

REVIEW

Turning cold tumors hot: Strategies to enhance antitumor immunity

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Immunologically cold tumors remain a major obstacle to effective cancer immunotherapy because they lack sufficient immune infiltration and fail to sustain productive antitumor immune responses. Although substantial progress has been made in understanding the mechanisms underlying immune evasion, only a minority of patients achieve durable benefit from current immunotherapeutic approaches. In this review, we discuss emerging strategies aimed at converting cold tumors into immune-responsive lesions by enhancing tumor antigenicity and promoting effective immune priming. We examine how these approaches may cooperate with interventions that induce immunogenic cell death, improve T cell trafficking, reverse immunosuppression, and remodel the tumor microenvironment. We further discuss advanced synthetic immunotherapeutic strategies designed to overcome multiple layers of immune resistance. Collectively, current evidence suggests that no single mechanism is sufficient to drive durable cold-to-hot tumor conversion, highlighting the need for integrated therapeutic approaches capable of simultaneously targeting distinct biological barriers to antitumor immunity.

Introduction

The advent of cancer immunotherapy, particularly immune checkpoint inhibitors (ICIs), has revolutionized the therapeutic landscape of oncology over the past decade (Sharma et al., 2023). Mechanistically, ICIs restore antitumor immunity by disrupting inhibitory checkpoint signaling, thereby reinvigorating cytotoxic T cell activity against tumor cells (Wei et al., 2018). Cytotoxic T lymphocyte-associated protein 4 (CTLA-4) is expressed on activated T cells and regulatory T cells (Tregs). It functions by competing with the co-stimulatory receptor CD28 for binding to the ligand CD80/CD86 on dendritic cells (DCs) and inhibiting T cell activation and proliferation. Ipilimumab, an anti-CTLA-4 antibody, was the first Food and Drug Administration (FDA)-approved ICI (Krummel and Allison, 1995). Programmed cell death protein 1 (PD-1) is expressed on a variety of immune cells and binds to programmed death-ligand 1 (PD-L1) expressed on APCs and tumor cells. This interaction suppresses T cell activation and downregulates the antitumor immune responses (Okazaki et al., 2013). Nivolumab and pembrolizumab (Wei et al., 2018) are antibodies that were FDA-approved soon after ipilimumab, expanding the clinical application of ICIs across multiple malignancies (Robert et al., 2015a; Robert et al., 2015b; Hamid et al., 2013; Rittmeyer et al., 2017; Rosenberg et al., 2016; Antonia et al., 2017; Kaufman et al., 2016). However, only a minority of patients achieve durable responses, highlighting primary or acquired resistance (Sharma et al., 2017).

