of the nanomedicine-based cancer immunotherapy agents should focus on externally or internally triggering the immune system and/or suppressing cancer progression. Numerous cancer immunotherapy agents have been developed in the last decades to solve immune cell activation problems. Examples include nano-based cancer vaccines, nanomedicine with ICD-induced immunotherapy, and ICI synergistic therapeutic agents. The innovative design of nanomedicine-based cancer immunotherapy agents is still in the nascent stage to surmount various obstacles hampering their clinical utility. In this context, problems associated with nanomedicine degradation also need to be. Recently, a growing number of degradable nanomedicines with sensitive TME responses have

been reported, for example, hollow mesoporous organosilica nanoparticles (HMON), a nanocarrier with highly sensitive degradation under high-level GSH at the tumor location. Another example is Fe3O4 nanoparticles, which are commonly used as T1 or T2-weighted contrast agents for magnetic resonance imaging and can be degraded at tumor location due to the low pH (6.5–6.8) of TME.

In the future, additional strategies are expected to enhance nanomedicine-based cancer immunotherapy by triggering immune response and improving immune cell delivery at the tumor site. It would be worthwhile combining cross-interdisciplinary research efforts, including chemistry, oncology, radiology, and material science, to pursue a more rational design of effective nanomedicine-based cancer immunotherapy.

AUTHOR CONTRIBUTIONS

Shuai Guo: Conceptualization (equal); data curation (lead); writing – original draft (lead). **Zongheng Li:** Data curation (supporting); writing – original draft (supporting). **Sugeun Yang:** Conceptualization (equal); writing – review and editing (supporting). **Zheyu Shen:** Conceptualization (lead); writing – review and editing (lead). **Yikai Xu:** Conceptualization (equal); writing – review and editing (equal). **Xiaozhong Qiu:** Conceptualization (supporting); writing – review and editing (equal). **Jie Feng:** Data curation (equal); writing – original draft (equal).

FUNDING INFORMATION

This work was supported in part by the Guangdong Provincial Natural Science Foundation of China (2021A1515010605), the Guangzhou Key Research and Development Program of China (202103000094), and the Zhejiang Provincial Natural Science Foundation of China (LR19E030001).

CONFLICT OF INTEREST

The authors declare no competing financial interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Zheyu Shen https://orcid.org/0000-0002-0350-375X

RELATED WIREs ARTICLE

Applications of molecular engineering in T-cell-based immunotherapies

FURTHER READING

Nishikawa, H., & Sakaguchi, S. (2014). Regulatory T cells in cancer immunotherapy. *Current Opinion in Immunology*, *27*, 1–7. https://doi.org/10.1016/j.coi.2013.12.005

REFERENCES

Abastado, J. P. (2012). The next challenge in cancer immunotherapy: Controlling T-cell traffic to the tumor. *Cancer Research*, *72*(9), 2159–2161. https://doi.org/10.1158/0008-5472.Can-11-3538

Ahmed, S., & Rai, K. R. (2003). Interferon in the treatment of hairy-cell leukemia. *Best Practice & Research Clinical Haematology*, *16*(1), 69–81. https://doi.org/10.1016/s1521-6926(02)00084-1

Baxevanis, C. N., Perez, S. A., & Papamichail, M. (2009). Cancer immunotherapy. *Critical Reviews in Clinical Laboratory Science*, *46*(4), 167–189. https://doi.org/10.1080/10408360902937809

Becker, P. S., Suck, G., Nowakowska, P., Ullrich, E., Seifried, E., Bader, P., Tonn, T., & Seidl, C. (2016). Selection and expansion of natural killer cells for NK cell-based immunotherapy. *Cancer Immunology, Immunotherapy*, *65*(4), 477–484. https://doi.org/10.1007/s00262-016-1792-y

Berraondo, P., Sanmamed, M. F., Ochoa, M. C., Etxeberria, I., Aznar, M. A., Pérez-Gracia, J. L., Rodríguez-Ruiz, M. E., Ponz-Sarvise, M., Castañón, E., & Melero, I. (2019). Cytokines in clinical cancer immunotherapy. *British Journal of Cancer*, *120*(1), 6–15. https://doi.org/10.1038/s41416-018-0328-y

Bersuker, K., Hendricks, J. M., Li, Z., Magtanong, L., Ford, B., Tang, P. H., Roberts, M. A., Tong, B., Maimone, T. J., Zoncu, R., Bassik, M. C., Nomura, D. K., Dixon, S. J., & Olzmann, J. A. (2019). The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. *Nature*, *575*(7784), 688–692. https://doi.org/10.1038/s41586-019-1705-2

Billingsley, M. M., Singh, N., Ravikumar, P., Zhang, R., June, C. H., & Mitchell, M. J. (2020). Ionizable lipid nanoparticle-mediated mRNA delivery for human CAR T cell engineering. *Nano Letters*, *20*(3), 1578–1589. https://doi.org/10.1021/acs.nanolett.9b04246

Bockamp, E., Rosigkeit, S., Siegl, D., & Schuppan, D. (2020). Nano-enhanced cancer immunotherapy: Immunology encounters nanotechnology. *Cells*, *9*(9), 2102. https://doi.org/10.3390/cells9092102

Brouillard, A., Deshpande, N., & Kulkarni, A. A. (2021). Engineered multifunctional nano- and biological materials for cancer immunotherapy. *Advanced Healthcare Materials*, *10*(6), e2001680. https://doi.org/10.1002/adhm.202001680

Brudno, J. N., & Kochenderfer, J. N. (2019). Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. *Blood Reviews*, *34*, 45–55. https://doi.org/10.1016/j.blre.2018.11.002

Cassim, S., & Pouyssegur, J. (2019). Tumor microenvironment: a metabolic player that shapes the immune response. *International Journal of Molecular Sciences*, *21*(1), 157. https://doi.org/10.3390/ijms21010157

Cha, J. H., Chan, L. C., Li, C. W., Hsu, J. L., & Hung, M. C. (2019). Mechanisms controlling PD-L1 expression in cancer. *Molecular Cell*, *76*(3), 359–370. https://doi.org/10.1016/j.molcel.2019.09.030

Chang, M., Hou, Z., Wang, M., Li, C., & Lin, J. (2021). Recent advances in hyperthermia therapy-based synergistic immunotherapy. *Advanced Matererials*, *33*(4), e2004788. https://doi.org/10.1002/adma.202004788

Chanier, T., & Chames, P. (2019). Nanobody engineering: Toward next generation immunotherapies and immunoimaging of cancer. *Antibodies*, *8*(1), 13. https://doi.org/10.3390/antib8010013

