

# Drug Delivery Engineering Strategies Targeting CD4<sup>+</sup>/CD8<sup>+</sup> T Cell Exhaustion to Improve the Tumor Immunosuppressive Microenvironment

Jingsi Yue<sup>1-3</sup>, Min Chen<sup>3</sup>, Zuanyu Xiong<sup>4</sup>, Jing Qiu<sup>5</sup>, Yi Liu<sup>6</sup>, Long Chen<sup>1-3</sup>

<sup>1</sup>The Second Affiliated Hospital of Chengdu Medical College, Nuclear Industry 416 Hospital, Chengdu, Sichuan, 610000, People's Republic of China; <sup>2</sup>Non-Coding RNA and Drug Discovery Key Laboratory of Sichuan Province, School of Basic Medical Sciences, Chengdu Medical College, Chengdu, Sichuan, 610550, People's Republic of China; <sup>3</sup>School of Basic Medical Sciences, Chengdu Medical College, Chengdu, Sichuan, 610550, People's Republic of China; <sup>4</sup>Department of Nanbu People's Hospital, Nanchong, Sichuan, 637300, People's Republic of China; <sup>5</sup>Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan, 610500, People's Republic of China; <sup>6</sup>Department of Pidu District People's Hospital and The Third Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan, 611700, People's Republic of China

Correspondence: Long Chen, Email chenlong@cmc.edu.cn

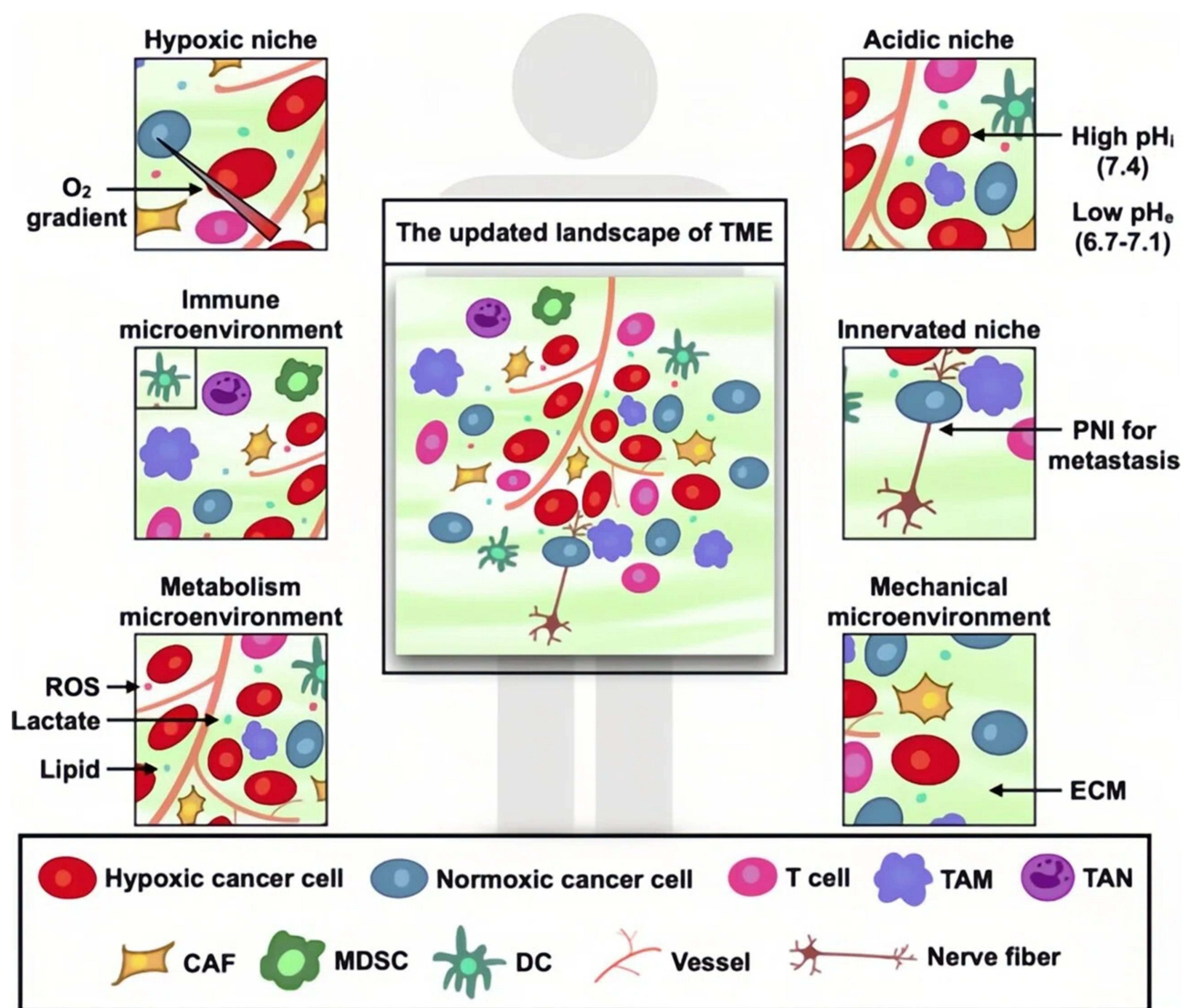
**Abstract:** CD4<sup>+</sup>/CD8<sup>+</sup> T cell exhaustion, characterized by impaired effector function, sustained expression of inhibitory receptors, and diminished proliferative capacity, is a core driver in the formation of the tumor immunosuppressive microenvironment (TME) and a major obstacle to antitumor immunotherapy. Nanomaterial-based drug delivery systems (NDDSs) have emerged as potential tools for targeting exhausted T cells (Tex), leveraging their unique advantages in precise targeting, controlled release, enhanced bioavailability, and reduced off-target toxicity. This article reviews the latest advances in NDDS-mediated delivery strategies targeting CD4<sup>+</sup>/CD8<sup>+</sup> Tex cells, encompassing the delivery of immune checkpoint inhibitors, cytokines, small molecule modulators, and nucleic acid drugs. These strategies aim to reverse Tex cell dysfunction by modulating key molecular pathways involved in T cell exhaustion (like, PD-1/PD-L1, CTLA-4, NF-κB, and STAT signaling pathways), thereby enhancing T cell-mediated antitumor immune responses and remodeling the tumor immunosuppressive microenvironment. Finally, the challenges and prospects of utilizing NDDSs to target T cell exhaustion for tumor immunotherapy are briefly discussed, providing a reference for the development of novel antitumor therapeutic strategies.

**Keywords:** nanomaterials, tumor immunotherapy, T cells, T cell exhaustion, tumor microenvironment

## Introduction

Cancer, a genetic disease arising from somatic mutation accumulation, is increasingly recognized as an evolutionary-ecological process<sup>1</sup> shaped by the multifaceted tumor microenvironment (TME). While past research focused on cancer cells (Figure 1), TME is now understood to be a complex ecosystem encompassing hypoxic, acidic, innervated, metabolic, mechanical, and immune niches, where non-tumor cells (like stromal, immune cells) and non-cellular components (extracellular matrix, signaling molecules, extracellular vesicles) in the TME are critical for tumor progression—supporting key hallmarks like sustained proliferation, angiogenesis, and immune evasion. Notably, only 5–10% of cancers stem from hereditary defects, with 90–95% linked to environmental factors and lifestyle.<sup>2</sup> Targeting the TME offers therapeutic advantages (stable non-tumor cell genomes, lower resistance risk<sup>3</sup> but requires addressing the heterogeneity and plasticity of its distinct niches, laying the foundation for subsequent immunotherapeutic strategies.

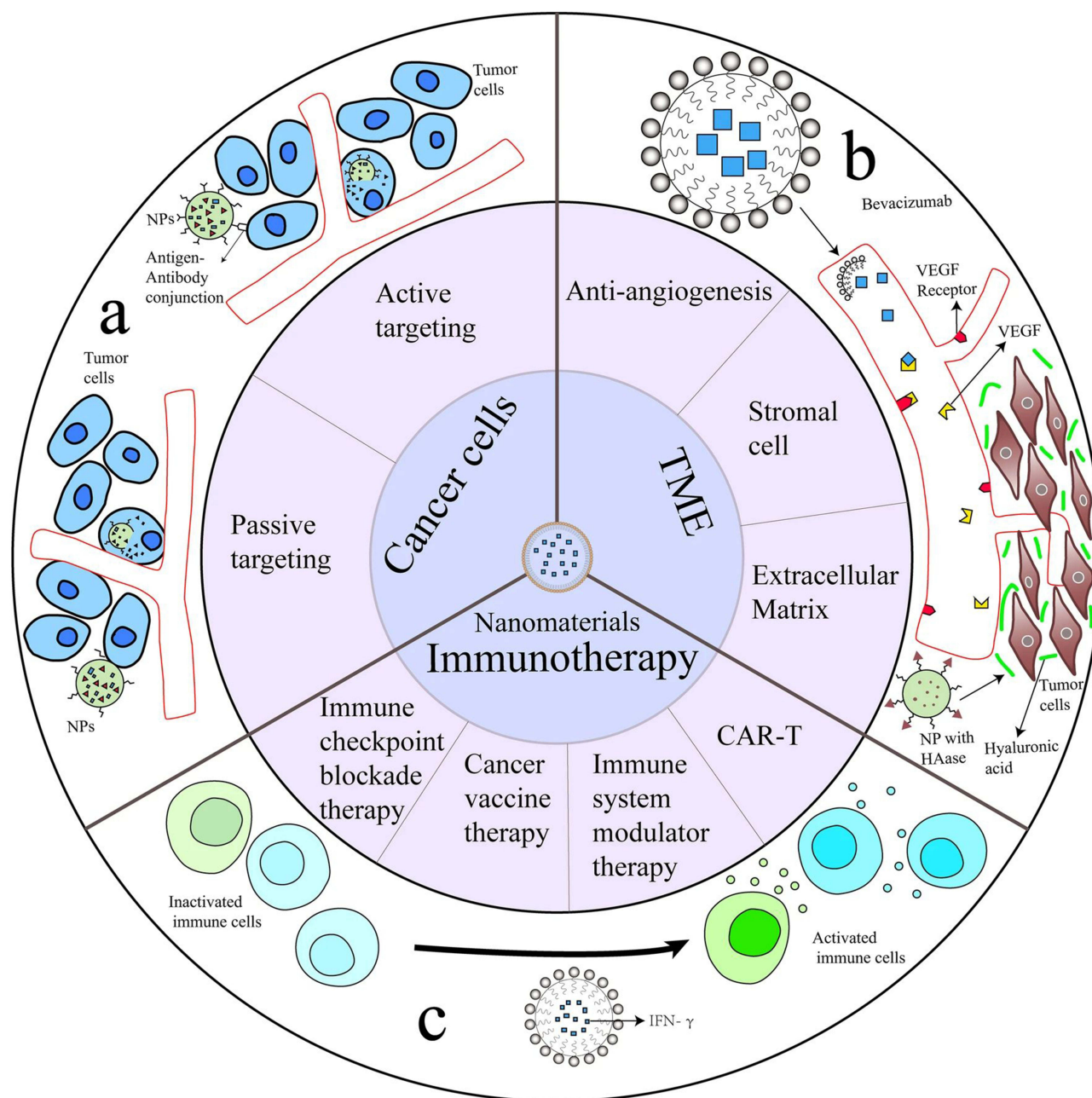
T cell dysfunction, particularly exhaustion, is a major mechanism of TME immune impairment,<sup>5,6</sup> characterized by reduced effector function, high inhibitory receptor expression, and unique transcriptional/epigenetic patterns. Exhausted T cells under chronic TCR stimulation highly express PD-1,<sup>7,8</sup> which has directly driven the development of immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis—<sup>9,10</sup> notably, antibody blockade of this pathway effectively restores CD8<sup>+</sup> T cell cytotoxicity<sup>11–13</sup> and exhibits robust clinical efficacy across multiple cancer types.<sup>14–17</sup> Beyond CD8<sup>+</sup> T cells, CD4<sup>+</sup> T cells (encompassing Th subsets, Tregs) also play key roles: some directly kill tumor cells via MHC-II



**Figure 1** The updated landscape of tumor microenvironment (TME) TME comprises cancer cells, stromal cells, blood vessels, nerve fibers, extracellular matrix, and associated acellular components. TME is home for cancer cells and serves as a bridge connecting cancer with the whole organism. TME can be classified into six specialized microenvironments, namely, hypoxic niche, immune microenvironment, metabolism microenvironment, acidic niche, innervated niche, and mechanical microenvironment.<sup>4</sup> @Copyright©2020.

recognition,<sup>18–21</sup> with adoptive transfer yielding antitumor effects<sup>22</sup> and MHC-II trans-activator overexpression enhancing their interferon- $\gamma$ /granzyme B production.<sup>20,21</sup> However, T cell exhaustion remains a persistent bottleneck in antitumor immunotherapy, attributed to its inherent heterogeneity, irreversible functional decline in advanced stages, and the inability of conventional ICIs to specifically target exhausted T cell subsets and this underscores an urgent need for advanced delivery systems capable of precisely reaching T cells within the TME and amplifying therapeutic outcomes. Nanomaterials with a size range of 1–100 nm serve as the core component of novel drug delivery systems and possess distinctive physicochemical properties such as enhanced conductivity, a high specific surface area, and unique fluorescent characteristics.<sup>23–25</sup> These inherent properties endow such nanomaterials with notable medical applicability, including the ability to facilitate biological barrier penetration, enhance tissue permeability, and enable the controlled release of loaded therapeutic agents. Despite lingering biocompatibility concerns for long-term accumulating types, therapeutic nanomaterials have shown improved safety.<sup>26</sup>

Leveraging passive/active targeting mechanisms (as illustrated in panel a of Figure 2),<sup>27</sup> they enable precise delivery of anticancer agents, thereby enhancing immunotherapy efficacy (like synergizing with ICI effects) and reducing off-



**Figure 2** Cancer treatment approaches based on nanomaterials. (a) Targeting cancer cells by passive targeting or active targeting. (b) Targeting TME including anti-angiogenesis, stromal cell and extracellular matrix. Bevacizumab was loaded in liposome and conjugated with VEGF to inhibit angiogenesis. HAase was modified onto NP surface and enhanced NP penetration ability. (c) IFN- $\gamma$  as an immune modulator delivered by liposomes activated immune cells in cancer immunotherapy.<sup>29</sup> @Copyright©2021.

**Abbreviations:** HAase, hyaluronidase; IFN- $\gamma$ , Cytokine Interferon gamma; NP, nanoparticle; TME, tumor microenvironment; VEGF, vascular endothelial growth factor.

target toxicity.<sup>28</sup> Beyond direct cancer cell targeting these nanomaterials also exert critical effects on the tumor microenvironment(TME), they can mediate anti-angiogenesis (eg., by delivering bevacizumab to block VEGF signaling, as shown in panel b), remodel the extracellular matrix (ECM), and modulate stromal cell function. Additionally, nanomaterials can reactivate inactivated immune cells (as depicted in panel c), such as by delivering IFN- $\gamma$  to promote the transition from immunosuppressive to pro-inflammatory immune states, thus emerging as a promising tool to address the challenges of TME and T cell-based cancer therapies (Figure 2).