Chen, D. S., & Mellman, I. (2013). Oncology meets immunology: The cancer-immunity cycle. *Immunity*, *39*(1), 1–10. https://doi.org/10.1016/j.immuni.2013.07.012

Chen, S., Li, J., Li, Q., & Wang, Z. (2016). Bispecific antibodies in cancer immunotherapy. *Human Vaccines & Immunotherapeutics*, *12*(10), 2491–2500. https://doi.org/10.1080/21645515.2016.1187802

Chen, W., Yuan, Y., & Jiang, X. (2020). Antibody and antibody fragments for cancer immunotherapy. *Journal of Controlled Release*, *328*, 395–406. https://doi.org/10.1016/j.jconrel.2020.08.021

Chen, X., Yu, C., Kang, R., Kroemer, G., & Tang, D. (2021). Cellular degradation systems in ferroptosis. *Cell Death and Differentiation*, *28*(4), 1135–1148. https://doi.org/10.1038/s41418-020-00728-1

Cheng, Y. Q., Wang, S. B., Liu, J. H., Jin, L., Liu, Y., Li, C. Y., Su, Y. R., Liu, Y. R., Sang, X., Wan, Q., Liu, C., Yang, L., & Wang, Z. C. (2020). Modifying the tumour microenvironment and reverting tumour cells: New strategies for treating malignant tumours. *Cell Proliferation*, *53*(8), e12865. https://doi.org/10.1111/cpr.12865

Chhabra, N., & Kennedy, J. (2021). A review of cancer immunotherapy toxicity: Immune checkpoint inhibitors. *Journal of Medical Toxicology*, *17*(4), 411–424. https://doi.org/10.1007/s13181-021-00833-8

Chong, G., Zang, J., Han, Y., Su, R., Weeranoppanant, N., Dong, H., & Li, Y. (2020). Bioengineering of nano metal-organic frameworks for cancer immunotherapy. *Nano Research*, *1–16*, 1244–1259. https://doi.org/10.1007/s12274-020-3179-9

Dane, E. L., Belessiotis-Richards, A., Backlund, C., Wang, J., Hidaka, K., Milling, L. E., Bhagchandani, S., Melo, M. B., Wu, S., Li, N., Donahue, N., Ni, K., Ma, L., Okaniwa, M., Stevens, M. M., Alexander-Katz, A., & Irvine, D. J. (2022). STING agonist delivery by tumour-penetrating PEG-lipid nanodiscs primes robust anticancer immunity. *Nature Materials*, *21*(6), 710–720. https://doi.org/10.1038/s41563-022-01251-z

Darvin, P., Toor, S. M., Sasidharan, N. V., & Elkord, E. (2018). Immune checkpoint inhibitors: Recent progress and potential biomarkers. *Experimental & Molecular Medicine*, *50*(12), 1–11. https://doi.org/10.1038/s12276-018-0191-1

Dixon, S. J., Lemberg, K. M., Lamprecht, M. R., Skouta, R., Zaitsev, E. M., Gleason, C. E., Patel, D. N., Bauer, A. J., Cantley, A. M., Yang, W. S., Morrison, B., & Stockwell, B. R. (2012). Ferroptosis: An iron-dependent form of nonapoptotic cell death. *Cell*, *149*(5), 1060–1072. https://doi.org/10.1016/j.cell.2012.03.042

Du, Y., Zhang, R., Yang, J., Liu, S., Zhou, J., Zhao, R., He, F., Zhang, Y., Yang, P., & Lin, J. (2022). A "closed-loop" therapeutic strategy based on mutually reinforced ferroptosis and immunotherapy. *Advanced Functional Materials*, *32*(13), 2111784. https://doi.org/10.1002/adfm.202111784

Feins, S., Kong, W., Williams, E. F., Milone, M. C., & Fraietta, J. A. (2019). An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer. *American Journal of Hematology*, *94*(S1), s3–s9. https://doi.org/10.1002/ajh.25418

Fiedler, K., Lazzaro, S., Lutz, J., Rauch, S., & Heidenreich, R. (2016). mRNA cancer vaccines. *Recent Results in Cancer Research*, *209*, 61–85. https://doi.org/10.1007/978-3-319-42934-2_5

Fu, C., & Jiang, A. (2018). Dendritic cells and CD8 T cell immunity in tumor microenvironment. *Frontiers in Immunology*, *9*, 3059. https://doi.org/10.3389/fimmu.2018.03059

Fu, T., Dai, L. J., Wu, S. Y., Xiao, Y., Ma, D., Jiang, Y. Z., & Shao, Z. M. (2021). Spatial architecture of the immune microenvironment orchestrates tumor immunity and therapeutic response. *Journal of Hematology & Oncology*, *14*(1), 98. https://doi.org/10.1186/s13045-021-01103-4

Funes, S. C., Rios, M., Escobar-Vera, J., & Kalergis, A. M. (2018). Implications of macrophage polarization in autoimmunity. *Immunology*, *154*(2), 186–195. https://doi.org/10.1111/imm.12910

Gaikwad, H. K., Tsvirkun, D., Ben-Nun, Y., Merquiol, E., Popovtzer, R., & Blum, G. (2018). Molecular imaging of cancer using X-ray computed tomography with protease targeted iodinated activity-based probes. *Nano Letters*, *18*(3), 1582–1591. https://doi.org/10.1021/acs.nanolett.7b03813

Guillerey, C. (2020). NK cells in the tumor microenvironment. *Advances in Experimental Medicine and Biology*, *1273*, 69–90. https://doi.org/10.1007/978-3-030-49270-0_4

Han, X., Shen, S., Fan, Q., Chen, G., Archibong, E., Dotti, G., Liu, Z., Gu, Z., & Wang, C. (2019). Red blood cell-derived nanoerythrosome for antigen delivery with enhanced cancer immunotherapy. *Science Advances*, *5*(10), eaaw6870. https://doi.org/10.1126/sciadv.aaw6870

He, L., Ni, Q., Mu, J., Fan, W., Liu, L., Wang, Z., Li, L., Tang, W., Liu, Y., Cheng, Y., Tang, L., Yang, Z., Liu, Y., Zou, J., Yang, W., Jacobson, O., Zhang, F., Huang, P., & Chen, X. (2020). Solvent-assisted self-assembly of a metal–organic framework based biocatalyst for cascade reaction driven photodynamic therapy. *Journal of the American Chemical Society*, *142*(14), 6822–6832. https://doi.org/10.1021/jacs.0c02497

He, Y. J., Liu, X. Y., Xing, L., Wan, X., Chang, X., & Jiang, H. L. (2020). Fenton reaction-independent ferroptosis therapy via glutathione and iron redox couple sequentially triggered lipid peroxide generator. *Biomaterials*, *241*, 119911. https://doi.org/10.1016/j.biomaterials.2020.119911