## Molecular Mechanisms and Regulatory Networks of T Cell Exhaustion

### Core Biochemical Regulatory Pathways of Tex Cells

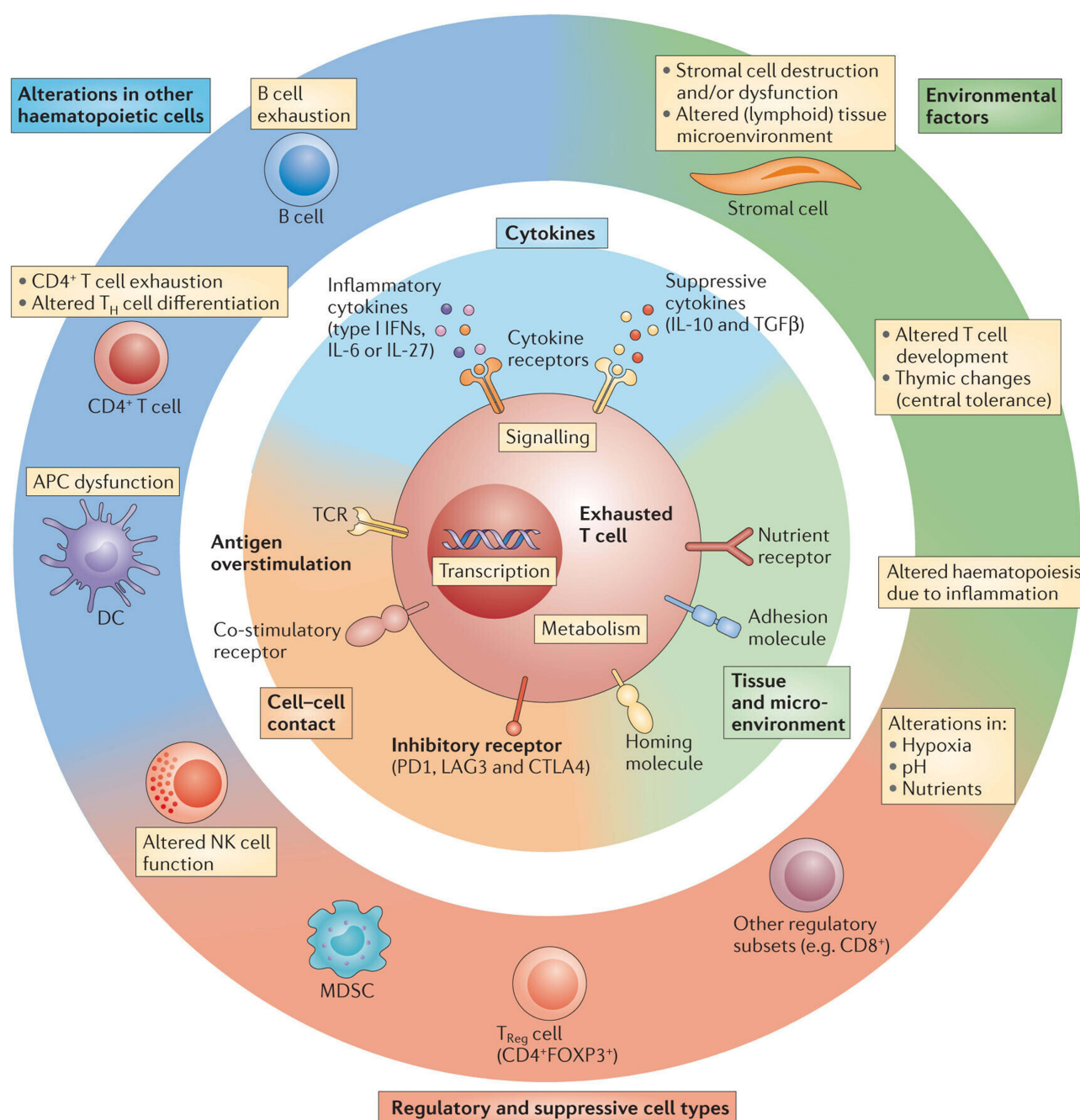
As the core executors of adaptive immune responses, T cells rely on a highly conserved and precisely cross-linked network of biochemical signaling cascades for the precise regulation of their activation, proliferation, lineage differentiation, and effector functions. Among these, the T cell receptor (TCR)-mediated signaling pathway forms the core scaffold of T cell activation: upon TCR-specific recognition of peptide-major histocompatibility complex (p-MHC) molecules on the surface of antigen-presenting cells (APCs), phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) on the CD3 $\zeta$  chain is first triggered, which in turn recruits and activates Src-family kinases (Lck) and Syk-family kinases (ZAP-70). Activation of ZAP-70 subsequently phosphorylates adaptor proteins LAT and SLP-76 to form the LAT signalosome, which recruits and activates phospholipase C- $\gamma$ 1 (PLC- $\gamma$ 1)—this key enzyme catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG), initiating downstream signaling cascades that govern T cell activation and effector function.<sup>30</sup>

Co-stimulatory molecules (represented by CD28) that act in synergy with TCR signaling recruit PI3K, which catalyzes the conversion of PIP2 to phosphatidylinositol 3,4,5-trisphosphate (PIP3), thereby activating the Akt-mTOR signaling axis—as an integrative hub for metabolic and survival signals, this axis not only regulates glucose metabolic reprogramming to meet the energy demands of activated T cells but also participates in T cell memory formation and fate determination through the regulation of transcription factors such as FoxO1. Meanwhile, co-inhibitory receptors including CTLA-4 and PD-1 exert reverse regulation on TCR-CD28 signal intensity by recruiting phosphatases (eg., SHP-1, SHP-2) or competing for PI3K binding sites, a critical mechanism for maintaining immune homeostasis and preventing autoimmune damage induced by excessive activation. The synergistic action of the above core pathways ensures the specific clearance of pathogens and malignant cells by T cells while maintaining self-immune tolerance; disruption of the precision of their molecular regulation directly leads to immune dysfunction, manifesting as T cell exhaustion or abnormal activation in diseases such as chronic infections and tumors.<sup>31–33</sup> (Figures 3 and 4).

In the microenvironment of chronic antigen exposure, the above core signaling cascades undergo dysregulation with distinct subset-specific molecular characteristics in T cells, ultimately driving the formation of T cell exhaustion (Tex) phenotypes, and the perturbation patterns of core biochemical signaling cascades between CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs) and CD4<sup>+</sup> T cells are significantly different, which is closely related to their distinct functional positioning and regulatory logic in the immune response.

For CD8<sup>+</sup> CTLs, the core feature of signaling cascade perturbation is the sustained hypoactivation of TCR core signaling and the hyperactivation of co-inhibitory receptor-mediated negative regulatory pathways. Chronic antigen stimulation leads to the persistent phosphorylation and dysfunction of key kinases in the TCR signaling pathway, such as Lck and ZAP-70, and the impaired assembly and activation of the LAT signalosome, which directly blocks the downstream calcineurin-NFAT, RasGRP-Ras-ERK and NF- $\kappa$ B pathways, resulting in the significant downregulation of cytotoxic effector molecules such as perforin and granzyme B. At the same time, CD8<sup>+</sup> Tex cells exhibit high and co-expression of multiple co-inhibitory receptors including PD-1, TIM-3 and LAG-3, and the recruitment of phosphatases such as SHP-1 and SHP-2 by these receptors is significantly enhanced, which further dephosphorylates key signaling molecules of the TCR-CD28 pathway and forms a “signal suppression loop”, and the Akt-mTOR metabolic signaling axis is also persistently inhibited, leading to the metabolic reprogramming of CD8<sup>+</sup> Tex cells to an inefficient oxidative phosphorylation state, which cannot support the exertion of cytotoxic functions.

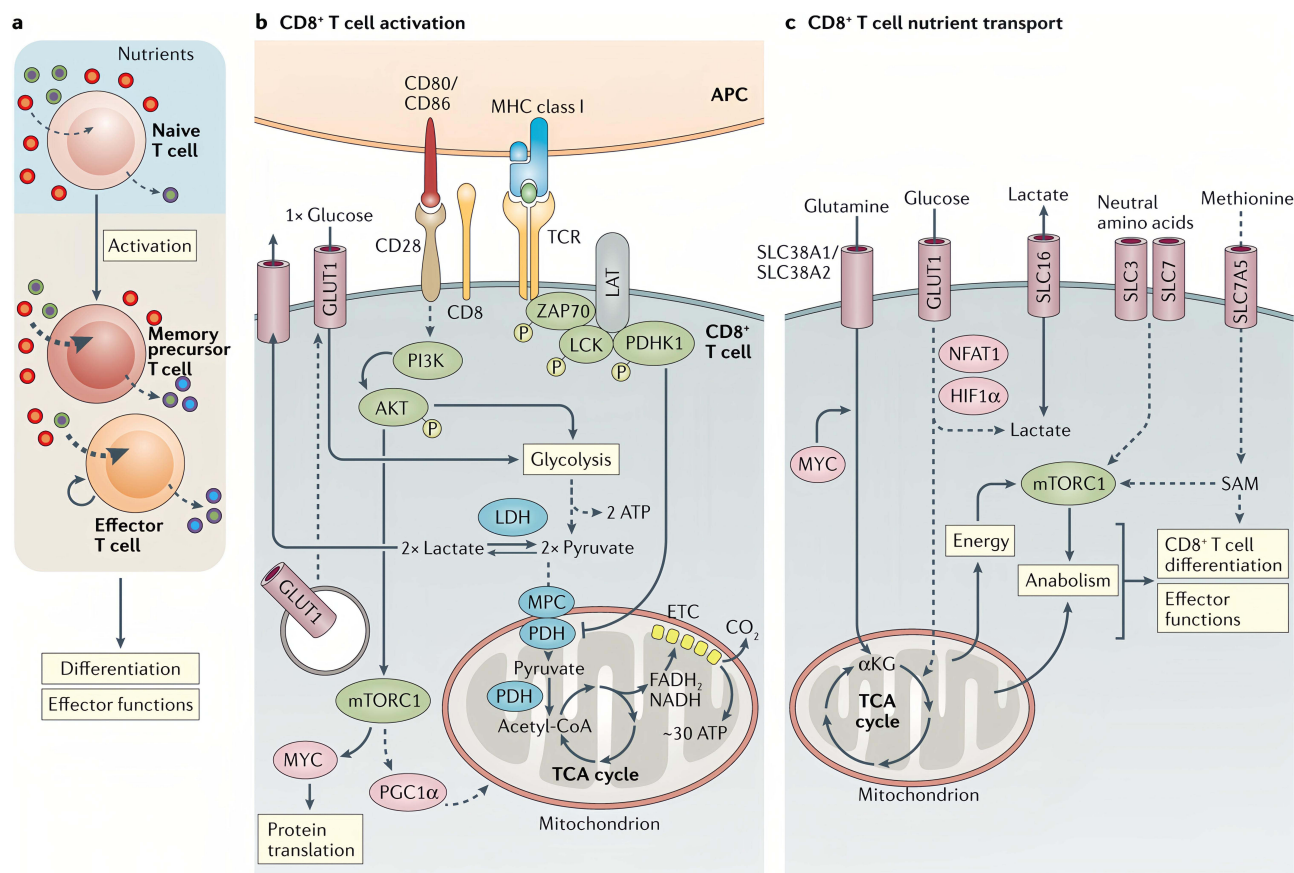
As the central hub for immune response regulation, CD4<sup>+</sup> T cells also undergo functional exhaustion in chronic disease microenvironments, and their core biochemical signaling cascade perturbation is characterized by the imbalance of TCR signal intensity and the abnormal differentiation of downstream functional subsets driven by biased activation of specific signaling branches, which is quite different from the overall hypoactivation of TCR signaling in CD8<sup>+</sup> CTLs. On the one hand, the TCR core signaling of CD4<sup>+</sup> Tex cells is not completely inhibited, but the activation of key signaling branches is unbalanced: the RasGRP-Ras-ERK pathway is moderately activated to maintain the basic proliferation of cells, while the calcineurin-NFAT and NF- $\kappa$ B pathways are selectively inhibited, resulting in the inability to secrete effective pro-inflammatory cytokines such as IL-2 and IFN- $\gamma$ . On the other hand, the co-inhibitory receptor-mediated



**Figure 3** Pathways implicated in regulating T cell exhaustion can be classified into three general categories (center and inner circle): cell-to-cell signals including prolonged T cell receptor (TCR) engagement (signal 1) and co-stimulatory and/or co-inhibitory signals (signal 2); soluble factors such as excessive levels of inflammatory cytokines (for example, type I interferons (IFNs)) and suppressive cytokines including interleukin-10 (IL-10) and transforming growth factor- $\beta$  (TGF $\beta$ ); and tissue and microenvironmental influences driven by changes in the expression levels of chemokine receptors, adhesion molecules and nutrient receptors. This last class of influences may include altered tissue distribution and/or migratory patterns and lead to changes in pathways sensing oxygen tension (the von Hippel-Lindau tumor suppressor (VHL) and/or hypoxia-inducible factor (HIF) pathways), pH and nutrient levels. Tissue destruction and altered lymphoid organization may have a major role. Other immune cell types and stromal cells could be the source of many of these changes (outer circle). Cell types such as antigen-presenting cells (APCs), CD4<sup>+</sup> T cells, natural killer (NK) cells, B cells and regulatory cells (for example, myeloid-derived suppressor cells (MDSCs) and regulatory T ( $T_{reg}$ ) cells) have been implicated in CD8<sup>+</sup> T cell exhaustion. Overall, during chronic infections, cell-intrinsic and cell-extrinsic signals are probably integrated and thereby negatively influence T cell differentiation and promote exhaustion. The precise balance of these signals may determine the severity and/or qualitative aspects of T cell exhaustion in different disease settings.<sup>7</sup> ©copyright©2015.

**Abbreviations:** CTLA4, cytotoxic T lymphocyte antigen 4; DC, dendritic cell; FOXP3, fork-head box P3; LAG3, lymphocyte activation gene 3 protein; PD1, programmed cell death protein 1;  $T_H$  cell, T helper cell.

negative regulation in CD4<sup>+</sup> Tex cells is relatively milder than that in CD8<sup>+</sup> Tex cells, with PD-1 being the main highly expressed co-inhibitory receptor, and the lack of high co-expression of multiple receptors; instead, the dysregulation of the PI3K-Akt-mTOR signaling axis is the core perturbation point, and the biased activation of its downstream mTORC2



**Figure 4** (a) CD8<sup>+</sup> T cell activation increases metabolic activity — including nutrient uptake (red circles) and secretion of metabolic by-products (purple circles) — to fuel increased anabolism and proliferation needed to mount effector T cell responses and differentiation into long-lived memory CD8<sup>+</sup> T cells. (b) Immediately after CD8<sup>+</sup> T cell activation, glucose-derived carbons are diverted from the TCA cycle into lactate production, a less efficient but faster route of ATP production, without increasing the overall glucose uptake. This is achieved in a CD28-independent fashion by engaging the pyruvate dehydrogenase kinase 1 (PDHK1)-dependent inhibition of pyruvate dehydrogenase (PDH) at the T cell synapse. Shortly after, glucose uptake is boosted by increasing the amount of glucose transporters on the cell surface, and the overall flux through glycolysis is upregulated by PI3K–AKT-dependent signalling downstream of CD28. Kinases are coloured green, metabolic enzymes are coloured blue, transporters are coloured pink and transcription factors are coloured light pink. (c) CD8<sup>+</sup> T cell activation requires increased nutrient consumption from the environment to support differentiation of T cells into effector and memory subsets.<sup>6</sup> ©copyright© 2021.

**Abbreviations:**  $\alpha$ KG,  $\alpha$ -ketoglutarate; APC, antigen-presenting cell; ETC, electron transport chain; FADH<sub>2</sub>, dihydroflavin adenine dinucleotide; LAT, linker for activation of T cells family member 1; LDH, lactate dehydrogenase; MPC, mitochondrial pyruvate carrier; mTORC1, mechanistic target of rapamycin complex 1; NFAT1, nuclear factor of activated T cells 1; PGC1 $\alpha$ , peroxisome proliferator-activated receptor- $\gamma$  coactivator 1 $\alpha$ ; PI3K, phosphoinositide 3-kinase; SAM, S-adenosylmethionine; SLC, solute carrier; TCA, tricarboxylic acid; TCR, T cell receptor.

branch drives the abnormal differentiation of CD4<sup>+</sup> T cells to immunosuppressive subsets such as Treg cells, while the mTORC1 branch is inhibited, leading to the significant reduction of effector Th1 and Th17 subsets. In addition, the metabolic reprogramming of CD4<sup>+</sup> Tex cells is milder, and they can still maintain a certain level of glycolytic metabolism, which is consistent with their functional characteristics of participating in immune regulation rather than direct cytotoxicity.

Such distinct perturbation patterns of core biochemical signaling cascades between CD4<sup>+</sup> and CD8<sup>+</sup> T cells fully reflect the functional specialization and differentiated regulatory logic of different T cell subsets in the immune system, and the targeted intervention of their specific signaling perturbation nodes is the key to developing precise reversal strategies for CD4<sup>+</sup> and CD8<sup>+</sup> Tex cells in chronic infections and tumor microenvironments.

In the chronic antigen-exposed microenvironment, dysregulation of the aforementioned core signaling cascades presents distinct subset-specific molecular features in CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs), ultimately driving the establishment of the CD8<sup>+</sup> T cell exhaustion phenotype. Correspondingly, CD4<sup>+</sup> T cells, which serve as the central hub for immune response regulation, also undergo functional exhaustion in chronic diseases, and the perturbation patterns of

their core biochemical signaling cascades are significantly different from those of CD8<sup>+</sup> T cells, reflecting the functional characteristics and regulatory logic of different T cell subsets.

## CD8<sup>+</sup> T Cells in Exhaustion

CD8<sup>+</sup> T cells play a pivotal role in antitumor immune responses through MHC-restricted antigen recognition and cytokine secretion. However, persistent antigen stimulation within the TME can lead to functional exhaustion of CD8<sup>+</sup> T cells. Recent studies have uncovered substantial heterogeneity among exhausted CD8<sup>+</sup> T cells, which are broadly classified into two functionally distinct subsets: progenitor-like exhausted T cells (Tpex) and terminally exhausted T cells (Tex) based on their functional states and therapeutic responsiveness.<sup>34</sup> The former exhibit a stem cell-like phenotype, possess self-renewal capacity, and respond to immune checkpoint blockade therapy, thereby sustaining antitumor immune activity.<sup>35</sup> The latter show upregulation of multiple inhibitory receptors (like, PD-1, Tim-3, TIGIT, LAG-3, CTLA-4), accompanied by aberrant transcriptional and epigenetic reprogramming, severely impaired proliferative potential and effector functions (including cytotoxicity and cytokine secretion), and resistance to current immunotherapeutic strategies.<sup>36</sup>

Currently, the causal relationship between tumor metabolic reprogramming and CD8<sup>+</sup> T cell exhaustion is not fully understood. This exhaustion phenomenon is widespread across various tumor types, constitutes a key mechanism of tumor immune evasion and progression, and is often associated with poor clinical prognosis. Therefore, reversing T cell exhaustion has become a core mechanism of action for immune checkpoint blockade therapies represented by PD-1/CTLA-4 inhibitors, aiming to restore T cell function and enhance antitumor immune responses. (Figures 3 and 4).