Hegde, P. S., & Chen, D. S. (2020). Top 10 challenges in cancer immunotherapy. *Immunity*, *52*(1), 17–35. https://doi.org/10.1016/j.immuni.2019.12.011

Helmy, K. Y., Patel, S. A., Nahas, G. R., & Rameshwar, P. (2013). Cancer immunotherapy: Accomplishments to date and future promise. *Therapeutic Delivery*, *4*(10), 1307–1320. https://doi.org/10.4155/tde.13.88

Hoong, B. Y. D., Gan, Y. H., Liu, H., & Chen, E. S. (2020). cGAS-STING pathway in oncogenesis and cancer therapeutics. *Oncotarget*, *11*(30), 2930–2955. https://doi.org/10.18632/oncotarget.27673

Hou, L., Tian, C., Yan, Y., Zhang, L., Zhang, H., & Zhang, Z. (2020). Manganese-based nanoactivator optimizes cancer immunotherapy via enhancing innate immunity. *ACS Nano*, *14*(4), 3927–3940. https://doi.org/10.1021/acsnano.9b06111

Hu, C., He, X., Chen, Y., Yang, X., Qin, L., Lei, T., Zhou, Y., Gong, T., Huang, Y., & Gao, H. (2021). Metformin mediated PD-L1 down-regulation in combination with photodynamic-immunotherapy for treatment of breast cancer. *Advanced Functional Materials*, *31*(11), 2007149. https://doi.org/10.1002/adfm.202007149

Huang, P., Wang, X., Liang, X., Yang, J., Zhang, C., Kong, D., & Wang, W. (2019). Nano-, micro-, and macroscale drug delivery systems for cancer immunotherapy. *Acta Biomaterialia*, *85*, 1–26. https://doi.org/10.1016/j.actbio.2018.12.028

Islam, M. A., Rice, J., Reesor, E., Zope, H., Tao, W., Lim, M., Ding, J., Chen, Y., Aduluso, D., Zetter, B. R., Farokhzad, O. C., & Shi, J. (2021). Adjuvant-pulsed mRNA vaccine nanoparticle for immunoprophylactic and therapeutic tumor suppression in mice. *Biomaterials*, *266*, 120431. https://doi.org/10.1016/j.biomaterials.2020.120431

Jiang, F., Ding, B., Liang, S., Zhao, Y., Cheng, Z., Xing, B., Ma, P., & Lin, J. (2021). Intelligent MoS_2-CuO heterostructures with multiplexed imaging and remarkably enhanced antitumor efficacy via synergetic photothermal therapy/ chemodynamic therapy/ immunotherapy. *Biomaterials*, *268*, 120545. https://doi.org/10.1016/j.biomaterials.2020.120545

Jiang, L., Kon, N., Li, T., Wang, S.-J., Su, T., Hibshoosh, H., Baer, R., & Gu, W. (2015). Ferroptosis as a p53-mediated activity during tumour suppression. *Nature*, *520*(7545), 57–62. https://doi.org/10.1038/nature14344

Jiang, M., Chen, P., Wang, L., Li, W., Chen, B., Liu, Y., Wang, H., Zhao, S., Ye, L., He, Y., & Zhou, C. (2020). cGAS-STING, an important pathway in cancer immunotherapy. *Journal of Hematology & Oncology*, *13*(1), 81. https://doi.org/10.1186/s13045-020-00916-z

Kijanka, M., Dorresteijn, B., Oliveira, S., & van Bergen En Henegouwen, P. M. (2015). Nanobody-based cancer therapy of solid tumors. *Nanomedicine*, *10*(1), 161–174. https://doi.org/10.2217/nnm.14.178

Kim, J. H., Lee, K. J., & Lee, S. W. (2021). Cancer immunotherapy with T-cell targeting cytokines: IL-2 and IL-7. *BMB Reports*, *54*(1), 21–30. https://doi.org/10.5483/BMBRep.2021.54.1.257

Kim, K. S., Kim, D. H., & Kim, D. H. (2021). Recent advances to augment NK cell cancer immunotherapy using nanoparticles. *Pharmaceutics*, *13*(4), 525. https://doi.org/10.3390/pharmaceutics13040525

Knuschke, T., Rotan, O., Bayer, W., Sokolova, V., Hansen, W., Sparwasser, T., Dittmer, U., Epple, M., Buer, J., & Westendorf, A. M. (2016). Combination of nanoparticle-based therapeutic vaccination and transient ablation of regulatory T cells enhances anti-viral immunity during chronic retroviral infection. *Retrovirology*, *13*, 24. https://doi.org/10.1186/s12977-016-0258-9

Knutson, K. L., & Disis, M. L. (2005). Tumor antigen-specific T helper cells in cancer immunity and immunotherapy. *Cancer Immunology, Immunotherapy*, *54*(8), 721–728. https://doi.org/10.1007/s00262-004-0653-2

Kong, N., Zhang, H., Feng, C., Liu, C., Xiao, Y., Zhang, X., Mei, L., Kim, J. S., Tao, W., & Ji, X. (2021). Arsenene-mediated multiple independently targeted reactive oxygen species burst for cancer therapy. *Nature Communications*, *12*(1), 4777. https://doi.org/10.1038/s41467-021-24961-5

Kruger, S., Ilmer, M., Kobold, S., Cadilha, B. L., Endres, S., Ormanns, S., Schuebbe, G., Renz, B. W., D'haese, J. G., Schloesser, H., Heinemann, V., Subklewe, M., Boeck, S., Werner, J., & von Bergwelt-Baildon, M. (2019). Advances in cancer immunotherapy 2019—Latest trends. *Jouranl of Experimental & Clinical Cancer Research*, *38*(1), 268. https://doi.org/10.1186/s13046-019-1266-0

Labanieh, L., Majzner, R. G., & Mackall, C. L. (2018). Programming CAR-T cells to kill cancer. *Nature Biomedical Engineering*, *2*(6), 377–391. https://doi.org/10.1038/s41551-018-0235-9

Lanfermeijer, J., Borghans, J. A. M., & van Baarle, D. (2020). How age and infection history shape the antigen-specific CD8(+) T-cell repertoire: Implications for vaccination strategies in older adults. *Aging Cell*, *19*(11), e13262. https://doi.org/10.1111/acel.13262

Lavacchi, D., Pellegrini, E., Palmieri, V. E., Doni, L., Mela, M. M., Di Maida, F., Amedei, A., Pillozzi, S., Carini, M., & Antonuzzo, L. (2020). Immune checkpoint inhibitors in the treatment of renal cancer: Current state and future perspective. *International Journal of Molecular Sciences*, *21*(13), 4691. https://doi.org/10.3390/ijms21134691