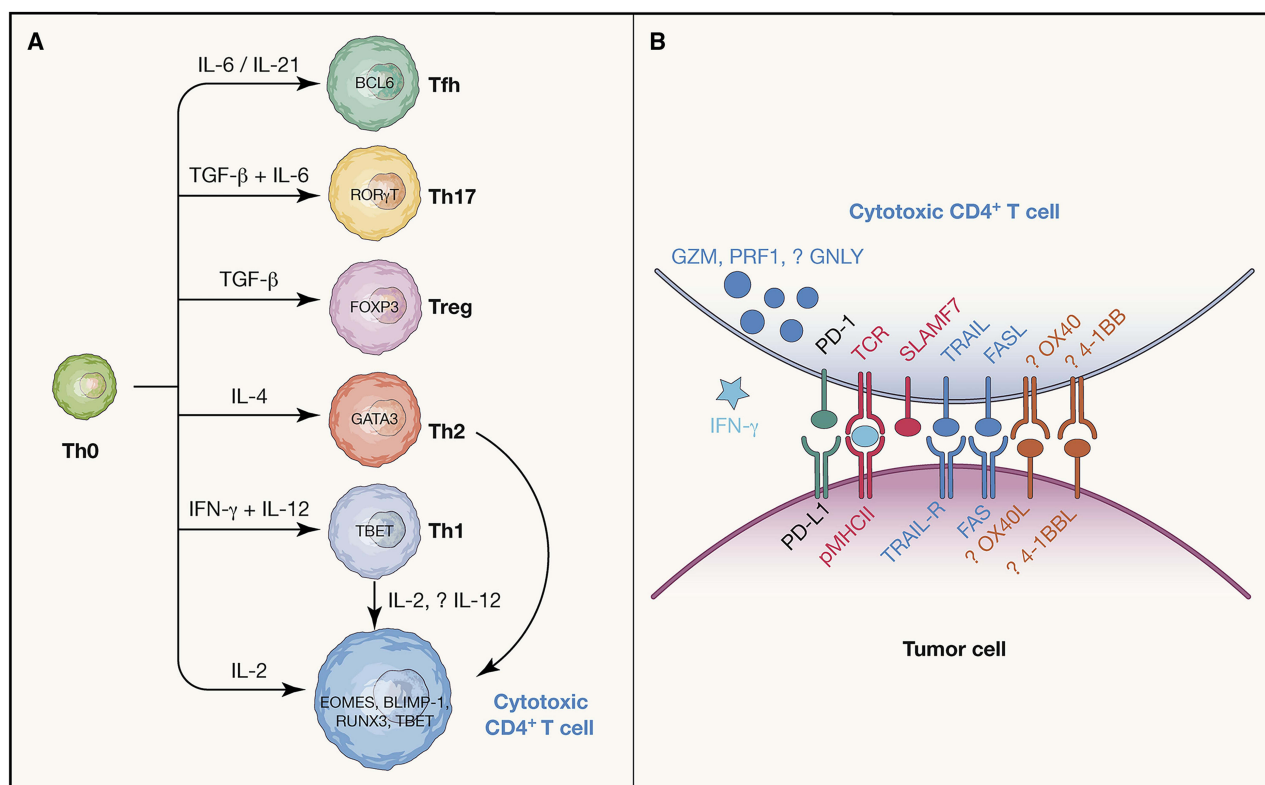
## CD4<sup>+</sup> T Cells in Immunotherapy and Its Exhaustion

In tumor immunotherapy, the recognition of tumor antigens by CD4<sup>+</sup> T cells has been proven crucial for therapeutic response. For example, infusion of CD4<sup>+</sup> T cell clones recognizing NY-ESO-1<sup>37</sup> or MAGE-A3,<sup>38</sup> as well as infusion of tumor-infiltrating lymphocytes targeting personalized neoantigens (like, ERBB2IP, CTBP1 mutations),<sup>39</sup> can induce objective clinical responses, often accompanied by interferon- $\gamma$  production, suggesting Th1-type polarization (Figure 4).

While T cell exhaustion is generally considered a feature of CD8<sup>+</sup> cells, CD4<sup>+</sup> T cell subsets regulate diverse immune responses—from autoimmune diseases to cancer—and serve as a core hub for maintaining immune homeostasis (Figure 5). Among these subsets, Foxp3<sup>+</sup>CD4<sup>+</sup> regulatory T (Treg) cells, a highly immunosuppressive population, promote malignant tumor progression by dampening anti-tumor immune responses, making the targeted modulation of their homeostasis and function a critical strategy for deciphering disease pathogenesis and developing novel cancer therapeutics.<sup>40,41</sup>

Notably, Treg cells in the tumor microenvironment (TME) also highly express exhaustion-associated immune checkpoint molecules;<sup>43–45</sup> although “exhaustion” was originally defined as a state of functional dysfunction in effector T cells (1), these findings indicate that exhaustion-like phenotypes in CD4<sup>+</sup> T cells are not restricted to conventional FOXP3<sup>+</sup>CD4<sup>+</sup> T cells—when antigens remain persistently exposed and uncleared, CD4<sup>+</sup> T cell subsets such as Treg cells can exhibit exhaustion-like characteristics. A key paradox emerges here: PD-1, which limits excessive T cell activation by inhibiting TCR and CD28 signaling,<sup>46,47</sup> is highly expressed on TME-resident Treg cells, and PD-1 blockade may inadvertently enhance their immunosuppressive function—with PD-1-deficient Treg cells showing robust suppressive activity and anti-PD-1 antibodies linked to Treg-mediated tumor hyper-progression in some patients,<sup>48</sup> and clinical studies have shown that anti-PD-1 monoclonal antibodies enhance Treg cell-mediated immunosuppression in some patients, leading to hyper-progression during PD-1 blockade therapy.<sup>45</sup> Additionally, PD-1<sup>+</sup>Treg cells in the TME are key mediators of resistance to PD-1 blockade (Figure 5). Further studies reveal that the transcriptional profile of tumor-infiltrating Treg cells differs from that of circulating Treg cells: multiple genes are co-expressed with PD-1 and enriched in interferon- $\gamma$  production, exhaustion-related pathways, and exhaustion signals, suggesting that tumor-infiltrating PD-1<sup>+</sup>Treg cells are dysfunctional, exhaustion-like Treg cells.

Recent research confirms that Treg cells exhibit robust PD-1 upregulation in highly glycolytic tumor microenvironments (eg., MYC-high tumors and liver tumors): via monocarboxylate transporter 1-mediated active lactate uptake, Treg cells promote nuclear translocation of the transcription factor NFAT1, which in turn drives PD-1 overexpression—



**Figure 5 (A)** A schematic of known CD4<sup>+</sup> T cell functional subtypes, the cytokines that promote their differentiation, and master transcription factors (TFs) involved in their specification. As indicated, cytotoxic CD4<sup>+</sup> T cells can arise from unpolarized Th0, Th1, or Th2 cells in response to IL-2 depending on the context; also, the contributions of the TFs RUNX3, TBET, BLIMP-1, and EOMES to specifying the cytotoxic CD4<sup>+</sup> T cell state are also context-dependent, as discussed in the text. **(B)** Mechanisms that may contribute to activation of cytotoxic CD4<sup>+</sup> T cells (red), anti-tumor cytotoxicity effector function (dark blue) including cytokines (light blue), as well as co-stimulatory (Orange) or co-inhibitory (green) immune checkpoints are shown. “?” questions that remain incompletely understood or controversial in current research.<sup>42</sup> ©copyright© 2021.

distinct from the suppressed PD-1 expression observed in effector T cells. PD-1 blockade activates PD-1<sup>+</sup>Treg cells, leading to treatment failure—indicating that lactate in the highly glycolytic TME can act as an active checkpoint regulating Treg cell function by upregulating PD-1, which provides a new direction for investigating the mechanisms of CD4<sup>+</sup> T cell exhaustion-like states and developing targeted therapies.

## Heterogeneity of the Tumor Microenvironment and Its Impact on T Cell Exhaustion

The tumor microenvironment (TME) exerts a profound and detrimental impact on T cell function, directly driving the development of T cell exhaustion, which is a state of irreversible functional impairment that undermines antitumor immunity. While naive T cells normally maintain metabolic quiescence through oxidative phosphorylation to preserve homeostasis.<sup>49</sup> T cells within the TME undergo a breakdown in the metabolic reprogramming critical for effector differentiation: upon antigen recognition, TCR cross-linking fails to induce the requisite upregulation of aerobic glycolysis and oxidative phosphorylation<sup>50,51</sup>—two processes indispensable for transitioning from quiescence to potent effector function. Compounding this defect, dysfunctional CD28 co-stimulatory signaling in the TME blunts PI3K and mTORC1 activation; as a central signaling hub that coordinates exit from quiescence and drives metabolic reprogramming,<sup>52</sup> mTORC1 hypoactivity traps T cells in a hypometabolic state, preventing their differentiation into functional effectors.

In stark contrast to memory T cells (which revert to oxidative phosphorylation for long-term survival and retain the capacity to rapidly initiate glycolysis upon secondary antigen challenge), TME-resident T cells exhibit severe mitochondrial dysfunction, including reduced mitochondrial fitness and impaired respiratory capacity which hallmarks that form the molecular basis of their exhaustion and hypofunction. These mitochondrial defects trigger excessive reactive oxygen

species (ROS) production, which promotes the exhausted T cell phenotype through multiple interconnected mechanisms—altering key metabolic enzyme expression, inducing DNA damage, and inhibiting phosphatase activity<sup>53–56</sup>—highlighting mitochondrial dysfunction as a core driver of T cell hypofunction. This can be achieved, for example, by forced expression of transcription factors such as PGC1 $\alpha$ <sup>57</sup> or BATF, which regulate mitochondrial biogenesis and function. Additionally, targeting specific mitochondrial metabolic pathways can redirect T cell fate toward memory-like CD8<sup>+</sup> T cells, enhancing their persistence and antitumor activity: deleting the mitochondrial pyruvate carrier (MPC)<sup>58</sup> or isocitrate dehydrogenase 2 (IDH2)<sup>59</sup> in T cells, or administering glutamine antagonists,<sup>60</sup> has been shown to improve tumor control by normalizing T cell metabolism in the TME. Future research must further elucidate the mechanistic links between TME-induced metabolic dysregulation and T cell exhaustion, with the goal of developing targeted therapies that reprogram T cell metabolism to reinvigorate antitumor immunity (Figure 6).

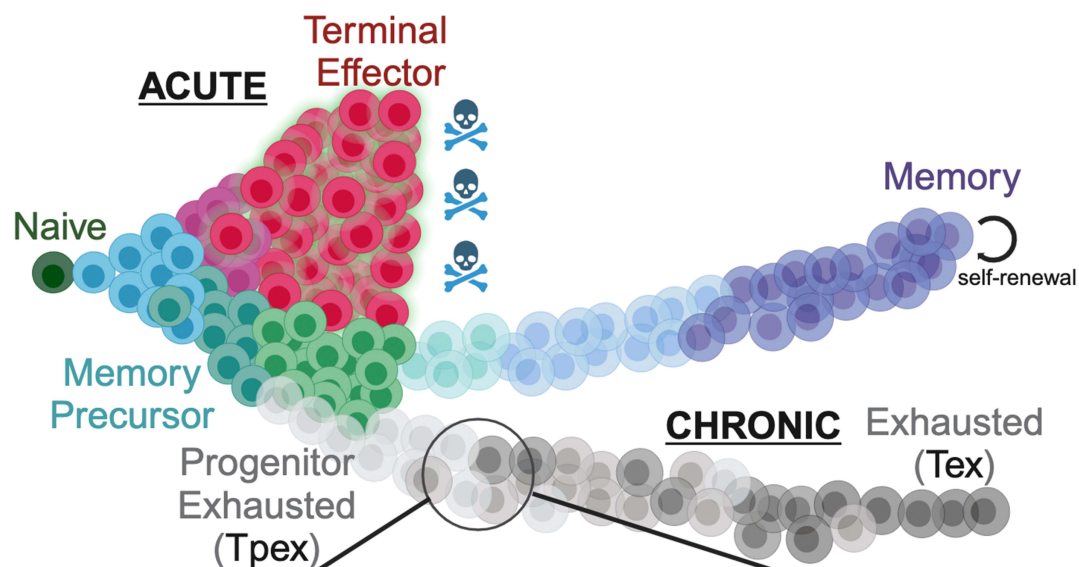
Beyond intrinsic T cell regulation, their antitumor function is often limited by nutrient scarcity within the TME. Due to their rapid proliferation and aggressive growth, tumor cells exhibit distinctive metabolic reprogramming characterized by enhanced uptake and metabolism of glucose and glutamine<sup>62</sup> which directly impairs T cell function by competitively depleting these nutrients essential for T cell activation and effector function. This metabolic reprogramming of cancer cells can directly impair T cell function by competitively consuming glucose and glutamine, both of which are essential for T cell activation and function. Specifically, tumor cells compete with T cells for glucose. The high glucose consumption by tumor cells limits T cell metabolic reprogramming and function, including reduced mTORC1 activity and glycolytic capacity.<sup>63,64</sup> Recent research emphasizes the complexity of nutrient interactions within the TME: myeloid cells exhibit the highest degree of glucose uptake, while tumor cells preferentially utilize glutamine.<sup>65</sup> Tumor cell dependency on glutamine impairs intratumoral type 1 conventional dendritic cell (cDC1) function, thereby weakening CD8<sup>+</sup> T cell antitumor immunity; intratumoral glutamine supplementation can enhance antitumor immunity and reverse resistance to immune checkpoint blockade (ICB).<sup>66</sup> Additionally, other amino acids such as arginine, methionine, and serine may also be scarce in the TME, and such nutritional deficiencies hinder effective T cell antitumor responses.<sup>66–68</sup> Beyond metabolic roles, glucose and amino acids can also convey signals through a tiered process involving nutrient transporters, protein sensors, and signal transduction elements, thereby permitting mTORC1 activation and licensing T cell immunity.<sup>69,70</sup> Recent studies found that the microbial-derived nucleoside inosine has strong immunostimulatory effects on T cells, enhancing antitumor function.<sup>71–73</sup> Dietary nutrition also influences CD8<sup>+</sup> T cell function and antitumor immunity, including the stimulatory effect of trans-vaccenic acid,<sup>74</sup> and the inhibitory effects of high-fat diets<sup>75</sup> and the artificial sweetener sucralose.<sup>76</sup> Notably, tumor-derived inhibitory metabolites—such as lactate,<sup>77</sup> cholesterol,<sup>78</sup> and oxidized lipids,<sup>79</sup> can also suppress T cell function and antitumor immunity. For instance, oxidized lipids and polyunsaturated fatty acids accumulate in the TME, and their increased uptake by CD8<sup>+</sup> T cells via the scavenger receptor CD36 leads to lipid peroxidation, ferroptosis, and CD8<sup>+</sup> T cell dysfunction. Blocking CD36 or inhibiting CD8<sup>+</sup> T cell ferroptosis enhances their antitumor function, highlighting the immunosuppressive role of oxidized lipids in cancer.<sup>79,80</sup> In summary, antitumor immunity mediated by T cells within the TME is regulated by the availability and composition of nutrients and metabolites, involving both stimulatory and inhibitory factors and mechanisms, which provides potential targets for therapeutic intervention.

## Nanomaterials in T Cell-Targeted Delivery

Before delving into T cell-targeted nanomaterial strategies, it is informative to first highlight the clinical precedent of nanomedicines in oncology. To date, multiple nanomedicine formulations have been FDA-approved for clinical cancer therapy. Table 1 summarizes these early approved nanomedicines, they are all chemotherapeutic agents encapsulated in liposomal (or PEGylated liposomal) carriers with a particle size range of 50–200 nm administered intravenously, and indicated for malignancies like Kaposi sarcoma and breast cancer. These examples illustrate the translational potential of nanomaterials in enhancing drug delivery by virtue of optimal particle size, biocompatible lipid composition and surface PEG functionalization, they enhance drug delivery efficiency while reducing systemic toxicity to clinically acceptable levels. Serving as typical examples of nanomaterials as safe therapeutic agents, they also establish a safety-and-efficacy integrated framework for the development of nanoscale drug delivery systems (NDDSs) for T cell targeting, the relevant strategies of which will be elaborated in subsequent sections.

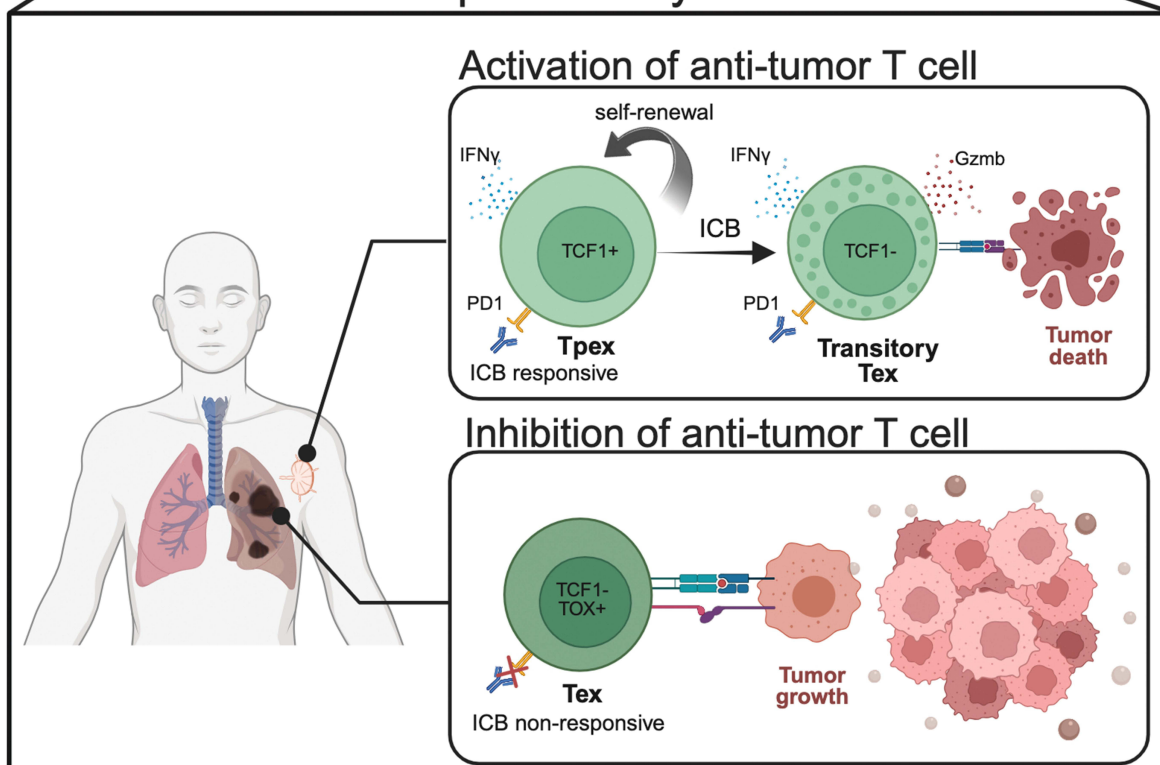
Notably, the phenotypic characteristics of tumor-infiltrating exhausted T cells (Tex) exhibit remarkable inter-tumor heterogeneity. Across different tumor types, and even among distinct lesions within the same tumor, significant variations exist in the exhaustion degree of Tex, the expression profile of surface markers, and the physicochemical properties of the tumor

# A Memory T cell differentiation and exhaustion



## B

### T cell tumor response & dysfunction



**Figure 6 (A)** In settings of acute antigen exposure, T cells differentiate into terminal effectors or a long-lived memory population. If exposed to chronic antigen, T cells can acquire functional features of terminal exhaustion. **(B)** The tumor microenvironment suppresses T cell anti-tumor function and maintenance of the ICB-responsive Tpex population. This suppression is in part a result of anatomical location of these cells within the lymph nodes. The TCF-1+ Tpex population can self-renew and mount a proliferative burst in response to ICB, whereas the Tex cell population within the tumor lacks the ability to respond to ICB.<sup>61</sup> @copyright© 2024.

**Table 1** Approved Nanomedicine for Cancer<sup>1</sup>

| Therapeutic Type | Product Name | Therapeutic Agent             | Nanocarrier                  | Administration Route | Indications                                                                                     | First Approval |
|------------------|--------------|-------------------------------|------------------------------|----------------------|-------------------------------------------------------------------------------------------------|----------------|
| Chemotherapy     | Doxil        | Doxorubicin                   | PEGylated liposomes          | iv.                  | Kaposi sarcoma, breast cancer, ovarian cancer, multiple myeloma                                 | USA 1995       |
| Chemotherapy     | Caelyx       | Doxorubicin                   | PEGylated liposome           | iv.                  | Metastatic breast, Kaposi's sarcoma, multiple myeloma                                           | USA 1996       |
| Chemotherapy     | DaunoXome    | Daunorubicin                  | Liposomes                    | iv.                  | Kaposi sarcoma                                                                                  | USA 1996       |
| Chemotherapy     | Myocet       | Doxorubicin                   | Liposomes                    | iv.                  | Metastatic breast cancer                                                                        | USA 1996       |
| Chemotherapy     | DepoCyt      | Cytarabine                    | Liposomes                    | iv.                  | Lymphomatous meningitis                                                                         | USA 1999       |
| Chemotherapy     | Eligard      | Leuprolide                    | Polymeric micelles           | iv.                  | Prostate cancer                                                                                 | USA 2002       |
| Chemotherapy     | Lipusu       | Paclitaxel                    | Liposomes                    | iv.                  | Ovarian cancer, metastatic gastric cancer                                                       | China 2003     |
| Chemotherapy     | Oncaspar     | Pegaspargase                  | Polymeric micelles           | iv.                  | Acute lymphoblastic leukemia                                                                    | USA 1994       |
| Chemotherapy     | MEPACT       | Mifamurtide                   | Liposomes                    | iv.                  | Osteosarcoma                                                                                    | Europe 2009    |
| Chemotherapy     | Ameluz       | 5-aminolevulinic acid         | Liposomes                    | iv.                  | Nodular basal cell carcinoma                                                                    | USA 2011       |
| Chemotherapy     | Marqibo      | Vincristine sulfate           | Liposomes                    | iv.                  | Philadelphia chromosome-negative acute lymphoblastic leukemia                                   | USA 2012       |
| Chemotherapy     | Lipodox      | Doxorubicin hydrochloride     | Liposome                     | iv.                  | Kaposi's sarcoma, ovarian cancer, multiple myeloma, metastatic pancreatic cancer                | China 2013     |
| Chemotherapy     | Kadcyla      | DMI (or Emtansine)            | Protein                      | iv.                  | Breast cancer                                                                                   | USA 2013       |
| Chemotherapy     | Paclical     | Paclitaxel                    | polymeric nanoparticle-based | iv.                  | Pancreatic cancer, metastatic breast cancer                                                     | USA 2015       |
| Chemotherapy     | Onivyde      | Irinotecan                    | PEGylated liposomes          | iv.                  | Metastatic pancreatic cancer                                                                    | USA 2015       |
| Chemotherapy     | VYXEOS       | Cytarabine/daunorubicin (5:1) | Liposomes                    | iv.                  | Acute myeloid leukemia                                                                          | USA 2017       |
| Chemotherapy     | Pazenir      | Paclitaxel                    | Micelle                      | iv.                  | Metastatic breast cancer, metastatic pancreatic cancer, non-small cell lung cancer              | USA 2019       |
| Chemotherapy     | Apealea      | Paclitaxel                    | Nanocrystal                  | iv.                  | Ovarian cancer, peritoneal cancer, fallopian tube cancer                                        | USA 2018       |
| Chemotherapy     | Abraxane     | Paclitaxel                    | Albumin                      | iv.                  | Breast cancer, non-metastatic small cell lung cancer, metastatic adenocarcinoma of the pancreas | USA 2005       |
| Chemotherapy     | Ontak        | Denileukin Diftitox           | Protein                      | iv.                  | Cutaneous T-cell lymphoma                                                                       | USA 1999       |
| Chemotherapy     | Genexol-PM   | Paclitaxel                    | Polymeric micelles           | iv.                  | Breast cancer, lung cancer                                                                      | Korea 2007     |
| Chemotherapy     | Nanoxel      | Paclitaxel                    | Polymeric micelles           | iv.                  | Breast cancer, ovarian cancer                                                                   | India 2007     |
| Chemotherapy     | Paclical     | Paclitaxel                    | Polymeric micelles           | iv.                  | Ovarian cancer                                                                                  | Russia 2015    |
| Chemotherapy     | PICN         | Paclitaxel                    | Polymer/lipid NP             | iv.                  | Metastatic breast cancer                                                                        | India 2014     |

microenvironment (TME) where Tex resides.<sup>81</sup> This heterogeneity dictates that the selection of NDDS-based therapies must be guided and stratified by specific biomarkers, which play an indispensable role in advancing the precision and individualization of T cell-targeted nano-delivery strategies.<sup>82</sup> Biomarkers not only enable accurate characterization of the biological features of Tex and the microenvironmental status of the TME, but also provide critical evidence for the rational design of NDDSs, patient stratification for treatment indication, and pre-treatment efficacy prediction—serving as a core prerequisite for the personalized and precise application of NDDS-based T cell-targeted therapies. For instance, lactate dehydrogenase (LDH) activity reflects the glycolytic metabolic intensity and nutrient deprivation level of the TME;<sup>83</sup> high LDH activity is often accompanied by TME acidification and exacerbated immunosuppression, and such tumors necessitate the prioritized use of acid-responsive NDDSs to achieve precise drug release in the acidic TME. The abundance of Tex with high PD-1 expression directly mirrors the level of immune exhaustion in tumors: this marker can be exploited as a target for the design of NDDS targeting ligands, and its expression level also allows for the screening of patients most likely to benefit from NDDSs delivering PD-1/PD-L1 pathway blockers.<sup>84</sup> Metabolic subtypes within the TME (eg., glycolytic or oxidative phosphorylation-dominant subtypes) are closely associated with the metabolic reprogramming status of Tex;<sup>85</sup> for TMEs with different metabolic subtypes, NDDSs loaded with metabolic modulators can be rationally designed to reverse Tex exhaustion by regulating the metabolic microenvironment of the TME. In addition, other biomarkers including the proportion of immunosuppressive cells in the TME, cytokine expression profiles, and the density of the extracellular matrix, can guide the selection of NDDS carrier types, surface modification strategies, and drug combination regimens from multiple dimensions, thereby greatly enhancing the clinical application value of NDDS-based T cell-targeted therapies.

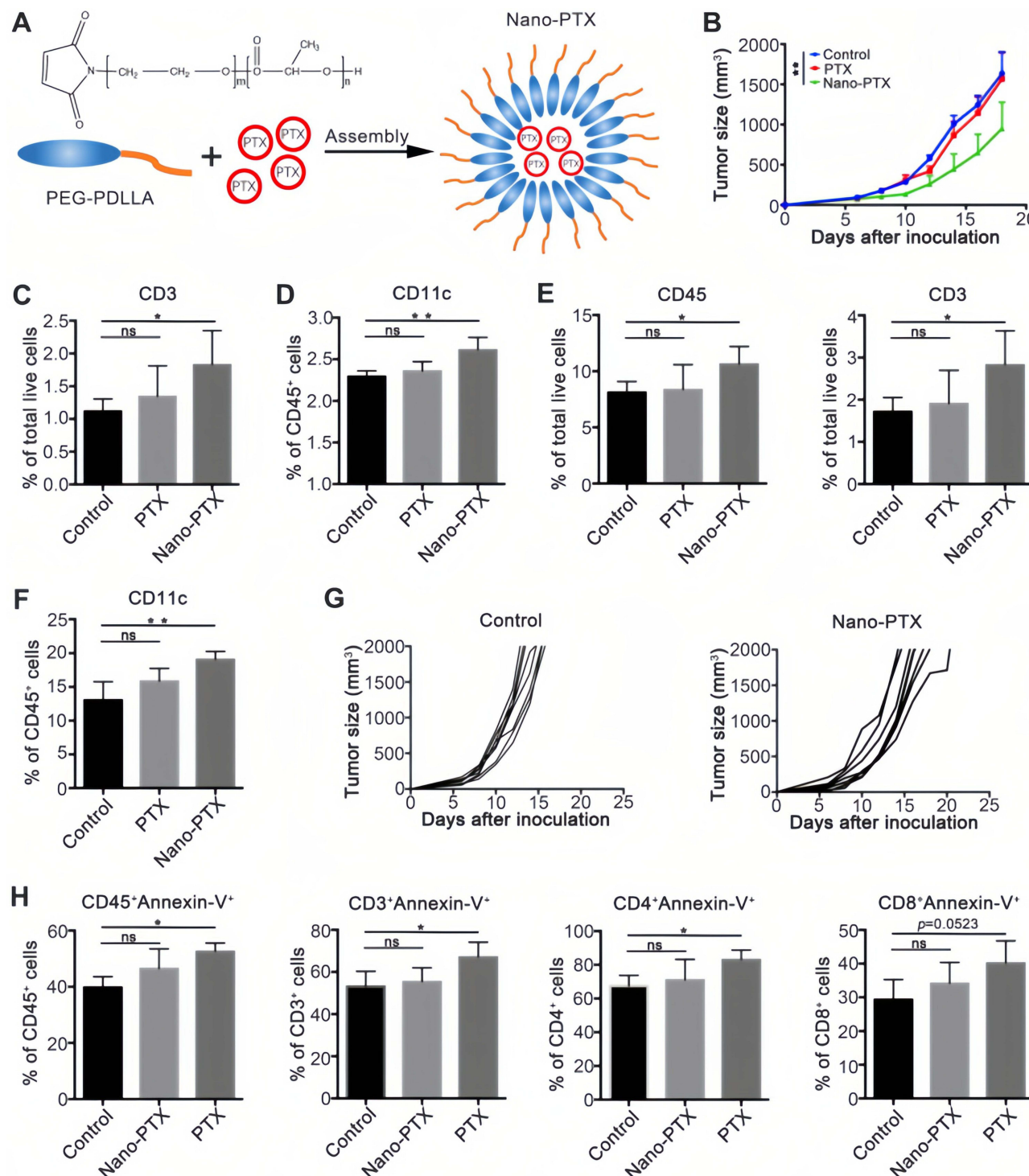
## Common Nano-Delivery Carriers

Liposomes are spherical vesicles formed by a bilayer phospholipid membrane enclosing an aqueous core, with a particle size of 50–450 nm for medical applications. They can co-encapsulate hydrophilic molecules in the aqueous core and hydrophobic molecules in the phospholipid bilayer,<sup>86</sup> first described by Alec Bangham in 1961<sup>87</sup> and clinically introduced as the first-generation lipid-based drug delivery systems.<sup>88</sup> Approved liposomal antitumor drugs include Myocet®, Doxil (liposomal doxorubicin), and Marqibo®.<sup>86,89,90</sup> with four main classifications: (A) Conventional (phospholipid-based); (B) PEGylated (surface-modified with PEG, longer circulation); (C) Ligand-targeted (peptides/antibodies/vitamins/carbohydrates for specific cells); (D) Theranostic (integrating targeting ligands, imaging agents, and therapeutics).<sup>91</sup>

Liposome systems offer targeted delivery, reduced systemic toxicity, drug stability, and evasion of biological clearance for gene therapy.<sup>92–98</sup> EphA2 antibody-conjugated liposomes with a docetaxel prodrug outperform non-nano and non-targeted nano formulations in lowering toxicity, improving tolerance, maintaining tumor drug exposure, and enhancing antitumor activity.<sup>99</sup> Limitations include low lipophilic drug loading, opsonization susceptibility, potential immunogenicity, and stability issues.<sup>100–102</sup> Physically stimuli-responsive liposomes are a research focus.<sup>103–105</sup> For site-specific controlled release but have few clinical translations,<sup>106–108</sup> facing challenges such as light parameter selection, development of stimuli-responsive phospholipids and toxicity control of synthetic lipids. For such clinically investigational liposomes, maintaining an optimal particle size of 100–200 nm, using natural phospholipids as the main component and modifying with neutral surface charge can significantly reduce their in vivo toxicity and immunogenicity.

Micelles are spherical aggregates self-assembled by amphiphilic molecules in aqueous media, with a particle size concentrated in the range of 10–100 nm, forming a typical structure with a hydrophilic shell and a hydrophobic core. Their self-assembly is governed by critical micelle concentration (CMC), chemical structure, and environmental cues.<sup>109,110</sup> They encapsulate substances to reduce distribution-related toxicity,<sup>111,112</sup> enhance delivery of poorly soluble lipophilic drugs, and facilitate clearance.<sup>113</sup> Block copolymers are central to their design: shell components (eg., PEG, PVA) minimize immune clearance and prolong circulation, while core materials (eg., polyesters) facilitate drug loading.<sup>114,115</sup> PEG forms a hydration sheath to reduce macrophage uptake and prolong circulation. Polymer selection considers drug type, biocompatibility, immunogenicity, toxicity, biodegradability, and special properties.<sup>116–119</sup> A micelle particle size of 50–100 nm, hydrophilic neutral surface charge and biodegradable polyester core are key parameters to ensure their safety and delivery efficiency. Micelles can be engineered to respond to endogenous stimuli (pH, enzymes, reactive oxygen species (ROS), ATP) or exogenous stimuli (light, temperature, ultrasound) to achieve spatiotemporally controlled drug release,<sup>120</sup> with dual-stimulus designs for targeted release (like, pH- and MMP-sensitive PEGylated

micelles for PD-1 antibody and paclitaxel sequential release).<sup>121</sup> Surface ligands/antibodies enhance penetration and retention for targeted delivery, as illustrated in Figure 7, a PEG-PDLLA micellar formulation loaded with paclitaxel (Nano-PTX), with its particle size regulated to 80–100 nm and surface functionalized with PEG, not only enhances



**Figure 7** PTX embedded with nanomicelle exerts immune dependent tumor control. **(A)** Schematic representation of PEG-PDLLA-paclitaxel nanomicelle. **(B–F)** Mice bearing CT26 were treated using PTX (10 mg/kg) embedded with or without nanomicelle for five times and the tissue was harvest on day 20. **(B)** The tumor growth after treatment, *n* = 5 mice per group. **(C)** The percentage of T cells (CD3<sup>+</sup>) in PBMC after treatment, *n* = 4 mice per group. **(D)** The percentage of CD11c<sup>+</sup> cells in draining lymph node after treatment, *n* = 4 mice per group. **(E)** The percentage of total immune cells (CD45<sup>+</sup>) and T cells (CD3<sup>+</sup>) in tumor after treatment, *n* = 4 mice per group. **(F)** The percentage of dendritic cells (CD11c<sup>+</sup>) in tumor after treatment, *n* = 4 mice per group. **(G)** CT26 tumor growth in immune deficiency mice after nano-PTX (10 mg/kg) treatment with low dose, *n* = 8 mice per group. **(H)** The percentage of apoptotic immune cells in peripheral blood on day 1 after treatment, *n* = 4 mice per group. Mean ± SEM was shown. \**P* < 0.05, \*\**P* < 0.01, ns (no statistical significance).<sup>122</sup> @copyright ©2020.

chemotherapeutic efficacy but also promotes the tumor infiltration of cytotoxic CD8<sup>+</sup> T cells, confirming that micelles can simultaneously modulate tumor growth and anti-tumor T cell immunity through rational physicochemical parameter design.

## Characteristics and Design Principles of T Cell-Targeting Nanomaterials

Nanoparticle (NP)-based strategies targeting the remodeling of immunosuppressive tumor microenvironment (TME) and the regulation of metabolic disorders in exhausted T cells (Tex) have emerged as highly promising tools to reverse T cell exhaustion, a key barrier to durable anti-tumor immunity. The hostile TME (encompassing CAFs, M2-TAMs, MDSCs, Tregs, and ECM barriers) drives T cell exhaustion directly (via factors like TGF- $\beta$ /ROS) and indirectly (via nutrient deprivation/hypoxia), meanwhile, it pushes Tex into a metabolically rigid state (impaired glucose uptake, damaged mitochondrial function). Leveraging tunable particle size (for EPR-based tumor targeting with an optimal range of 50–200 nm), ligand-modifiable surfaces, high drug payload capacity and stimuli-responsive release properties, NPs synergistically address these challenges because they co-deliver immunostimulatory agents / ECM-degrading enzymes to normalize the TME into an immunogenic niche, and transport metabolic modulators (glycolysis boosters, mitochondrial function enhancers) to rescue Tex cell metabolism—with spatiotemporal release minimizing off-target effects. This synergy between TME remodeling and metabolic reprogramming reverses T cell exhaustion, overcomes the drug resistance of conventional immunotherapy, and position NPs as a cutting-edge direction in personalized cancer immunotherapy. In the design of NPs, a particle size of 50–200 nm, biocompatible and biodegradable composition, neutral/weakly negative surface charge and directional functionalization with targeting ligands are the core design principles to balance their delivery efficacy and in vivo safety.