Lees, J. R. (2020). CD8+ T cells: The past and future of immune regulation. *Cellular Immunology*, *357*, 104212. https://doi.org/10.1016/j.cellimm.2020.104212

Li, B., Chan, H. L., & Chen, P. (2019). Immune checkpoint inhibitors: Basics and challenges. *Current Medicinal Chemistry*, *26*(17), 3009–3025. https://doi.org/10.2174/0929867324666170804143706

Li, S., Luo, M., Wang, Z., Feng, Q., Wilhelm, J., Wang, X., Li, W., Wang, J., Cholka, A., Fu, Y. X., Sumer, B. D., Yu, H., & Gao, J. (2021). Prolonged activation of innate immune pathways by a polyvalent STING agonist. *Nature Biomedical Engineering*, *5*(5), 455–466. https://doi.org/10.1038/s41551-020-00675-9

Li, S., Mirlekar, B., Johnson, B. M., Brickey, W. J., Wrobel, J. A., Yang, N., Song, D., Entwistle, S., Tan, X., Deng, M., Cui, Y., Li, W., Vincent, B. G., Gale, M., Jr., Pylayeva-Gupta, Y., & Ting, J. P. (2022). STING-induced regulatory B cells compromise NK function in cancer immunity. *Nature*, *610*(7931), 373–380. https://doi.org/10.1038/s41586-022-05254-3

Li, W., Yang, J., Luo, L., Jiang, M., Qin, B., Yin, H., Zhu, C., Yuan, X., Zhang, J., Luo, Z., Du, Y., Li, Q., Lou, Y., Qiu, Y., & You, J. (2019). Targeting photodynamic and photothermal therapy to the endoplasmic reticulum enhances immunogenic cancer cell death. *Nature Communications*, *10*(1), 3349. https://doi.org/10.1038/s41467-019-11269-8

Li, X., Khorsandi, S., Wang, Y., Santelli, J., Huntoon, K., Nguyen, N., Yang, M., Lee, D., Lu, Y., Gao, R., Kim, B. Y. S., De Gracia Lux, C., Mattrey, R. F., Jiang, W., & Lux, J. (2022). Cancer immunotherapy based on image-guided STING activation by nucleotide nanocomplex-decorated ultrasound microbubbles. *Nature Nanotechnology*, *17*(8), 891–899. https://doi.org/10.1038/s41565-022-01134-z

Li, Z., Cai, H., Li, Z., Ren, L., Ma, X., Zhu, H., Gong, Q., Zhang, H., Gu, Z., & Luo, K. (2023). A tumor cell membrane-coated self-amplified nanosystem as a nanovaccine to boost the therapeutic effect of anti-PD-L1 antibody. *Bioactive Materials*, *21*, 299–312. https://doi.org/10.1016/j.bioactmat.2022.08.028

Li, Z., Lai, X., Fu, S., Ren, L., Cai, H., Zhang, H., Gu, Z., Ma, X., & Luo, K. (2022). Immunogenic cell death activates the tumor immune microenvironment to boost the immunotherapy efficiency. *Advanced Science*, *9*(22), e2201734. https://doi.org/10.1002/advs.202201734

Li, Z., & Rong, L. (2020). Cascade reaction-mediated efficient ferroptosis synergizes with immunomodulation for high-performance cancer therapy. *Biomaterials Science*, *8*(22), 6272–6285. https://doi.org/10.1039/d0bm01168a

Liang, H., Wu, X., Zhao, G., Feng, K., Ni, K., & Sun, X. (2021). Renal clearable ultrasmall single-crystal Fe nanoparticles for highly selective and effective ferroptosis therapy and immunotherapy. *Journal of the American Chemical Society*, *143*(38), 15812–15823. https://doi.org/10.1021/jacs.1c07471

Liu, R., An, Y., Jia, W., Wang, Y., Wu, Y., Zhen, Y., Cao, J., & Gao, H. (2020). Macrophage-mimic shape changeable nanomedicine retained in tumor for multimodal therapy of breast cancer. *Journal of Controlled Release*, *321*, 589–601. https://doi.org/10.1016/j.jconrel.2020.02.043

Liu, T., Liu, W., Zhang, M., Yu, W., Gao, F., Li, C., Wang, S.-B., Feng, J., & Zhang, X.-Z. (2018). Ferrous-supply-regeneration nanoengineering for cancer-cell-specific ferroptosis in combination with imaging-guided photodynamic therapy. *ACS Nano*, *12*(12), 12181–12192. https://doi.org/10.1021/acsnano.8b05860

Liu, Y., Zhen, W., Wang, Y., Song, S., & Zhang, H. (2020). $Na_2S_2O_8$ nanoparticles trigger antitumor immunotherapy through reactive oxygen species storm and surge of tumor osmolarity. *Journal of the American Chemical Society*, *142*(52), 21751–21757. https://doi.org/10.1021/jacs.0c09482

Long, L., Zhao, C., Ozarina, M., Zhao, X., Yang, J., & Chen, H. (2019). Targeting immune checkpoints in lung cancer: Current landscape and future prospects. *Clinical Drug Investigation*, *39*(4), 341–353. https://doi.org/10.1007/s40261-018-00746-5

Luo, M., Wang, H., Wang, Z., Cai, H., Lu, Z., Li, Y., Du, M., Huang, G., Wang, C., Chen, X., Porembka, M. R., Lea, J., Frankel, A. E., Fu, Y.-X., Chen, Z. J., & Gao, J. (2017). A STING-activating nanovaccine for cancer immunotherapy. *Nature Nanotechnology*, *12*(7), 648–654. https://doi.org/10.1038/nnano.2017.52

Mao, C., Liu, X., Zhang, Y., Lei, G., Yan, Y., Lee, H., Koppula, P., Wu, S., Zhuang, L., Fang, B., Poyurovsky, M. V., Olszewski, K., & Gan, B. (2021). DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer. *Nature*, *593*(7860), 586–590. https://doi.org/10.1038/s41586-021-03539-7

Martin, J. D., Cabral, H., Stylianopoulos, T., & Jain, R. K. (2020). Improving cancer immunotherapy using nanomedicines: Progress, opportunities and challenges. *Nature Reviews. Clinical Oncology*, *17*(4), 251–266. https://doi.org/10.1038/s41571-019-0308-z

Matosevic, S. (2018). Viral and nonviral engineering of natural killer cells as emerging adoptive cancer immunotherapies. *Journal of Immunology Research*, *2018*, 4054815. https://doi.org/10.1155/2018/4054815

Mei, K. C., Liao, Y. P., Jiang, J., Chiang, M., Khazaieli, M., Liu, X., Wang, X., Liu, Q., Chang, C. H., Zhang, X., Li, J., Ji, Y., Melano, B., Telesca, D., Xia, T., Meng, H., & Nel, A. E. (2020). Liposomal delivery of mitoxantrone and a cholesteryl indoximod prodrug provides effective chemo-immunotherapy in multiple solid tumors. *ACS Nano*, *14*(10), 13343–13366. https://doi.org/10.1021/acsnano.0c05194

Mi, Y., Hagan, C. T. T., Vincent, B. G., & Wang, A. Z. (2019). Emerging nano-/microapproaches for cancer immunotherapy. *Advanced Science*, *6*(6), 1801847. https://doi.org/10.1002/advs.201801847

Mikelez-Alonso, I., Aires, A., & Cortajarena, A. L. (2020). Cancer nano-immunotherapy from the injection to the target: The role of protein corona. *International Journal of Molecular Sciences*, *21*(2), 519. https://doi.org/10.3390/ijms21020519

Mikelez-Alonso, I., Magadán, S., González-Fernández, Á., & Borrego, F. (2021). Natural killer (NK) cell-based immunotherapies and the many faces of NK cell memory: A look into how nanoparticles enhance NK cell activity. *Advanced Drug Delivery Reviews*, *176*, 113860. https://doi.org/10.1016/j.addr.2021.113860

Miotto, G., Rossetto, M., Di Paolo, M. L., Orian, L., Venerando, R., Roveri, A., Vučković, A. M., Bosello, T. V., Zaccarin, M., Zennaro, L., Maiorino, M., Toppo, S., Ursini, F., & Cozza, G. (2020). Insight into the mechanism of ferroptosis inhibition by ferrostatin-1. *Redox Biology*, *28*, 101328. https://doi.org/10.1016/j.redox.2019.101328

Nakamura, T., & Harashima, H. (2017). Integration of nano drug-delivery system with cancer immunotherapy. *Therapeutic Delivery*, *8*(11), 987–1000. https://doi.org/10.4155/tde-2017-0071

Nguyen, K. G., Vrabel, M. R., Mantooth, S. M., Hopkins, J. J., Wagner, E. S., Gabaldon, T. A., & Zaharoff, D. A. (2020). Localized interleukin-12 for cancer immunotherapy. *Frontiers in Immunology*, *11*, 575597. https://doi.org/10.3389/fimmu.2020.575597

Ni, K., Aung, T., Li, S., Fatuzzo, N., Liang, X., & Lin, W. (2019). Nanoscale metal-organic framework mediates radical therapy to enhance cancer immunotherapy. *Chem*, *5*(7), 1892–1913. https://doi.org/10.1016/j.chempr.2019.05.013

Osipov, A., Murphy, A., & Zheng, L. (2019). *Advances in cancer research* (pp. 63–144). Academic Press.

Pan, Y., Yu, Y., Wang, X., & Zhang, T. (2020). Tumor-associated macrophages in tumor immunity. *Frontiers in Immunology*, *11*, 583084. https://doi.org/10.3389/fimmu.2020.583084

Pardi, N., Hogan, M. J., Porter, F. W., & Weissman, D. (2018). mRNA vaccines - a new era in vaccinology. *Nature Reviews Drug Discovery*, *17*(4), 261–279. https://doi.org/10.1038/nrd.2017.243

Pérez-Ruiz, E., Melero, I., Kopecka, J., Sarmento-Ribeiro, A. B., García-Aranda, M., & de Las, R. J. (2020). Cancer immunotherapy resistance based on immune checkpoints inhibitors: Targets, biomarkers, and remedies. *Drug Resistance Updates*, *53*, 100718. https://doi.org/10.1016/j.drup.2020.100718

Phung, C. D., Tran, T. H., & Kim, J. O. (2020). Engineered nanoparticles to enhance natural killer cell activity towards onco-immunotherapy: a review. *Archives of Pharmacal Research*, *43*(1), 32–45. https://doi.org/10.1007/s12272-020-01218-1

Riley, R. S., June, C. H., Langer, R., & Mitchell, M. J. (2019). Delivery technologies for cancer immunotherapy. *Nature Reviews Drug Discovery*, *18*(3), 175–196. https://doi.org/10.1038/s41573-018-0006-z

Rojas-Sepúlveda, D., Tittarelli, A., Gleisner, M. A., Ávalos, I., Pereda, C., Gallegos, I., González, F. E., López, M. N., Butte, J. M., Roa, J. C., Fluxá, P., & Salazar-Onfray, F. (2018). Tumor lysate-based vaccines: On the road to immunotherapy for gallbladder cancer. *Cancer Immunology, Immunotherapy*, *67*(12), 1897–1910. https://doi.org/10.1007/s00262-018-2157-5

Sabado, R. L., Balan, S., & Bhardwaj, N. (2017). Dendritic cell-based immunotherapy. *Cell Research*, *27*(1), 74–95. https://doi.org/10.1038/cr.2016.157

Sahin, U., Oehm, P., Derhovanessian, E., Jabulowsky, R. A., Vormehr, M., Gold, M., Maurus, D., Schwarck-Kokarakis, D., Kuhn, A. N., Omokoko, T., Kranz, L. M., Diken, M., Kreiter, S., Haas, H., Attig, S., Rae, R., Cuk, K., Kemmer-Brück, A., Breitkreuz, A., ... Türeci, Ö. (2020). An RNA vaccine drives immunity in checkpoint-inhibitor-treated melanoma. *Nature*, *585*(7823), 107–112. https://doi.org/10.1038/s41586-020-2537-9

Santos, P. M., & Butterfield, L. H. (2018). Dendritic cell-based cancer vaccines. *The Journal of Immunology*, *200*(2), 443–449. https://doi.org/10.4049/jimmunol.1701024

Sau, S., Alsaab, H. O., Bhise, K., Alzhrani, R., Nabil, G., & Iyer, A. K. (2018). Multifunctional nanoparticles for cancer immunotherapy: A groundbreaking approach for reprogramming malfunctioned tumor environment. *Journal of Controlled Release*, *274*, 24–34. https://doi.org/10.1016/j.jconrel.2018.01.028

Schubert, M. L., Schmitt, M., Wang, L., Ramos, C. A., Jordan, K., Müller-Tidow, C., & Dreger, P. (2021). Side-effect management of chimeric antigen receptor (CAR) T-cell therapy. *Annals of Oncology*, *32*(1), 34–48. https://doi.org/10.1016/j.annonc.2020.10.478

Schumacher, T. N., & Schreiber, R. D. (2015). Neoantigens in cancer immunotherapy. *Science*, *348*(6230), 69–74. https://doi.org/10.1126/science.aaa4971