Nanoparticles can significantly improve delivery efficiency by protecting immunotherapeutic agents and enhancing their interaction with immune cells, thereby enhancing the effects of existing immunotherapies.<sup>123</sup> Modifying the surface of nanoparticles with antibodies and other targeting ligands can induce their specific and efficient uptake.<sup>124</sup> Inhibitory receptors often serve as molecular targets for NP-based immunotherapies targeting exhausted T cells. Recent research delivered PD-1 siRNA to T lymphocytes using a lipid-capsid complex with a particle size of 100–150 nm and PEG surface modification, which not only increased cellular siRNA uptake efficiency but also reduced off-target toxicity, effectively downregulating PD-1 expression.<sup>125</sup> Furthermore, PD-1 siRNA was directly delivered to T cells via gold nanoparticles coated with poly-amidoamine (PAMAM) dendrimers; these nanoparticles had a particle size of <50 nm and neutral surface charge, which not only enhanced the PD-1 gene silencing effect but also avoided the in vivo accumulation toxicity of gold nanomaterials, achieving effective regulation of T cell exhaustion.

Considering that the immunosuppressive molecule indoleamine 2,3-dioxygenase (IDO) can promote the exhausted phenotype and Treg generation, combining IDO inhibitors can further improve tumor immunotherapy efficacy and reverse T cell exhaustion.<sup>126</sup> Concurrently, some studies have developed long non-coding RNA (lncRNA)-edited tumor cell membrane-biomimetic nanoparticles. Their combination with anti-TIM-3 antibodies demonstrates significant anti-tumor effects by enhancing antigen cross-presentation, improving dendritic cell inflammasome activation, and alleviating T cell exhaustion.<sup>127</sup> Ionizable lipid nanoparticles with a particle size of 80–120 nm, featuring low toxicity and high transfection efficiency, were designed to deliver Epstein-Barr virus latent membrane protein 2 (LMP2) mRNA to lymph nodes. Subsequently, LMP2 mRNA is expressed in antigen-presenting cells (APCs), thereby activating CD8<sup>+</sup> T cells to target and kill LMP2-expressing cancer cells and promoting memory T cell formation. Combination with anti-PD-1 therapy can block the PD-L1 pathway, elicit potent anti-tumor immunity and reverse T cell exhaustion.<sup>128</sup> Additionally, peptide-based nanoparticle vaccines, loaded with Toll-like receptor 9 (TLR9) ligand CpG and the Gag epitope of Friend retrovirus-specific CD8<sup>+</sup> T cells, can effectively activate dendritic cells and enhance cellular immune responses.<sup>129–131</sup> Combining anti-PD-L1 antibodies with therapeutic vaccines yields better effects in reactivating CD8<sup>+</sup> T cell responses and clearing virus.<sup>132</sup> All these vaccine-based nanoparticles are designed with a particle size of 50–100 nm and take biodegradable peptides as the main component, ensuring their safety for in vivo application.

T cell-derived nanovesicles provide another effective strategy for regulating T cell exhaustion. These nanovesicles are produced by cytotoxic T cells through sequential extrusion through membranes with micro/nano pores, and with a particle size of 100–200 nm. They are surface-modified with PD-1 and transforming growth factor- $\beta$  (TGF- $\beta$ ) receptors.

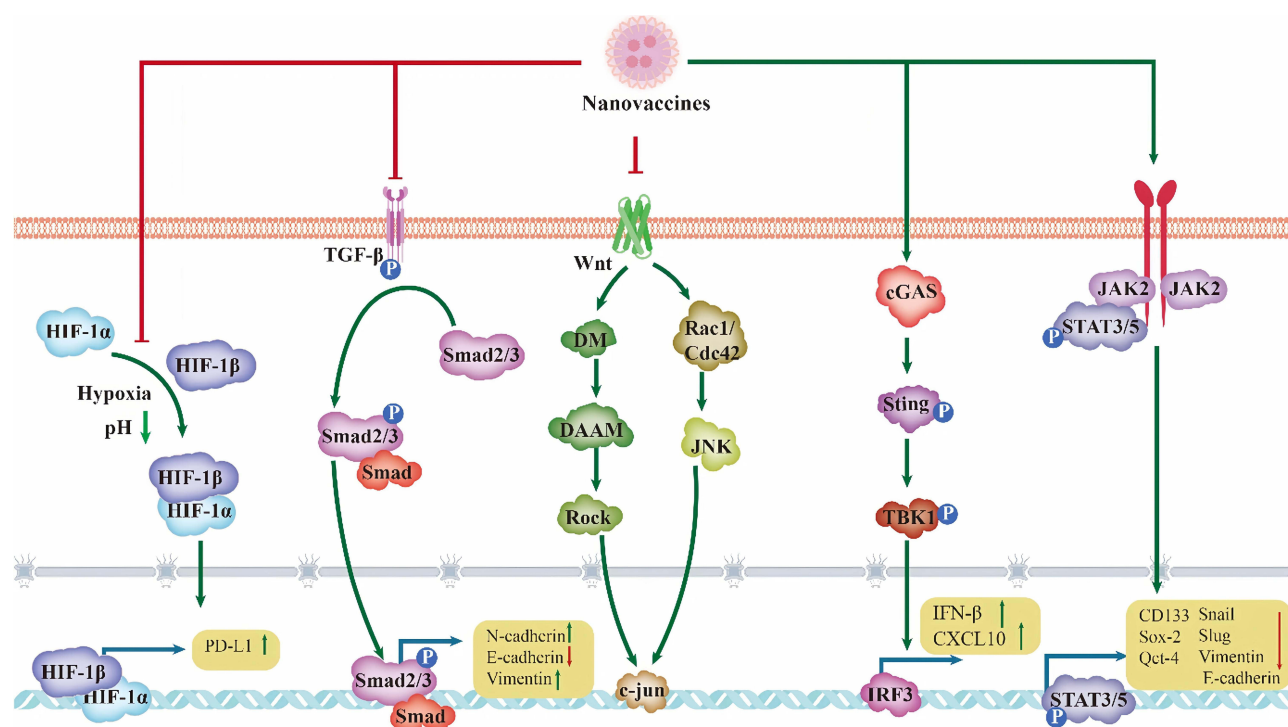
They can block the PD-L1 pathway on cancer cells, scavenge TGF- $\beta$  secretion, ultimately kill cancer cells, and prevent cytotoxic T cell exhaustion (Figure 7). To address the limited efficacy of immune checkpoint blockade therapy, researchers developed T cell membrane-coated nanoparticles (TCMNPs). These TCMNPs carry T cell membrane-derived proteins and are modified with the adhesion protein LFA-1, with a particle size controlled at 150–200 nm; they can not only achieve tumor targeting but also block immune checkpoint interactions.<sup>133</sup> Furthermore, they can be loaded with anticancer drugs like dacarbazine, inducing FasL-mediated apoptosis through drug release, mimicking the function of cytotoxic T lymphocytes (CTLs). However, TCMNPs are unresponsive to immunosuppressive molecules like TGF- $\beta$ 1 and PD-L1 but can clear them.<sup>134</sup>

Beyond antibody blockade, various alternatives such as PD-L1 aptamers and novel nanocarriers are under development to reduce the cost of tumor immunotherapy. Some studies utilize PD-L1 aptamer-modified gold nanorods with a particle size of 50–80 nm to construct a PD-L1-targeted therapeutic system. This system can simultaneously block immune checkpoints, promote NP accumulation within tumors and generate strong photoacoustic signals. When combined with synchronous photothermal therapy, this approach significantly enhances anti-tumor immunity and inhibits T cell exhaustion by activating CD8<sup>+</sup> T cells and suppressing Treg cells.<sup>135</sup> For remodeling the tumor microenvironment, components within the TME involved in regulating the T cell exhaustion process are increasingly becoming a focus of attention.<sup>78,136</sup> Tumor-associated macrophages (TAMs) are the most abundant immune cell type in the TME<sup>137,138</sup> and, as key components of this microenvironment, can influence tumor progression.<sup>137</sup> TAMs can be categorized into M1 and M2 types: M1 TAMs typically possess tumor-killing capabilities, whereas M2 TAMs exhibit immunosuppressive properties, pro-tumor functions, and the ability to promote distant metastasis.<sup>139</sup> Furthermore, the TME contains various regulatory immunosuppressive cells, such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and regulatory dendritic cells, which play roles in tumor immune escape and pose challenges to cancer immunotherapy.<sup>140</sup> Therefore, remodeling the TME by targeting TAMs (including inducing M2-to-M1 repolarization, inhibiting TAM recruitment, and depleting TAMs) and targeting other immunosuppressive cells has become an important strategy for cancer treatment and reversing T cell exhaustion.<sup>139</sup> Most NDDSs for TME remodeling are designed with a particle size of 100–200 nm and surface-functionalized to respond to the TME, which can enhance targeting efficacy while avoiding systemic toxicity.

Nanoscale strategies targeting T cell metabolism have emerged as a promising approach to reverse T cell exhaustion. Mitochondrial functional impairment and hypoxia are core metabolic features and drivers of T cell exhaustion. While low expression of major histocompatibility complex class I (MHC I) molecules on tumor cells leads to inefficient T cell recognition, thereby affecting treatment efficacy. Zhang et al utilized oxidized sodium alginate-modified tumor cell membrane vesicles with a particle size of 80–120 nm—featuring biocompatibility and tumor targeting—loaded with axitinib, 4-1BB antibody and PCSK9 inhibitor PF-06446846. Axitinib alleviates tumor hypoxia, 4-1BB antibody promotes T cell mitochondrial biogenesis, and PF-06446846 enhances MHC I expression, synergistically restoring T cell function.<sup>141</sup> Mitochondrial dysfunction is an intrinsic trigger of exhaustion. Wu Hua et al demonstrated that mitochondrial dysfunction pushes T cells toward terminal exhaustion by maintaining stable hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) protein expression and associated glycolytic reprogramming. Moreover, HIF-1 $\alpha$  initiates downstream PD-L1 gene transcription. Given that hypoxia and reactive oxygen species are major drivers of immune exhaustion, research teams have developed ROS-responsive manganese dioxide nanoparticles with a particle size of 50–100 nm and biocompatible surface modification, achieving precise delivery of the HIF-1 $\alpha$  inhibitor acriflavine to tumor sites, which successfully alleviates T cell exhaustion and activates tumor-specific immune responses.

Mitochondrial dysfunction is an intrinsic trigger of T cell exhaustion. As illustrated in Figure 8, Wu et al demonstrated that mitochondrial dysfunction can drive T cells toward a terminally exhausted state by maintaining the stable expression of hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) and mediating glycolytic reprogramming.<sup>142</sup>

Overall, the above studies confirm the great potential of NP-based strategies in reversing T cell exhaustion. However, to date, ultrasmall-sized nanomaterials (<10 nm) still pose significant safety risks: such materials can easily penetrate physiological barriers and induce adverse effects including endocrine disruption, reduced fertility and metabolic diseases. Their shape, composition and surface charge can further exacerbate toxicity—for example, rod-shaped ultrasmall nanomaterials have stronger in vivo accumulation, positively charged ultrasmall nanomaterials tend to non-specifically



**Figure 8** Signaling pathways intervened by nano-vaccines in tumor metastatic cascades. This schematic depicts how nano-vaccines regulate key signaling pathways in the tumor microenvironment to enhance anti-tumor immunity: they inhibit hypoxia-driven HIF-1 $\alpha$ / $\beta$  signaling (reducing PD-L1-mediated T cell suppression), block TGF- $\beta$ /Smad and Wnt cascades (reversing epithelial-mesenchymal transition), and activate cGAS-STING-TBK1 signaling (inducing IFN- $\beta$ /CXCL10 for immune recruitment while suppressing tumor stemness via STAT3/5 inhibition). Collectively, these actions reshape the immunosuppressive niche and promote anti-tumor responses. The upward (↑) and downward (↓) arrows in the figure denote the upregulation and downregulation of the expression or activity of the corresponding molecules, respectively. These changes reflect the activation of key signaling pathways in the tumor microenvironment, which are inhibited by nano-vaccines to suppress tumor metastatic cascades.<sup>143</sup> @copyright© 2024.

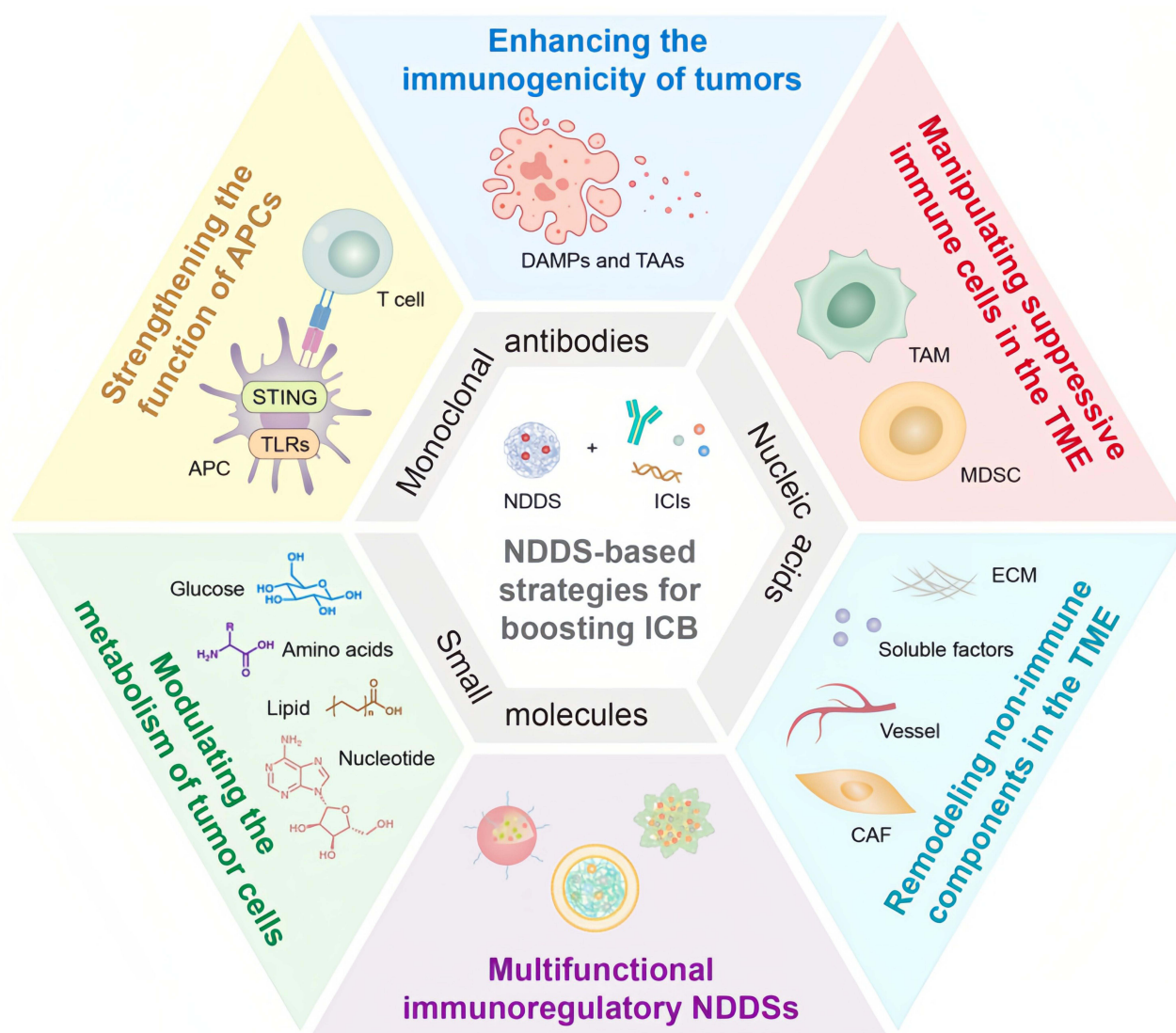
bind to biological macromolecules, and non-biodegradable inorganic ultrasmall nanomaterials can accumulate in organs such as the liver, lungs and kidneys for a long time. In contrast, clinically approved and mainstream investigational nano-delivery systems effectively balance delivery efficacy and in vivo safety by controlling the particle size within 50–200 nm, adopting biocompatible/biodegradable materials (lipids, biodegradable polyesters, natural polysaccharides), designing neutral/weakly negative surface charge and performing surface functionalization with PEG or targeting ligands. Further in-depth research is still needed in the future; through precise regulation of the physicochemical parameters of nanomaterials, the dual improvement of efficacy and safety of T cell-targeted nano-therapies can be achieved.

## Novel Nano-Delivery Engineering and Strategies

### Delivery of Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) have revolutionized cancer immunotherapy, but their clinical utility is often limited by poor tumor targeting, insufficient TME penetration, and systemic immune-related adverse events. To overcome these challenges, strategies to optimize ICI delivery have become a focal point of translational research—and Figure 9 encapsulates the multifaceted framework of nanoscale drug delivery systems (NDDSs) as a transformative solution for enhancing ICI efficacy.