Shae, D., Baljon, J. J., Wehbe, M., Christov, P. P., Becker, K. W., Kumar, A., Suryadevara, N., Carson, C. S., Palmer, C. R., Knight, F. C., Joyce, S., & Wilson, J. T. (2020). Co-delivery of peptide neoantigens and stimulator of interferon genes agonists enhances response to cancer vaccines. *ACS Nano*, *14*(8), 9904–9916. https://doi.org/10.1021/acsnano.0c02765

Shahrivarkevishahi, A., Luzuriaga, M. A., Herbert, F. C., Tumac, A. C., Brohlin, O. R., Wijesundara, Y. H., Adlooru, A. V., Benjamin, C., Lee, H., Parsamian, P., Gadhvi, J., de Nisco, N. J., & Gassensmith, J. J. (2021). PhotothermalPhage: a virus-based photothermal therapeutic agent. *Journal of the American Chemical Society*, *143*, 16428–16438. https://doi.org/10.1021/jacs.1c05090

Shao, K., Singha, S., Clemente-Casares, X., Tsai, S., Yang, Y., & Santamaria, P. (2015). Nanoparticle-based immunotherapy for cancer. *ACS Nano*, *9*(1), 16–30. https://doi.org/10.1021/nn5062029

Sharma, P., Hu-Lieskovan, S., Wargo, J. A., & Ribas, A. (2017). Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell*, *168*(4), 707–723. https://doi.org/10.1016/j.cell.2017.01.017

Shen, S., Dai, H., Fei, Z., Chai, Y., Hao, Y., Fan, Q., Dong, Z., Zhu, Y., Xu, J., Ma, Q., Han, X., Xu, L., Peng, F., Liu, Z., & Wang, C. (2021). Immunosuppressive nanoparticles for management of immune-related adverse events in liver. *ACS Nano*, *15*(5), 9111–9125. https://doi.org/10.1021/acsnano.1c02391

Shen, Z., Liu, T., Li, Y., Lau, J., Yang, Z., Fan, W., Zhou, Z., Shi, C., Ke, C., Bregadze, V. I., Mandal, S. K., Liu, Y., Li, Z., Xue, T., Zhu, G., Munasinghe, J., Niu, G., Wu, A., & Chen, X. (2018). Fenton-reaction-acceleratable magnetic nanoparticles for ferroptosis therapy of orthotopic brain tumors. *ACS Nano*, *12*(11), 11355–11365. https://doi.org/10.1021/acsnano.8b06201

Shen, Z., Song, J., Zhou, Z., Yung, B. C., Aronova, M. A., Li, Y., Dai, Y., Fan, W., Liu, Y., Li, Z., Ruan, H., Leapman, R. D., Lin, L., Niu, G., Chen, X., & Wu, A. (2018). Dotted core–shell nanoparticles for T1-weighted MRI of tumors. *Advanced Materials*, *30*(33), 1803163. https://doi.org/10.1002/adma.201803163

Showalter, A., Limaye, A., Oyer, J. L., Igarashi, R., Kittipatarin, C., Copik, A. J., & Khaled, A. R. (2017). Cytokines in immunogenic cell death: Applications for cancer immunotherapy. *Cytokine*, *97*, 123–132. https://doi.org/10.1016/j.cyto.2017.05.024

Signore, A., Chianelli, M., Bei, R., Oyen, W., & Modesti, A. (2003). Targeting cytokine/chemokine receptors: a challenge for molecular nuclear medicine. *European Journal of Nuclear Medicine and Molecular Imaging*, *30*(1), 149–156. https://doi.org/10.1007/s00259-002-0941-z

Singh, A. K., & Mcguirk, J. P. (2020). CAR T cells: Continuation in a revolution of immunotherapy. *Lancet Oncology*, *21*(3), e168–e178. https://doi.org/10.1016/s1470-2045(19)30823-x

Sun, C., Mezzadra, R., & Schumacher, T. N. (2018). Regulation and function of the PD-L1 checkpoint. *Immunity*, *48*(3), 434–452. https://doi.org/10.1016/j.immuni.2018.03.014

Tagliamonte, M., Petrizzo, A., Tornesello, M. L., Buonaguro, F. M., & Buonaguro, L. (2014). Antigen-specific vaccines for cancer treatment. *Human Vaccines & Immunotherapeutics*, *10*(11), 3332–3346. https://doi.org/10.4161/21645515.2014.973317

Tan, C., Hu, W., He, Y., Zhang, Y., Zhang, G., Xu, Y., & Tang, J. (2018). Cytokine-mediated therapeutic resistance in breast cancer. *Cytokine*, *108*, 151–159. https://doi.org/10.1016/j.cyto.2018.03.020

Tan, L., Han, S., Ding, S., Xiao, W., Ding, Y., Qian, L., Wang, C., & Gong, W. (2017). Chitosan nanoparticle-based delivery of fused NKG2D-IL-21 gene suppresses colon cancer growth in mice. *International Journal of Nanomedicine*, *12*, 3095–3107. https://doi.org/10.2147/ijn.S128032

Tang, H., Xu, X., Chen, Y., Xin, H., Wan, T., Li, B., Pan, H., Li, D., & Ping, Y. (2021). Reprogramming the tumor microenvironment through second-near-infrared-window photothermal genome editing of PD-L1 mediated by supramolecular gold nanorods for enhanced cancer immunotherapy. *Advanced Matererials*, *33*(12), e2006003. https://doi.org/10.1002/adma.202006003

Teng, M. W., Galon, J., Fridman, W. H., & Smyth, M. J. (2015). From mice to humans: Developments in cancer immunoediting. *Journal of Clinical Investigation*, *125*(9), 3338–3346. https://doi.org/10.1172/jci80004

Thomas, R., Al-Khadairi, G., Roelands, J., Hendrickx, W., Dermime, S., Bedognetti, D., & Decock, J. (2018). NY-ESO-1 based immunotherapy of cancer: Current perspectives. *Frontiers in Immunology*, *9*, 947. https://doi.org/10.3389/fimmu.2018.00947

Thommen, D. S., & Schumacher, T. N. (2018). T cell dysfunction in cancer. *Cancer Cell*, *33*(4), 547–562. https://doi.org/10.1016/j.ccell.2018.03.012

Valipour, B., Velaei, K., Abedelahi, A., Karimipour, M., Darabi, M., & Charoudeh, H. N. (2019). NK cells: An attractive candidate for cancer therapy. *Journal of Cellular Physiology*, *234*(11), 19352–19365. https://doi.org/10.1002/jcp.28657

van den Bulk, J., Verdegaal, E. M., & De Miranda, N. F. (2018). Cancer immunotherapy: Broadening the scope of targetable tumours. *Open Biology*, *8*(6), 180037. https://doi.org/10.1098/rsob.180037

Waldman, A. D., Fritz, J. M., & Lenardo, M. J. (2020). A guide to cancer immunotherapy: From T cell basic science to clinical practice. *Nature Reviews Immunology*, *20*(11), 651–668. https://doi.org/10.1038/s41577-020-0306-5

Wang, C., Ma, C., Gong, L., Guo, Y., Fu, K., Zhang, Y., Zhou, H., & Li, Y. (2021). Macrophage polarization and its role in liver disease. *Frontiers in Immunology*, *12*, 803037. https://doi.org/10.3389/fimmu.2021.803037

Wang, C., Zhang, R., Wei, X., Lv, M., & Jiang, Z. (2020). Metalloimmunology: The metal ion-controlled immunity. *Advances in Immunology*, *145*(145), 187–241. https://doi.org/10.1016/bs.ai.2019.11.007

Wang, K., Zhang, Y., Mao, W., Feng, W., Lu, S., Wan, J., Song, X., Chen, Y., & Peng, B. (2022). Engineering ultrasmall ferroptosis-targeting and reactive oxygen/nitrogen species-scavenging nanozyme for alleviating acute kidney injury. *Advanced Functional Materials*, *32*(10), 2109221. https://doi.org/10.1002/adfm.202109221

Wang, Q., Bergholz, J. S., Ding, L., Lin, Z., Kabraji, S. K., Hughes, M. E., He, X., Xie, S., Jiang, T., Wang, W., Zoeller, J. J., Kim, H. J., Roberts, T. M., Konstantinopoulos, P. A., Matulonis, U. A., Dillon, D. A., Winer, E. P., Lin, N. U., & Zhao, J. J. (2022). STING agonism reprograms tumor-associated macrophages and overcomes resistance to PARP inhibition in BRCA1-deficient models of breast cancer. *Nature Communications*, *13*(1), 3022. https://doi.org/10.1038/s41467-022-30568-1

Wang, T., Xu, X., & Zhang, K. (2021). Nanotechnology-enabled chemodynamic & immunotherapy. *Current Cancer Drug Targets*, *21*, 545–557. https://doi.org/10.2174/1568009621666210219101552

Wang, W., Green, M., Choi, J. E., Gijón, M., Kennedy, P. D., Johnson, J. K., Liao, P., Lang, X., Kryczek, I., Sell, A., Xia, H., Zhou, J., Li, G., Li, J., Li, W., Wei, S., Vatan, L., Zhang, H., Szeliga, W., ... Zou, W. (2019). CD8 + T cells regulate tumour ferroptosis during cancer immunotherapy. *Nature*, *569*(7755), 270–274. https://doi.org/10.1038/s41586-019-1170-y

Wang, Y., Li, Z., Mo, F., Gu, Z., & Hu, Q. (2021). Engineered platelets: Advocates for tumor immunotherapy. *Nano Today*, *40*, 101281. https://doi.org/10.1016/j.nantod.2021.101281

Willsmore, Z. N., Coumbe, B. G. T., Crescioli, S., Reci, S., Gupta, A., Harris, R. J., Chenoweth, A., Chauhan, J., Bax, H. J., Mccraw, A., Cheung, A., Osborn, G., Hoffmann, R. M., Nakamura, M., Laddach, R., Geh, J. L. C., Mackenzie-Ross, A., Healy, C., Tsoka, S., ... Karagiannis, S. N. (2021). Combined anti-PD-1 and anti-CTLA-4 checkpoint blockade: Treatment of melanoma and immune mechanisms of action. *European Journal of Immunology*, *51*(3), 544–556. https://doi.org/10.1002/eji.202048747

Xiao, X., Cai, H., Huang, Q., Wang, B., Wang, X., Luo, Q., Li, Y., Zhang, H., Gong, Q., Ma, X., Gu, Z., & Luo, K. (2023). Polymeric dual-modal imaging nanoprobe with two-photon aggregation-induced emission for fluorescence imaging and gadolinium-chelation for magnetic resonance imaging. *Bioactive Materials*, *19*, 538–549. https://doi.org/10.1016/j.bioactmat.2022.04.026

Xu, H., Ye, D., Ren, M., Zhang, H., & Bi, F. (2021). Ferroptosis in the tumor microenvironment: Perspectives for immunotherapy. *Trends in Molecular Medicine*, *27*(9), 856–867. https://doi.org/10.1016/j.molmed.2021.06.014

Xu, Z., Wang, Y., Zhang, L., & Huang, L. (2014). Nanoparticle-delivered transforming growth factor-β siRNA enhances vaccination against advanced melanoma by modifying tumor microenvironment. *ACS Nano*, *8*(4), 3636–3645. https://doi.org/10.1021/nn500216y

Yang, B., Jeang, J., Yang, A., Wu, T. C., & Hung, C. F. (2014). DNA vaccine for cancer immunotherapy. *Human Vaccines & Immunotherapeutics*, *10*(11), 3153–3164. https://doi.org/10.4161/21645515.2014.980686

Yang, C., Li, Y., Yang, Y., & Chen, Z. (2020). Overview of strategies to improve therapy against tumors using natural killer cell. *Journal of Immunology Research*, *2020*, 8459496. https://doi.org/10.1155/2020/8459496

Yang, W., Zhang, F., Deng, H., Lin, L., Wang, S., Kang, F., Yu, G., Lau, J., Tian, R., Zhang, M., Wang, Z., He, L., Ma, Y., Niu, G., Hu, S., & Chen, X. (2020). Smart nanovesicle-mediated immunogenic cell death through tumor microenvironment modulation for effective photodynamic immunotherapy. *ACS Nano*, *14*(1), 620–631. https://doi.org/10.1021/acsnano.9b07212

Yang, W. S., & Stockwell, B. R. (2016). Ferroptosis: Death by lipid peroxidation. *Trends in Cell Biology*, *26*(3), 165–176. https://doi.org/10.1016/j.tcb.2015.10.014

Yang, Y. (2015). Cancer immunotherapy: Harnessing the immune system to battle cancer. *Journal of Clinical Investigation*, *125*(9), 3335–3337. https://doi.org/10.1172/jci83871

Yang, Y., Zhou, D., Zhang, Y., Zhang, C., Tang, S., Guo, Y., Ma, F., Yang, H., & Xiong, L. (2020). NIR/photoacoustic imaging of multitype gallbladder cancer using carboxyl/amino functionalized polymer dots. *Biomaterials Science*, *8*(23), 6657–6669. https://doi.org/10.1039/d0bm01451f

Yu, S., Yi, M., Qin, S., & Wu, K. (2019). Next generation chimeric antigen receptor T cells: Safety strategies to overcome toxicity. *Molecular Cancer*, *18*(1), 125. https://doi.org/10.1186/s12943-019-1057-4

Zhai, L., Bell, A., Ladomersky, E., Lauing, K. L., Bollu, L., Sosman, J. A., Zhang, B., Wu, J. D., Miller, S. D., Meeks, J. J., Lukas, R. V., Wyatt, E., Doglio, L., Schiltz, G. E., Mccusker, R. H., & Wainwright, D. A. (2020). Immunosuppressive IDO in cancer: Mechanisms of action, animal models, and targeting strategies. *Frontiers in Immunology*, *11*, 1185. https://doi.org/10.3389/fimmu.2020.01185

Zhang, Q., & Li, L. (2018). Photodynamic combinational therapy in cancer treatment. *Journal of BUON*, *23*(3), 561–567.