As illustrated (Figure 8), NDDS-based ICI delivery integrates synergistic approaches to address ICI limitations: it enables co-delivery of ICIs with immunostimulatory agents (like, DAMPs/TAAAs to boost tumor immunogenicity, STING/TLR agonists to activate APCs), modulates the TME (targeting immunosuppressive cells like TAMs/MDSCs, remodeling ECM barriers, or regulating tumor metabolism to alleviate nutrient competition), and combines ICIs with other therapeutics (monoclonal antibodies, small molecules) to counteract resistance. These functions converge in



**Figure 9** NDDS-based strategies for boosting ICB therapeutic effects. ICIs include monoclonal antibodies, nucleic acids, and small molecules. The combination therapy strategies include enhancing the immunogenicity of tumors, strengthening the function of APCs, manipulating suppressive immune cells in the TME, modulating the metabolism of tumor cells, remodeling non-immune components in the TME, and employing multifunctional immunoregulatory NDDSs.<sup>144</sup>@copyright©2025.

**Abbreviations:** NDDS, nano drug delivery system; ICB, immune checkpoint blockade; ICIs, immune checkpoint inhibitors; APCs, antigen presenting cells; TME, tumor microenvironment.

multifunctional immunoregulatory NDDSs, which not only improve the spatiotemporal control of ICI delivery but also reshape the TME into an immunostimulatory niche.

Such NDDS platforms—tailored via advanced nanomaterial engineering—are particularly well-suited to address ICI delivery challenges, as their tunable physicochemical properties (like, size, surface ligands, stimulus-responsive release) enable precise targeting, reduced off-target toxicity, and coordinated modulation of both ICIs and the TME.

Nanodrug delivery systems have been widely used for the targeted delivery of various immune checkpoint inhibitors, with most research focusing on PD-1/PD-L1 inhibitors (Table 2). Currently, various types of immune checkpoint inhibitors, such as antibodies, nucleic acids, and small molecule inhibitors, can be specifically delivered to tumor tissues via nano-delivery systems to enhance their antitumor effects. These drugs primarily function by disrupting antibody-ligand interactions. However, monoclonal antibodies, as macromolecular drugs, have inherent limitations, such as poor tumor tissue penetration and insufficient targeting, leading to off-tumor, on-target effects upon systemic administration, severely affecting treatment efficiency and causing immune-related adverse events. To address these challenges,

**Table 2** Characteristics of Nanodelivery Systems for T Cell Targeting

| Type of Nano-Delivery System                                   | Core Materials                                                                       | Typical Particle Size Range(nm)      | T Cell Targeting-Related Functions                                                                                                                                                                           | Advantages                                                                                                                                                                           | Limitations                                                                                                    |
|----------------------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| Liposomes                                                      | Natural/synthetic phospholipids, cholesterol; PEG (polyethylene glycol modification) | (FDA-approved /optimal:100–200)      | Encapsulate immune checkpoint inhibitors/ cytokines for tumor-targeted delivery; modify T cell surface receptor ligands (eg., PD-1, CD3) to enhance targeting                                                | Excellent biocompatibility; co-loading of hydrophilic/hydrophobic drugs achievable; mature clinical translation (multiple FDA-approved formulations); reduced systemic drug toxicity | Low loading capacity for lipophilic drugs; susceptible to opsonization and clearance; potential immunogenicity |
| Polymeric Micelles                                             | Block copolymers (PEG-PDLLA, peg-PVA); natural polymers (hydroxyethyl starch)        | 10-100 (optimal:50–100)              | Encapsulate hydrophobic chemotherapeutics/ metabolic modulators to synergistically activate CD8+T cells; surface ligand modification to enhance tumor penetration and Tex targeting                          | High drug loading capacity with strong structural tunability; long in vivo circulation time; precise stimulus-responsive drug release                                                | Poor biodegradability of some polymers; difficult to control batch consistency in large-scale production       |
| Lipid Nanoparticles (LNPs)                                     | Ionizable lipids, helper phospholipids, cholesterol, PEG lipids                      | 80-120                               | Encapsulate mRNA/siRNA (eg., PD-1 siRNA, LMP2 mRNA) and deliver to T cells/antigen-presenting cells to activate specific T cell immunity                                                                     | First-choice carrier for nucleic acid drug delivery; lymph node targeting achievable; regulable biocompatibility                                                                     | Prone to clearance by the reticuloendothelial system in vivo; poor long-term storage stability                 |
| Gold Nanomaterials (Gold Nanoparticles/ Gold Nanorods)         | Gold element; PAMAM dendrimers, PD-L1 aptamers (surfaces modification)               | <50 (nanoparticles);50–80 (nanorods) | Surface modification with PD-1 antibodies/ aptamers to block immune checkpoints; deliver siRNA for Tex gene regulation; photothermal effect to synergistically activate T cells                              | Precise targeting modification; integrated therapeutic and imaging functions (theranostics); high gene delivery efficiency                                                           | Non-biodegradable with potential in vivo accumulation at high doses; toxicity risks for certain sizes (<10 nm) |
| Bioinspired Vesicles/ Membrane-Coated Nanoparticles            | T cell membranes, tumor cell membranes; lipid core(TCMNPs)                           | 100-200 (TCMNPs:150–200)             | T cell membrane vesicles modified with PD-1/ TGF- $\beta$ receptors to block the PD-L1 pathway and scavenge TGF- $\beta$ ; TCMNPs mimicking CTL functions to kill tumors and activate T cells                | Strong targeting ability with easy TME penetration; low off-target effects; dual regulation of the immune microenvironment achievable                                                | Complex preparation process with high cost; great difficulty in storage and large-scale production             |
| Inorganic Nanoparticles (Manganese Dioxide/ Mesoporous Silica) | Manganese dioxide (MnO <sub>2</sub> )                                                | 50-100                               | MnO <sub>2</sub> nanoparticles delivering HIF-1 $\alpha$ inhibitors to alleviate tumor hypoxia and reverse Tex exhaustion; mesoporous silica co-loading chemotherapeutics and immunomodulators to induce ICD | Strong stimulus-responsiveness (adapting to TME characteristics); excellent multi-drug co-loading capacity; regulable TME metabolic/oxidative microenvironment                       | Poor biodegradability of some inorganic materials; potential organ toxicity due to long-term accumulation      |
| Polymeric Nanoparticles                                        | Poly HPMA, oxidized sodium alginate,polyesters (PLGA); dendrimers                    | 80-120                               | Modification with tumor cell membrane-targeting peptides for co-delivery of anti-angiogenic drugs and immunomodulators; dendrimers enhancing drug-T cell interactions                                        | Good biodegradability with low in vivo toxicity; broad drug loading range (small molecules/proteins/nucleic acids); precise regulation of TME and Tex metabolism achievable          | Poor water solubility of some polymers; shorter in vivo circulation time than micelles                         |

nanodrug delivery systems have been developed to improve drug distribution *in vivo*, enhance tumor-targeting capability, and increase penetration.<sup>145,146</sup>

Antibodies can be encapsulated in diverse nanocarriers, including liposomes, polymeric micelles, gold nanoparticles, and dendrimers, which minimize their off-target distribution and enhance site-specific delivery efficiency.<sup>147–150</sup> Research has explored using nano-delivery systems to deliver anti-PD-1 antibodies targeting tumor cells and anti-PD-L1 antibodies targeting naïve T cells.<sup>151</sup> Furthermore, by modifying functional binding groups on the nanocarrier surface, tissue-specific targeting can also be achieved. For example, leveraging glucose transporter 1 (GLUT1), a transporter highly expressed in brain capillaries, researchers constructed a glycosylated polyethylene glycol-modified nano-delivery system for targeted drug release in brain tumors. The PEG chains on this system can be cleaved under the reductive conditions of the tumor microenvironment, enabling selective drug release within brain tissue.<sup>152</sup>

Simultaneously, the CRISPR/Cas system, as an efficient gene-editing tool, can be used to knockout PD-1/PD-L1 genes. To improve nucleic acid stability and delivery efficiency, researchers have introduced nano-delivery systems to protect them from degradation. Rational design of nano-systems for CRISPR/Cas delivery requires comprehensive consideration of multiple factors, including selecting appropriate nanomaterials to reduce non-specific *in vivo* distribution and promote targeted release, as well as adopting suitable gene-editing systems to improve editing efficiency and reduce off-target effects.<sup>153</sup> For example, one study utilized genetically engineered adenovirus to construct a silk fibroin-derived hydrogel for delivering CRISPR/Cas9 to edit the PD-L1 gene in HEPA 1–6 hepatocellular carcinoma cells. This nano-system promoted local retention of CRISPR/Cas9 and achieved efficient gene transduction within 9 days.<sup>154</sup> Additionally, stimuli-responsive nano-delivery systems can react to specific tumor microenvironment features to mitigate side effects of the CRISPR/Cas9 system.<sup>155,156</sup> For instance, a double-locked nanoparticle (DLNP) loads CRISPR/Cas13a in its core, with a shell composed of dual-responsive polymer layers. This structure not only improves the NP's stability in the circulatory system and biosafety but also enables responsive release of CRISPR/Cas13a from its core within tumor tissue.<sup>157</sup>

Through optimization of gene-editing systems and nanomaterials, PD-L1 gene knockout efficiency has been significantly improved. Current research involves gene-editing systems including CRISPR/Cas9 and CRISPR/Cas13a, applicable for gene editing in tumor cells or T cells. In terms of nanomaterials, polymeric nanoparticles, lipid-based nanoparticles, hydrogels, gold nanoparticles, and exosomes have all been proven to be promising strategies for constructing efficient NDDSs to transport these gene-editing tools. The diverse applications of NDDSs in ICI delivery also provide engineered design insights for the delivery optimization of another class of key drugs in cancer immunotherapy—cytokines and small molecule modulators, and nanomaterial-based drug repurposing strategies have emerged as an important approach to address the inherent defects of these drugs and enhance their efficacy in cancer immunotherapy.

Notably, recent cutting-edge research has further advanced nanomaterial-based strategies for direct T cell targeting, developing novel engineered platforms to precisely modulate T cell activation, trafficking and functional polarization in the TME,<sup>158–161</sup> which provides new translational insights for the optimization of NDDSs in ICI delivery and T cell-based immunotherapy.

## Delivery of Cytokines and Small Molecule Modulators

Drug repurposing (also known as repositioning or redirecting) refers to the therapeutic strategy of applying failed drug candidates or marketed drugs to new indications.<sup>162</sup> Leveraging the active targeting ability of nanodrug delivery systems to tumor sites and their enhanced permeability and retention (EPR) effect—a classic paradigm whose clinical validity and universality have been increasingly challenged by recent studies demonstrating the EPR mechanism is likely incorrect in human tumors<sup>163–165</sup> cytotoxic drugs, cytokines, and adjuvants can overcome their inherent toxicity and side effects, ultimately achieving repositioning in the field of tumor immunotherapy.<sup>166</sup> (Table 3) The engineered design and rational selection of different nanocarriers are the core of achieving efficient delivery of these drugs, which requires a comprehensive consideration of key indicators such as targeting efficiency, drug loading capacity, release kinetics, and *in vivo* stability. Mainstream nanocarriers including liposomes, polymeric micelles, and inorganic nanoparticles have their own focuses on design principles and application scenarios, which form an important foundation for the engineered development of nanodrugs.

**Table 3** Summary of the Three Categories of Nanomaterial-Based Delivery Systems for Drug Repurposing

| Category                                          | Agent             | Composition                                           | Outcomes                                                                                                                              | References |
|---------------------------------------------------|-------------------|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|------------|
| Nanomaterial-based cytotoxic drug delivery system | DOX               | Polymeric lipid and manganese dioxide nanomaterial    | Alter the immunosuppressive environment of breast cancer by enhancing T-cell activity and attenuating acidosis                        | [2]        |
|                                                   | Oxaliplatin       | IDO and mesoporous silica nanomaterial                | Improve in situ pancreatic ductal adenocarcinoma by inducing ICD that recruits CTL from TME and releases HMGB-1 required for DC       | [3]        |
|                                                   | PTX               | sEVs nanomaterials with PTX                           | Enhance anti-mammary tumor activity through activation of macrophage-mediated inflammation                                            | [5]        |
| Nanomaterial-based cytokine delivery system       | IL-2              | Hydroxyethyl starch nanomaterials and their ligands   | Promote efficient targeting of the T-cell population and proliferation of activated CD4 CD25 T cells                                  | [6]        |
|                                                   | TRAIL             | Liposomal nanomaterials with TRAIL                    | Increase pro-apoptotic activity of the exogenous TRAIL pathway and apoptosis-inducing caspases for the treatment of colorectal cancer | [7]        |
|                                                   | Anti-HER2 and CRT | Polystyrene nanomaterials with anti HER2 and CRT      | Target cancer cell-specific receptors and enhance tumor lethality by T cell                                                           | [8]        |
| Nanomaterial-based adjuvant delivery system       | Poly I:C          | OVA and Poly ( $\gamma$ -glutamic acid) nanomaterials | Enhance the secretion of type I IFN- $\alpha$ and IFN- $\beta$ by uptake of antigen-presenting cells to activate anti-tumor immunity  | [9]        |
|                                                   | CpG               | AlbiAg, AlbiCpG and Albumin binding nanocomplexes     | Induce antigen-specific T-cell responses, alter immunosuppression in TME and enhance immunotherapy                                    | [10]       |

**Abbreviations:** DOX, doxorubicin; IDO, Indoleamine 2,3-dioxygenase; ICD, immunogenic cell death; HMGB-1, high mobility group protein B1; PTX, paclitaxel; TRAIL, tumor necrosis factor related apoptosis-inducing ligand; CRT, calreticulin; OVA, ovalbumin; AlbiAg, albumin-binding antigen; AlbiCpG, albumin-binding adjuvant.

## Repurposing of Cytotoxic Drugs

Nanomaterial-based cytotoxic drug delivery systems can reduce off-target toxicity in immune cells and systemic toxicity, reverse the immunosuppressive state of tumor tissue by inducing immunogenic cell death (ICD), and prolong drug retention time at tumor sites. In terms of carrier selection, liposomes or polymeric micelles are mostly used for these drugs. The bilayer membrane structure of liposomes has good biocompatibility with biological membranes, can efficiently encapsulate hydrophobic cytotoxic drugs, has strong in vivo circulation stability, and can easily achieve tumor targeting through surface modification with targeting peptides.<sup>167</sup> Polymeric micelles have higher drug loading capacity and structural tunability, and their stimulus-responsive design (pH, ROS responsiveness) can achieve precise drug release in the TME and reduce exposure to normal tissues.<sup>168</sup> For example, a study in a mouse model of breast tumors found that a manganese dioxide nanomaterial sustained-release system loaded with polymeric lipids and doxorubicin (DOX) could improve the immunosuppressive environment by enhancing T cell activity and alleviating acidosis, thereby achieving immune enhancement.<sup>169</sup> Another study confirmed that mesoporous silica nanomaterials loaded with oxaliplatin (OX) and an IDO inhibitor could improve an orthotopic pancreatic cancer model by inducing ICD; this process recruits cytotoxic T lymphocytes (CTLs) from the TME and releases high mobility group box 1 (HMGB-1) required for dendritic cell (DC) activation.<sup>170</sup> As inorganic nanoparticles, mesoporous silica has a porous structure that endows it with high drug loading capacity and multi-drug co-delivery ability, making it an ideal carrier for the co-delivery of cytotoxic drugs and immunomodulators.

## Repurposing of Cytokines

Nanomaterial-based NDDSs can address the challenges faced by cytokines, such as drug resistance, off-target effects, short half-life, high toxicity, inflammatory immune responses, and generally low clinical efficacy, thereby maximizing the role of cytokines in cancer immunotherapy. Cytokines are mostly water-soluble proteins, and polymeric micelles and liposomes are the main carrier choices. Natural polymeric micelles such as hydroxyethyl starch can form stable

composite systems with cytokines through hydrophilic chains, improve their *in vivo* stability to avoid rapid degradation, and achieve specific binding to cytokine receptors through surface modification.<sup>171</sup> Liposomes can achieve intracellular delivery of cytokines through membrane fusion, improving their action efficiency in immune cells.<sup>172</sup> Nanomaterial-based drug delivery systems can overcome challenges faced by cytokines, such as resistance, off-target effects, short half-life, high toxicity, inflammatory immune responses, and generally low clinical efficacy, thereby maximizing the role of cytokines in tumor immunotherapy. For instance, incorporating hydroxethyl starch nanomaterials allows interleukin-2 (IL-2) to bind more closely to its receptor, ultimately promoting more efficient targeting of T cell subsets.<sup>173,174</sup> Furthermore, ligands on the surface of hydroxethyl starch nanomaterials can indirectly promote the proliferation of activated CD25<sup>+</sup> T cells, thereby enhancing immune responses.<sup>175</sup>

### Repurposing of Adjuvants Nanodrug Delivery Systems

NDDs have been proven capable of co-delivering adjuvants and antigens to achieve effective antigen cross-presentation, mainly due to their ability to overcome the strong toxicity of adjuvants and the limited range of suitable patients. The co-delivery of adjuvants and antigens has high requirements for the co-loading capacity and release synchrony of carriers, so polymeric micelles and inorganic nanoparticles have become the mainstream choices: polymeric micelles can separately encapsulate hydrophobic adjuvants and hydrophilic antigens through a core-shell structure to achieve their synchronous delivery and stimulus-responsive co-release;<sup>176</sup> inorganic nanoparticles such as gold nanoparticles and mesoporous silica can achieve the loading of adjuvants and antigens through both surface adsorption and pore encapsulation, and their stable physicochemical properties can enhance the interaction with APCs through surface modification.<sup>177</sup> Kim et al developed a novel delivery system using two different nanomaterials to carry the adjuvant—Toll-like receptor 3 (TLR3) agonist (Poly I:C)—and the tumor antigen mimic ovalbumin (OVA), respectively. This system, upon uptake by antigen-presenting cells, promotes the secretion of type I interferons (IFN- $\alpha$  and IFN- $\beta$ ), thereby activating antitumor immunity.<sup>178</sup> Other research showed that nanomaterial-delivered albumin-bound antigen (AlbiAg) and albumin-bound adjuvant (AlbiCpG) could induce antigen-specific T cell responses in mice, which is crucial for reversing immunosuppression in the TME and improving immunotherapy efficacy.<sup>179,180</sup> Additionally, nanomaterial-based antigen-adjuvant co-delivery can direct immune responses toward specific types, such as T helper 1 (Th1) or T helper 2 (Th2) responses.<sup>181</sup>

In the engineered development of tumor-targeting NDDSs, rational material selection, surface modification, advanced manufacturing technologies, and predictive models are the core design principles for optimizing T cell targeting efficiency. Material selection needs to balance biocompatibility, drug loading characteristics, and *in vivo* metabolic rules; the composite modification of natural polymers (chitosan, gelatin) and synthetic polymers (PEG, polylactic acid) can achieve a balance between biocompatibility and structural stability.<sup>182</sup> Surface modification achieves enhanced targeting of carriers to tumor tissues and specific T cells through the precise grafting of ligands such as targeting peptides (eg., RGD, TAT), antibodies, and glycosyl groups, and simultaneously realizes “stealth” design through PEGylation to reduce clearance by the mononuclear phagocyte system.<sup>183</sup> Advanced manufacturing technologies such as microfluidic preparation and supercritical fluid technology can achieve large-scale preparation of nanocarriers and precise regulation of particle size and morphology, improving batch-to-batch consistency.<sup>184</sup> Machine learning predictive models can simulate and optimize targeting efficiency and release kinetics based on carrier physicochemical properties, drug characteristics, and *in vivo* delivery data, realizing the prospective design of NDDSs.<sup>185</sup> The engineered modification and combined application of different nanocarriers will further enhance the delivery efficiency of cytokines and small molecule modulators, providing a more complete technical support for the multi-drug synergistic application in cancer immunotherapy.