Zhang, W., Wang, F., Hu, C., Zhou, Y., Gao, H., & Hu, J. (2020). The progress and perspective of nanoparticle-enabled tumor metastasis treatment. *Acta Pharmaceutica Sinica B*, *10*(11), 2037–2053. https://doi.org/10.1016/j.apsb.2020.07.013

Zhang, W., Zhang, C. C., Wang, X. Y., Li, L., Chen, Q. Q., Liu, W. W., Cao, Y., & Ran, H. T. (2020). Light-responsive core-shell nanoplatform for bimodal imaging-guided photothermal therapy-primed cancer immunotherapy. *ACS Applied Materials & Interfaces*, *12*(43), 48420–48431. https://doi.org/10.1021/acsami.0c16526

Zhao, J., Ma, S., Xu, Y., Si, X., Yao, H., Huang, Z., Zhang, Y., Yu, H., Tang, Z., Song, W., & Chen, X. (2021). In situ activation of STING pathway with polymeric SN38 for cancer chemoimmunotherapy. *Biomaterials*, *268*, 120542. https://doi.org/10.1016/j.biomaterials.2020.120542

Zheng, C., Wang, Q., Wang, Y., Zhao, X., Gao, K., Liu, Q., Zhao, Y., Zhang, Z., Zheng, Y., Cao, J., Chen, H., Shi, L., Kang, C., Liu, Y., & Lu, Y. (2019). *In situ* modification of the tumor cell surface with immunomodulating nanoparticles for effective suppression of tumor growth in mice. *Advanced Materials*, *31*(32), e1902542. https://doi.org/10.1002/adma.201902542

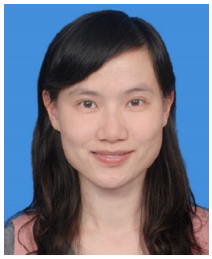
Zhou, F., Wang, M., Luo, T., Qu, J., & Chen, W. R. (2021). Photo-activated chemo-immunotherapy for metastatic cancer using a synergistic graphene nanosystem. *Biomaterials*, *265*, 120421. https://doi.org/10.1016/j.biomaterials.2020.120421

Zhu, Y., Yu, X., Thamphiwatana, S. D., Zheng, Y., & Pang, Z. (2020). Nanomedicines modulating tumor immunosuppressive cells to enhance cancer immunotherapy. *Acta Pharmaceutica Sinica B*, *10*(11), 2054–2074. https://doi.org/10.1016/j.apsb.2020.08.010

Zou, S.-S., Qiao, Y., Zhu, S., Gao, B., Yang, N., Liu, Y.-J., & Chen, J. (2021). Intrinsic strategies for the evasion of cGAS-STING signaling-mediated immune surveillance in human cancer: How therapy can overcome them. *Pharmacological Research*, *166*, 105514. https://doi.org/10.1016/j.phrs.2021.105514

AUTHOR BIOGRAPHIES

Dr Shuai Guo received her MSc from Peking University in 2013 and PhD from Hong Kong Polytechnic University in 2017. Her postdoctoral training is under the supervision of Prof. Ed. X. Wu at the University of Hong Kong (2018–2020) and Prof. Zheyu Shen at Southern Medical University (2020–2022). Her research interests include MRI contrast agents, tumor ferroptosis therapy, and immunotherapy.



Dr. Jie Feng received her Ph.D. from Southern Medical University in 2010 under the supervision of Prof. Yikai Xu. After that, she joined in Medical Imaging Center, Nanfang Hospital, Southern Medical University as an attending doctor. Her research interests include magnetic resonance imaging, contrast agents, and nanobiomaterials.

Mr. Zongheng Li graduated from the Southern Medical University in 2021. Currently, he is a master student at the School of Biomedical Engineering, Southern Medical University under the supervision of Prof. Zheyu Shen. His research is basically focused on tumor ferroptosis therapy, and immunotherapy.

Prof Sugeun Yang received his Ph.D. from the Seoul National University College of Pharmacy (Korea). He joined University of Southwestern Medical Center at Dallas (USA) as a research associate in 2006. He is a professor of Inha University College of Medicine (Korea) since 2012. His lab focuses on drug/gene design and delivery, targeted cancer therapy, and tumor immunotherapy.

Professor Xiaozhong Qiu received his MSc from Sun Yat-Sen University in 1995 and PhD from First Military Medical University (Southern Medical University) in 1998. After that, he joined the Basic Medical School of Southern Medical University as a professor. His lab focuses on biomaterials and tissue engineering.

Prof. Yikai Xu received his master's degree from the First Military Medical University in 1989 and PhD from the Fourth Military Medical University in 1995. He has been working in Medical Imaging Center, Nanfang Hospital, Southern Medical University since 1984. He was appointed as an associate professor in 1994 and promoted to full professor and chief physician in 2000. His research interests include immunoimaging and new contrast agents for magnetic resonance imaging.

Prof. Zheyu Shen received his PhD from the Institute of Process Engineering, Chinese Academy of Sciences, under the supervision of Prof. Guanghui Ma and Prof. Toshiaki Dobashi (Gunma University, Japan). After postdoctoral studies with Prof. Kazuhiro Kohama (Gunma University, Japan) and Prof. Sheng Dai (The University of Adelaide, Australia), he was appointed an Associate Professor (2012) and promoted to Full Professor (2015) at the Ningbo Institute of Materials Technology & Engineering, Chinese Academy of Sciences. After 3 years as visiting scholar at the National Institutes of Health (USA) under the supervision of Prof. Xiaoyuan Chen, he joined Southern Medical University as a full-professor in 2019. His lab focuses on MRI contrast agents, tumor ferroptosis therapy, and immunotherapy.

How to cite this article: Guo, S., Feng, J., Li, Z., Yang, S., Qiu, X., Xu, Y., & Shen, Z. (2023). Improved cancer immunotherapy strategies by nanomedicine. *WIREs Nanomedicine and Nanobiotechnology*, *15*(3), e1873. https://doi.org/10.1002/wnan.1873