### Nanoparticles Regulating T Cell Exhaustion Through Synergistic Actions

T cell exhaustion is defined by compromised effector function and elevated inhibitory checkpoints such as PD-1, represents a major barrier to durable anti-tumor immunity. However, rationally engineered nanomaterials offer a powerful, multi-pronged approach to reverse this immunosuppressive state. As shown in Figures 9 and 10, the pG2-Gem nanopatform (a dendron-functionalized poly(HPMA)-based nanoparticle loaded with gemcitabine and  $\alpha$ PD-1)

targets tumor cells to boost MHC-I expression (enhancing antigen presentation to T cells), modulates mitochondrial dynamics to elevate immunogenicity, and delivers PD-1 blockade: this synergy reactivates exhausted T cells, as evidenced by pG2-Gem+αPD-1 treatment yielding 7/8 long-term surviving mice (vs. minimal efficacy of monotherapies; Figure 10). These findings underscore how nanomaterial-based strategies can simultaneously address the multiple, interconnected drivers of T cell exhaustion within the tumor microenvironment, offering a transformative path to improving cancer immunotherapy outcomes.

Targeting T cell metabolism with nanoparticles (NPs) has emerged as a novel strategy for reversing functional exhaustion. T cell exhaustion is primarily characterized by metabolic features such as impaired mitochondrial function and hypoxia, which are also key driving factors of exhaustion. Additionally, low expression of major histocompatibility complex class I (MHC I) molecules on tumor cells leads to reduced recognition efficiency by T cells, thereby affecting immunotherapy efficacy. Zhang Ding et al utilized tumor cell-conditioned medium (CM)-modified vesicles, further modified with oxidized sodium alginate, and co-loaded with axitinib, 4-1BB antibody, and the PCSK9 inhibitor PF-06446846. Among these, axitinib alleviates tumor hypoxia, the 4-1BB antibody promotes T cell mitochondrial biogenesis, and PF-06446846 upregulates MHC I expression, synergistically enhancing T cell recognition efficiency of tumor cells. The synergistic action of these drugs significantly restored the function of exhausted T cells.<sup>141</sup>

Mitochondrial dysfunction is an intrinsic trigger of T cell exhaustion. Wu Hua et al demonstrated that mitochondrial dysfunction can drive T cells toward a terminally exhausted state by maintaining stable hypoxia-inducible factor 1α (HIF-1α) protein expression and its mediated glycolytic reprogramming. Furthermore, hypoxia-inducible factor-1α can initiate transcription of the downstream PD-L1 gene. Given that hypoxia and reactive oxygen species (ROS) are major drivers of immune exhaustion, the research team developed ROS-responsive manganese dioxide (MnO<sub>2</sub>) nanoparticles to deliver the HIF-1α inhibitor acriflavine to tumor sites, successfully alleviating T cell exhaustion and activating tumor-specific immune responses.

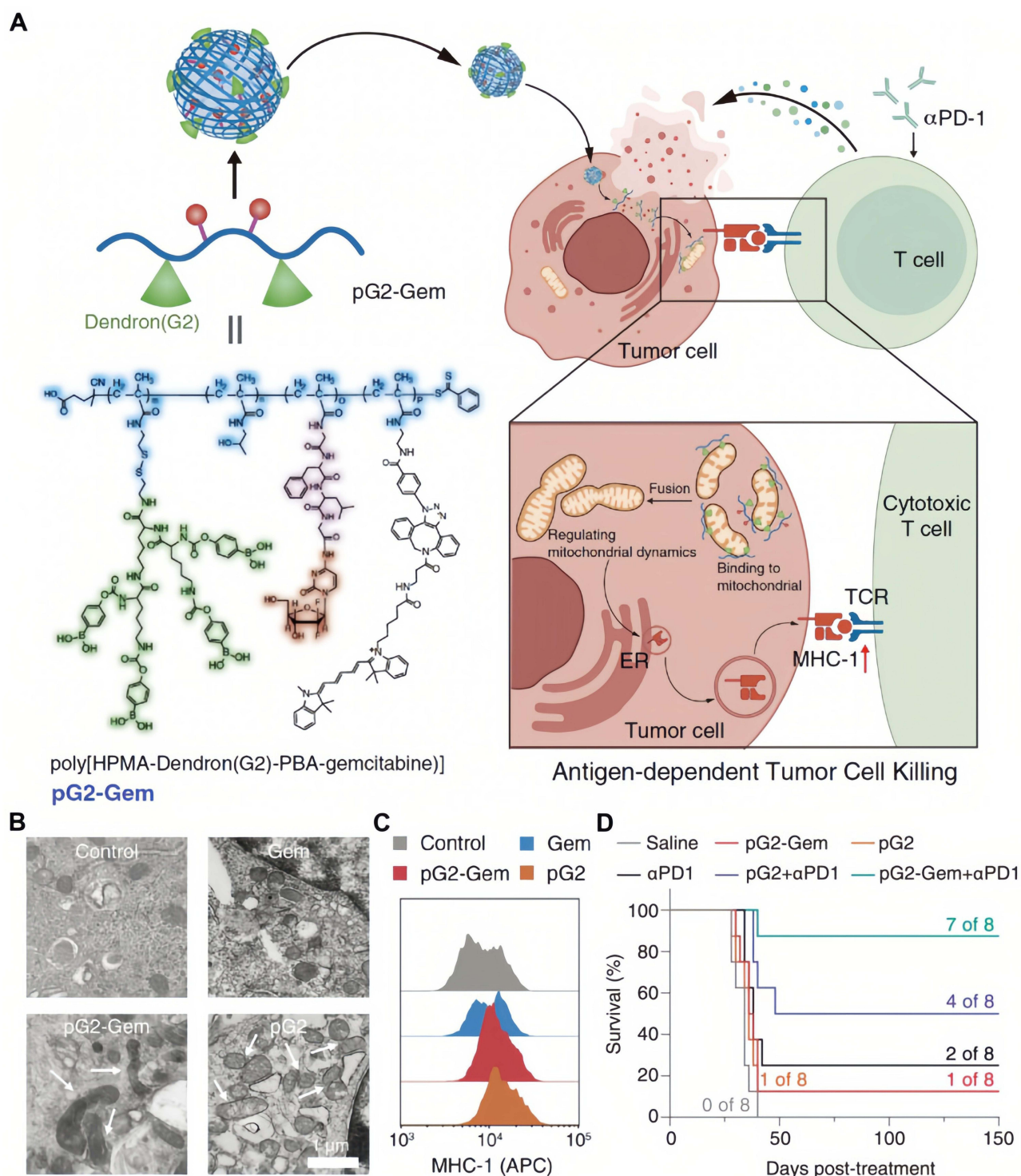
Overall, existing data indicate that NP-based strategies have potential in reversing T cell exhaustion, but their specific mechanisms and applications require further in-depth research. Recent advances in T cell-targeted nanomedicine have expanded the translational landscape of NP-based immunotherapy, with novel studies reporting engineered nano-systems that enable selective delivery of immunomodulatory payloads to distinct T cell subsets, spatiotemporally regulate T cell metabolic and signaling pathways, and enhance the infiltration and effector function of tumor-reactive T cells in immunosuppressive TMEs.<sup>158–161</sup> These latest findings further highlight the versatility of nanomaterial engineering in addressing T cell dysfunction, and provide critical new design principles for the development of next-generation NDDSs to reverse T cell exhaustion and boost durable anti-tumor immunity.

## Challenges and Future Directions

### Existing Key Challenges for Therapeutics Targeting Exhausted T Cells

Despite the increasingly widespread application of nanomaterial drug delivery systems in tumor immunotherapy, their development is still confronted with numerous challenges.<sup>187</sup> Firstly, unlike mouse models used in clinical research, which lack the complexity of human tumors, human tumors are highly heterogeneous, and cells within the same tumor may undergo different mutations.<sup>188</sup> This results in each tumor having a distinct tumor microenvironment (TME), which drastically impairs the targeted delivery efficiency of nanodrug delivery systems toward T cells (Tex). Although humanized mouse models may help partially address these issues, the complexity of the clinical environment cannot be fully predicted and simulated.<sup>189</sup> In the future, conducting more clinical trials combined with biomarker analysis may provide more reliable outcomes for the application of nanomaterial-based drug delivery systems in tumor immunotherapy.

Secondly, considering the many gaps in TME research, the complexity and heterogeneity of TMEs make it difficult to accurately assess the targeting efficiency of nanomaterial-based drug delivery systems, ultimately impairing the efficacy of tumor immunotherapy. The complexity and heterogeneity of the TME not only make it difficult to accurately evaluate the targeting efficiency of nanomaterial-based drug delivery systems for Tex, ultimately compromising the efficacy of Tex-targeted tumor immunotherapy, but also entail a potential risk of promoting tumor metastasis during the remodeling of the immunosuppressive TME into an immune-supportive niche to reverse Tex exhaustion. Therefore, further research



**Figure 10** An NDDS derived from a mitochondrion-targeting dendronized polymer for synergic therapy with aPD-1 by promoting mitochondrial fusion and enhancing the expression of major histocompatibility complex (MHC)-I. **(A)** pG2-Gem released gemcitabine to exert its cytotoxic effects and the drug-free polymer, pG2, to regulate mitochondrial dynamics and promote mitochondrial fusion, thereby mediating MHC-I antigen presentation and leading to the activation of cytotoxic T cells for effective synergic therapy with aPD-1. **(B)** TEM images of mitochondrial fusion in 4T1 tumor cells treated with pG2 and pG2-Gem. Free Gem did not impact the mitochondrial morphology (Scale bar = 1  $\mu$ m). **(C)** Expression levels of MHC-I in 4T1 cells after treatment with Gem, pG2, and pG2-Gem. **(D)** Kaplan-Meier survival curves of the 4T1 tumor model after various therapies. The upward ( $\uparrow$ ) and downward ( $\downarrow$ ) arrows in the figure indicate the upregulation and downregulation of the expression or activity of corresponding molecules, respectively. The white arrows in the transmission electron microscopy (TEM) images highlight specific subcellular structures or morphological changes induced by the different treatments. Reproduced with permission from ref.<sup>186</sup> Copyright 2024, Wiley.<sup>144</sup>@copyright ©2025.

into the mechanisms of immune interactions within the TME and their long-term effects, along with developing corresponding regulatory strategies, appears particularly necessary.

Thirdly, toxicity remains a major drawback of nanomaterials. Ultrasmall-sized nanomaterials may induce adverse effects such as endocrine disruption, reduced fertility, and metabolic diseases when penetrating physiological barriers. This may be attributed to when nanomaterials react with biological substances in the body, their properties may change, and there is considerable uncertainty regarding their final form and potential toxicity.<sup>190,191</sup> Reducing the toxicity of nanomaterials to acceptable levels is a key factor for their large-scale entry into clinical therapy. The fundamental approach to reducing toxicity should start with comprehensive toxicological studies by performing detailed characterization of nanomaterials, the data obtained from toxicological testing can be made more reliable, reproducible, and comparable. Additionally, modifying specific material properties is also a better method for designing less toxic nanomaterials, such as controlling nanotube length, applying surface-active coatings, and removing impurities,<sup>192</sup> thereby reducing non-specific damage of nanomaterials to normal T cell subsets and ensuring the safety of Tex-targeted therapeutics.

Fourthly, from the perspectives of clinical translation and large-scale manufacturing, a major issue is whether the biological characteristics, stability, and manufacturability of nanomaterial drug delivery systems are guaranteed. To address this, academic researchers and pharmaceutical companies have been studying and improving the quality control and manufacturing reproducibility of delivery systems. For example, by using monodisperse preparation methods to precisely control critical quality attributes (such as particle size, drug loading, and targeting ligand coating), the quality and yield of nanomaterials have been improved. Such production control enables drugs to act precisely on specific sites for cancer treatment while ensuring safety and quality. However, the large-scale production of Tex-targeted nano-delivery systems is still faced with challenges such as high difficulty in process standardization and high cost of batch-to-batch consistency control, which have become important obstacles to their clinical translation.

T cell exhaustion is a common phenomenon in the development of various pathogen infections and tumors, and it often aggravates with disease progression. Although its occurrence involves multiple factors, it is still necessary to deeply analyze how these mechanisms interact to affect immune responses and explore new targets for immunotherapy. In research on restoring T cell function, nanoparticle (NP)-based regulatory strategies have been widely investigated. Studies show that NP-based combination immunotherapies can elicit strong T cell responses and reverse T cell exhaustion. Although related research has deepened the understanding of exhaustion mechanisms and promoted new explorations in NP-targeted therapy, many key questions remain insufficiently answered. For example, although antibodies targeting pathways like PD-1/PD-L1 have shown some therapeutic efficacy, their underlying mechanisms are still not fully clear. Moreover, when simultaneously targeting multiple pathways to reverse T cell exhaustion, we lack a comprehensive molecular-level understanding of their synergistic effects. This also renders such combination therapies confronted with unique regulatory barriers—regulatory authorities have far higher requirements for combination therapies than single-agent therapies in terms of clarifying mechanisms of action, rationality of dose compatibility, and superimposed safety risks. However, the complexity of Tex exhaustion regulation makes it difficult to accurately define the action targets and effector links of combination therapies, increasing the difficulty of clinical application and approval. At the same time, Tex-targeted personalized therapy is also faced with the challenge of difficult patient stratification. Currently, there is a lack of specific biomarkers to distinguish the exhaustion degree, subtypes of Tex and their responsiveness to different therapeutics, making it impossible to achieve precision medication based on the individual Tex characteristics of patients and resulting in some patients being unable to benefit from targeted therapies.

Simultaneously, the application of nanoparticles in delivery systems still has several limitations, such as toxicity, low cellular uptake, off-target effects, and immune tolerance induced by tissue retention.<sup>193</sup> Among these, cytotoxicity is the most common issue.<sup>194</sup> Nanoparticles also possess a degree of immunogenicity, making them easily recognized and cleared by immune cells.<sup>195</sup> Furthermore, the size of nanoparticles affects cellular uptake efficiency because it regulates the enthalpic and entropic capabilities controlling nanoparticle adsorption processes.<sup>196</sup> Therefore, non-degradable nanoparticles within a certain size range may accumulate in tissues and organs such as the lungs, liver, and kidneys, which not only reduces the delivery efficiency targeting Tex but also poses potential long-term risks. In addition, Tex-targeted therapeutics also face long-term immunogenicity and safety issues associated with T cell memory: in the process

of reversing Tex exhaustion, nanomaterials or combination therapies may over-activate T cell immune responses, disrupt the homeostasis of T cell memory formation, lead to insufficient generation of memory T cells, and thus fail to induce long-lasting anti-tumor immunity. At the same time, the long-term *in vivo* retention of nanomaterials may trigger persistent immune stimulation, induce non-specific immune activation, and increase the risk of autoimmune diseases.

Hence, rationally designed nanoparticles are crucial for improving the efficacy of precision therapy. This review discusses various nanoparticle design strategies for reversing T cell exhaustion. Nanoparticle platforms possess a series of tunable characteristics such as size, morphology, surface properties, charge, and stimulus responsiveness, which can be optimally selected according to the specific application scenarios of Tex targeting in the treatment of chronic infections and tumors. For example, surface modifications have been implemented in some NP designs to reduce side effects from non-specific distribution; additionally, many nanoparticles incorporate polyethylene glycol (PEG) to avoid rapid clearance. However, the most critical question remains how to design NPs for targeted intervention to achieve optimal outcomes by deeply understanding the characteristics of exhausted T cells and their immunosuppressive microenvironment during exhaustion.

It is worth noting that NP-based strategies have shown significant effects in preclinical studies, indicating their important potential in combating tumors and infectious diseases. However, to date, only a few nanomaterials have entered clinical trials, and no related formulations have been approved for marketing.<sup>196</sup> Furthermore, NP-based antigen delivery may also induce immune tolerance, which provides possibilities for their application in autoimmune disease treatments.<sup>197,198</sup> Meanwhile, the *in vivo* distribution monitoring of Tex-targeted nanomaterial drug delivery systems still lacks reliable biomarkers and mature imaging technologies. Currently, there are no specific biomarkers that can real-time reflect the delivery trajectory of nanoparticles in the body, the efficiency of targeting Tex, and their accumulation in tissues. Existing imaging technologies are also unable to achieve accurate colocalization detection of nanoparticles and Tex, failing to provide real-time evidence for dose adjustment and efficacy evaluation in clinical medication, which has become another important obstacle to the clinical translation of Tex-targeted therapeutics. Therefore, in-depth research on the pathogenesis of T cell exhaustion and NP-based Tex-targeted immunotherapeutic strategies, as well as the development of highly specific biomarkers and precise imaging technologies for monitoring the *in vivo* distribution of nanoscale drug delivery systems (NDDSs), are the keys to developing novel anti-exhaustion intervention strategies targeting Tex.

## Future Perspectives: Development and Clinical Translation of Responsive Nanocarriers

A critical unresolved paradox in Treg cell-targeted immunotherapy lies in the conflicting functional phenotypes of PD-1<sup>+</sup> Treg cells, which are highly expressed in the tumor microenvironment (TME) and exhibit exhaustion-like characteristics. Conventional studies (like, Takeshima et al, 2019, PNAS) have demonstrated that PD-1<sup>+</sup> Treg cells possess enhanced immunosuppressive activity—PD-1 blockade can further amplify their ability to inhibit anti-tumor immunity, leading to tumor hyper-progression in some patients. However, emerging evidence challenges this paradigm, these evidence shows that in highly glycolytic TMEs (like, pancreatic cancer), PD-1<sup>+</sup> Treg cells undergo metabolic overload due to excessive lactate accumulation. This metabolic stress impairs the stability of Foxp3 (a master transcription factor maintaining Treg cell identity), driving their conversion into “effector-like Tregs” that secrete IFN- $\gamma$  and exert anti-tumor effects.<sup>199</sup> Such functional duality of PD-1<sup>+</sup> Treg cells, dictated by TME metabolic heterogeneity (like, lactate concentration), poses a major dilemma for universal therapeutic strategies: non-selective PD-1 blockade may either enhance immunosuppression or disrupt beneficial Treg conversion, while unregulated Treg depletion risks systemic autoimmunity.

Nanoparticle-based immunotherapy has now become a pivotal research direction in cancer immunotherapy. A variety of immunotherapeutic products based on different nanocarriers have obtained clinical trial approvals from drug regulatory authorities at home and abroad, covering multiple fields including mRNA tumor vaccines, targeted delivery of immune checkpoint inhibitors, and vectors for adoptive cell therapy. These products provide new solutions to the problems of poor targeting and high toxicity in traditional immunotherapy.<sup>200</sup> LK101 Injection, a personalized neoantigen mRNA tumor vaccine, has obtained clinical trial approvals from both China's NMPA and the US FDA, being the first domestic personalized neoantigen mRNA tumor vaccine. Its Phase I clinical trial in combination with ablation

therapy for hepatocellular carcinoma showed that it reduced the 2-year recurrence rate of patients to 36.4% and achieved a 100% 3-year survival rate, demonstrating significant clinical benefits.<sup>201</sup> JCXH-211, a self-replicating mRNA nanoparticle drug, has obtained IND approvals in China and the US, being the world's first self-replicating RNA drug encoding IL-12. Encapsulated by lipid nanoparticles (LNPs), it enables tumor tissue-specific delivery. In the Phase Ia clinical trial for advanced solid tumors such as melanoma and breast cancer, the maximum tumor shrinkage rate reached 43%, and it significantly increased the infiltration levels of T cells and NK cells at tumor sites;<sup>202</sup> ABO2102, a KRAS mutation-targeted mRNA nanoparticle vaccine, has obtained clinical approvals in China and the US, capable of encoding five common KRAS mutant antigens simultaneously. It is intended to be combined with sintilimab for the treatment of KRAS-mutant solid tumors such as pancreatic cancer and non-small cell lung cancer. Preclinical studies have confirmed that it can activate dual anti-tumor immune responses, breaking through the limitation of single target of traditional small-molecule inhibitors.<sup>203</sup> The clinical trial of LNP-mediated mRNA-5671 (targeting KRAS mutations) in combination with pembrolizumab,<sup>204</sup> conducted for solid tumors such as non-small cell lung cancer and pancreatic cancer, is one of the early international clinical studies on the combination of LNP-mRNA vaccines and immune checkpoint inhibitors. Despite the phased progress in clinical trials of nanoparticle-based immunotherapy, numerous common shortcomings have been exposed in the existing approved studies and clinical applications, becoming key obstacles to their clinical translation. First, defects in *in vivo* delivery and targeting: nanoparticles tend to accumulate in organs of the mononuclear phagocyte system such as the liver and spleen, leading to low delivery efficiency at tumor sites. In addition, some LNPs can trigger complement activation-related pseudo-allergic reactions, increasing the risk of systemic toxicity. Second, challenges in preparation and large-scale production: the particle size distribution and payload encapsulation efficiency of nanoparticles are difficult to achieve stable replication at the clinical scale, with significant batch-to-batch variations. In particular, the quality control of encapsulating sensitive biomacromolecules such as mRNA and cytokines is even more challenging. Third, insufficient therapeutic persistence: the expression of antigens or proteins mediated by mRNA nanoparticles is transient. Although it avoids the risk of genomic integration, it is difficult to induce long-term anti-tumor immune memory, and some vaccines require multiple administrations to maintain efficacy. Fourth, limited solid tumor infiltration capacity: the dense extracellular matrix and high interstitial pressure of tumors hinder the penetration of nanoparticles into the deep tumor tissue, resulting in limited efficacy in solid tumors such as pancreatic cancer and colorectal cancer. Fifth, persistent immune-related adverse events: nanocarriers themselves may induce non-specific immune activation, which further increases the incidence of adverse events such as immune enteritis and dermatitis when combined with immune checkpoint inhibitors.

To address the functional paradox of PD-1<sup>+</sup> Treg cells and overcome the clinical defects of existing nanoparticle-based immunotherapy, the development of metabolic-responsive nanocarriers represents a highly promising innovative direction, enabling spatiotemporally precise modulation of PD-1<sup>+</sup> Treg cells based on TME lactate levels. For low-lactate TMEs (eg., non-small cell lung cancer, where PD-1<sup>+</sup> Treg cells retain potent immunosuppressive function), the nanocarriers can be engineered with lactate-sensitive cleavage linkers to preferentially release PD-1 inhibitors (eg., anti-PD-1 antibodies or PD-1 siRNA) upon encountering low lactate concentrations. This blocks the PD-1/PD-L1 signaling axis in Treg cells, attenuating their immunosuppressive activity without interfering with effector T cell function. In contrast, for high-lactate TMEs (eg., pancreatic cancer, where PD-1<sup>+</sup> Treg cells are prone to Foxp3 instability and pro-tumor-to-anti-tumor conversion), the nanocarriers can be loaded with Foxp3 stabilizers (eg., CD28 agonists or histone deacetylase inhibitors) and triggered to release cargo under high lactate conditions. This maintains Treg cell identity and immunosuppressive capacity, preventing the uncontrolled conversion of Treg cells into effector-like subsets that may disrupt immune homeostasis or even promote chronic inflammation-related tumor progression.

The core advantage of this strategy lies in its ability to “adapt” to TME metabolic heterogeneity rather than adopting a one-size-fits-all approach. By integrating metabolic sensing elements (like, lactate-responsive polymers or pH-sensitive nanoparticles, as lactate accumulation lowers TME pH) with cell-targeting ligands (like, CTLA-4 or CD25 antibodies to specifically bind Treg cells), the nanocarriers ensure precise cargo delivery to PD-1<sup>+</sup> Treg cells while avoiding off-target effects on effector T cells or normal immune cells. Furthermore, this design can be combined with other therapeutic modalities (like, co-delivery of metabolic modulators to normalize TME lactate levels) to synergistically enhance anti-tumor immunity. Future research should focus on optimizing the sensitivity of metabolic-responsive elements, validating

the strategy in patient-derived xenograft models with distinct TME metabolic profiles, and exploring biomarkers (like, lactate dehydrogenase activity or Foxp3 methylation status) to guide patient stratification—ultimately resolving the functional paradox of PD-1<sup>+</sup> Treg cells and improving the precision of Treg-targeted cancer immunotherapy.

## Conclusion and Outlook

The strategy of targeting CD4<sup>+</sup>/CD8<sup>+</sup> exhausted T cells (Tex) with nanodrug delivery systems (NDDSs), through the organic combination of materials engineering and molecular targeting, has achieved precise regulation of key immune cell subsets within the tumor microenvironment (TME). This strategy breaks through the bottlenecks of traditional immunotherapy in delivery efficiency, targeting specificity, and toxicity control, providing a new technological pathway for reshaping the immunosuppressive TME and enhancing antitumor immune responses. Future research can focus on the following directions to further advance this field:

1. Precision Carrier Design: Develop NDDSs with subtype selectivity tailored to the heterogeneity of different Tex cell subtypes for finer immune regulation.
2. Multi-Mechanism Cooperative Delivery Systems: Construct integrated platforms capable of simultaneously delivering immunomodulators, metabolic reprogramming drugs, or gene-editing tools to reverse T cell exhaustion through multi-pathway synergy.
3. Deepening Clinical Translation Research: Strengthen the validation of NDDSs in preclinical models, promote their translation into clinical trials, and explore combinations with biomarker-guided patient stratification strategies.
4. Expanding Combination Therapy Strategies: Explore the synergistic effects of NDDSs targeting Tex cells with other tumor treatment modalities (such as chemotherapy, radiotherapy, immune checkpoint inhibitors, etc.) to enhance comprehensive treatment efficacy.

In summary, through continuous optimization of the design and application strategies of NDDSs, nanomaterial-based immunotherapy targeting Tex cells holds promise as an important direction for enhancing tumor immunotherapy efficacy and improving patient prognosis, possessing broad prospects for clinical translation.

## Abbreviations

Acriflavine, HIF-1 $\alpha$  Inhibitor; AlbiAg, Albumin-Binding Antigen; AlbiCpG, Albumin-Binding Adjuvant;  $\alpha$ KG, Alpha-Ketoglutarate; Albumin, Serum Albumin Nanoparticles; Apealea, Paclitaxel Nanocrystal Formulation; APC, Antigen-Presenting Cells; AKT, Protein Kinase B; Ameluz, 5-Aminolevulinic Acid Liposome Formulation; Axitinib, Tyrosine Kinase Inhibitor; Abraxane, Paclitaxel Albumin Nanoparticle Formulation; Bevacizumab, Monoclonal Antibody Targeting VEGF; CAF, Cancer-Associated Fibroblasts; cDC1, Type 1 Conventional Dendritic Cells; CMC, Critical Micelle Concentration; CRT, Calreticulin; cGAS, Cyclic GMP-AMP Synthase; CXCL10, C-X-C Motif Chemokine Ligand 10; CM, Conditioned Medium; CpG, Cytosine-Phosphate-Guanine; CRISPR/Cas, Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-Associated Proteins; CTBP1, C-Terminal Binding Protein 1; CTLA-4, Cytotoxic T-Lymphocyte Antigen 4; CTL, Cytotoxic T Lymphocytes; DAC, Dacarbazine; DAAM, Dishevelled-Associated Activator of Morphogenesis; DC, Dendritic Cells; DaunoXome, Daunorubicin Liposome Formulation; DepoCyt, Cytarabine Liposome Formulation; DOX, Doxorubicin; Doxil/Caelyx, PEGylated Doxorubicin Liposome Formulation; DM, Dimethyl Sulfoxide; DLNP, Double-Locked Nanoparticle; EC, Endothelial Cells; EBV, Epstein-Barr Virus; EPR, Enhanced Permeability and Retention; ETC, Electron Transport Chain; Eligard, Leuprolide Polymeric Micelle Formulation; FADH<sub>2</sub>, Flavin Adenine Dinucleotide Hydrogen; Ferroptosis, Iron-Dependent Cell Death; Gemcitabine, Antimetabolite Chemotherapeutic Agent; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; GLUT1, Glucose Transporter 1; GNRs, Gold Nanorods; HEPA 1-6, Hepatocellular Carcinoma Cell Line 1-6; HMGB-1, High Mobility Group Box 1; HIF-1 $\alpha$ , Hypoxia-Inducible Factor 1-Alpha; ICD, Immunogenic Cell Death; IDH2, Isocitrate Dehydrogenase 2; IDO, Indoleamine 2,3-Dioxygenase; IFN- $\gamma$ , Interferon-Gamma; IRF3, Interferon Regulatory Factor 3; IL-2, Interleukin-2; ICIs, Immune Checkpoint Inhibitors; JAK2, Janus Kinase 2; JNK, c-Jun N-Terminal Kinase; Kadcyla, Trastuzumab Emtansine (DM1-Conjugated Antibody); LAG-3, Lymphocyte-Activation Gene 3; LCK, Lymphocyte-Specific Protein Tyrosine

Kinase; LDH, Lactate Dehydrogenase; LFA-1, Lymphocyte Function-Associated Antigen 1; Lipodox, Doxorubicin Hydrochloride Liposome Formulation; Lipusu, Paclitaxel Liposome Formulation; LMP2, EBV Latent Membrane Protein 2; LncRNA, Long Non-Coding RNA; MDSCs, Myeloid-Derived Suppressor Cells; MHC-I, Major Histocompatibility Complex Class I; MHC-II, Major Histocompatibility Complex Class II; MAGE-A3, Melanoma-Associated Antigen A3; Marqibo, Vincristine Sulfate Liposome Formulation; MCRPC, Metastatic Castration-Resistant Prostate Cancer; MnO<sub>2</sub>, Manganese Dioxide; MEPACT, Mifamurtide Liposome Formulation; mTORC1, Mammalian Target of Rapamycin Complex 1; MYC, MYC Proto-Oncogene; MPC, Mitochondrial Pyruvate Carrier; Nanocrystal, Nanoscale Crystalline Particles; Nanoxel, Paclitaxel Polymeric Micelle Formulation; NADH, Nicotinamide Adenine Dinucleotide Hydrogen; NDDs, Nanomaterial-based Drug Delivery Systems; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; NFAT1, Nuclear Factor of Activated T Cells 1; N-Cadherin/E-Cadherin, Cadherin Family Proteins; NY-ESO-1, Cancer-Testis Antigen 1; Oncaspar, Pegaspargase Polymeric Micelle Formulation; Onivyde, Irinotecan PEGylated Liposome Formulation; Ontak, Denileukin Diftitox Protein Conjugate; OVA, Ovalbumin; OX, Oxaliplatin; PAMAM, Polyamidoamine; Pacical, Paclitaxel Polymeric Nanoparticle Formulation; Pazenir, Paclitaxel Micelle Formulation; PEG, Polyethylene Glycol; PEGylated Liposomes, Liposomes Modified with Polyethylene Glycol; PF-06446846, PCSK9 Inhibitor; PD-1, Programmed Death Protein 1; PD-L1, Programmed Death-Ligand 1; PDHK1, Pyruvate Dehydrogenase Kinase 1; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; PI3K, Phosphoinositide 3-Kinase; PHPMA, Poly[N-(2-Hydroxypropyl) Methacrylamide]; PICN, Paclitaxel Polymer/Lipid Nanoparticle Formulation; Poly I,C, Polyinosinic-Polycytidylic Acid; Poly(HPMA-Dendron(G2)-PBA-gemcitabine), Dendronized Polymer-Drug Conjugate; Polymeric Micelles, Amphiphilic Block Copolymer Micelles; PVA, Polyvinyl Alcohol; PVP, Poly(N-Vinyl-2-Pyrrolidone); PTX, Paclitaxel; Qct-4, Octamer-Binding Transcription Factor 4; Rac/Cdc42, Rho Family GTPases; Rock, Rho-Associated Protein Kinase; ROS, Reactive Oxygen Species; SAM, S-Adenosylmethionine; siRNA, Small Interfering RNA; Smad2/3, Mothers Against Decapentaplegic Homolog 2/3; Snail/Slug, Zinc Finger Transcription Factors; Sox-2, SRY-Box Transcription Factor 2; sEVs, Small Extracellular Vesicles; STAT, Signal Transducer and Activator of Transcription; STING, Stimulator of Interferon Genes; TAM, Tumor-Associated Macrophages; TAMs, Tumor-Associated Macrophages; TAN, Tumor-Associated Neutrophils; TBKI, TANK-Binding Kinase 1; TCR, T Cell Receptor; TCA, Tricarboxylic Acid; TCMNPs, T Cell Membrane-Coated Nanoparticles; Tex, Exhausted T Cells; TGF-β, Transforming Growth Factor-Beta; Tim-3, T Cell Immunoglobulin and Mucin Domain-Containing Protein 3; TIGIT, T Cell Immunoreceptor with Ig and ITIM Domains; TLR9, Toll-Like Receptor 9; TIL, Tumor-Infiltrating Lymphocyte; TRAIL, Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand; TME, Tumor Microenvironment; Th, Helper T Cells; Treg, Regulatory T Cells; trans-Vaccenic Acid, Unsaturated Fatty Acid; 4-1BB, Tumor Necrosis Factor Receptor Superfamily Member 9; VEGF, Vascular Endothelial Growth Factor; Vimentin, Intermediate Filament Protein; VYXEOS, Cytarabine/Daunorubicin Liposome Formulation; Wnt, Wnt Signaling Pathway; ERBB2IP, Erb-B2 Receptor Tyrosine Kinase 2 Interacting Protein; CD133, Prominin-1; CD36, Scavenger Receptor Class B Member 3; CAR-T, Chimeric Antigen Receptor T Cells; SLC38A1/2, Solute Carrier Family 38 Member 1/2; Smad, Mothers Against Decapentaplegic Homolog; Sucralose, Artificial Sweetener; CAF, Cancer-Associated Fibroblasts; DAAM, Dishevelled-Associated Activator of Morphogenesis; ECM, Extracellular Matrix; Tex, Exhausted T cells.

## Data Sharing Statement

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

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare that there are no competing interests associated with this work.

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