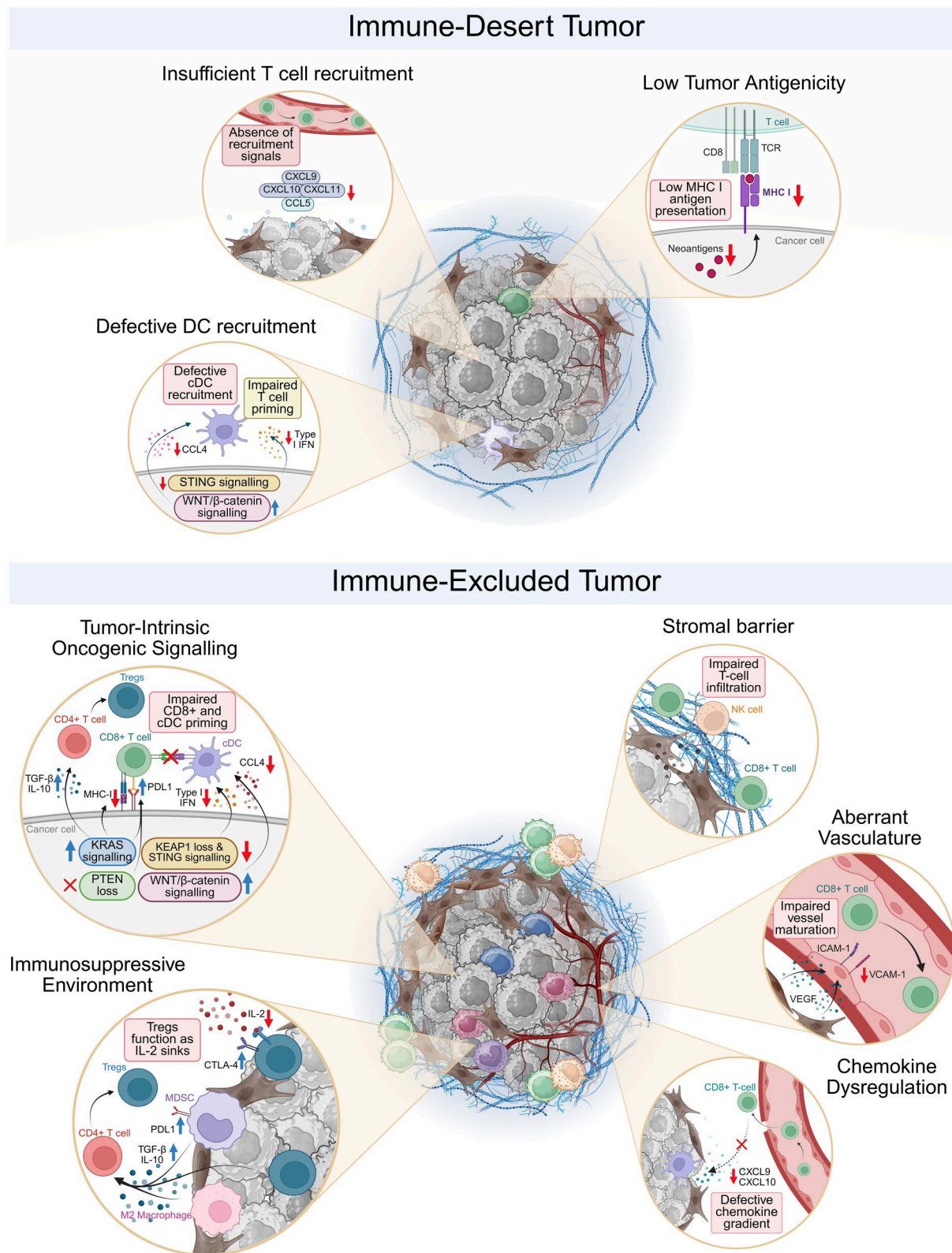
Resistance to ICIs arises from a complex interplay of tumor-intrinsic and tumor-extrinsic mechanisms that influence T cell immunity (Sharma et al., 2017). Intrinsic factors include genetic/nongenetic alterations that impair neoantigen presentation and T cell effector functions (Sharma et al., 2017; Zaretsky et al., 2016; Mellman et al., 2023). Extrinsic mechanisms involve immunosuppressive cells, stromal remodeling, aberrant vasculature, and alternative checkpoints, creating a suppressive tumor microenvironment (TME) (Sharma et al., 2017; Joyce and Fearon, 2015). Consequently, the immunological landscape of the TME is a central determinant of ICI responsiveness, with tumors broadly classified into three categories: immune-inflamed hot tumors, and immune-excluded or immune-desert cold tumors, reflecting the degree of immune cell infiltration and activity (Joyce and Fearon, 2015; Binnewies et al., 2018) (Fig. 1).

In some tumors, organized immune aggregates known as tertiary lymphoid structures (TLS) form within the TME, serving as local hubs for antigen presentation and lymphocyte activation. TLS are composed of B cell clusters surrounded by CD4⁺ and CD8⁺ T cells, often associated with high endothelial venules (HEVs) that recruit lymphocytes from the circulation (Schumacher and Thommen, 2022). Recent work from Miriam Merad's group has shown that TLS formation and maintenance are controlled by conventional type 1 DCs (cDC1s), with TLS induction requiring IFN- γ -driven maturation of the cDC1 subset

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Figure 1. **Molecular and cellular mechanisms of cold tumor immune microenvironments.** Schematic representation of the molecular and cellular mechanisms of cold TMEs, focusing on the immune-excluded and immune-desert phenotypes. Immune-desert tumors (top panel) are characterized by minimal immune-cell infiltration and impaired T cell priming. Key drivers of this phenotype are: reduced chemokine and cytokine signals (e.g., low CXCL9, CXCL10, CXCL11, and CCL5) creates an environment with absence of recruitment signals, preventing T cells migration to the TME; downregulation of MHC I expression,

and low neoantigen loads lead to insufficient neoantigen presentation for CD8⁺ T cell recognition; dysregulated pathways, such as the downregulation of the STING signaling pathway, and activation of Wnt/ β -catenin signaling lead to decreased type I IFN and CCL4 levels, resulting in defective cDC recruitment, therefore leading to an impaired T cell priming. Immune-excluded tumors (bottom panel) are characterized by the presence of immune cells confined to the tumor periphery or invasive margin and are prevented from infiltrating the tumor parenchyma by stromal and immunosuppressive barriers, respectively. Key drivers of this include tumor-intrinsic oncogenic signaling, where alterations such as KRAS activation, PTEN loss, KEAP1 loss, suppressed STING, and elevated Wnt/ β -catenin signaling upregulate immunosuppressive factors (e.g., TGF- β , IL-10, and PD-L1) and reduce type I IFN and CCL4, impairing CD8⁺ T cell and cDC priming; dense ECM and physical stromal elements act as a structural wall, impeding T cell entry into the tumor; dysfunctional tumor blood vessels, mediated by VEGF signaling and downregulation of adhesion molecules (ICAM-1 and VCAM-1), impair vessel maturation and extravasation of CD8⁺ T cells; disrupted chemokine gradients of CXCL9 and CXCL10 inhibit directional T cell migration into the tumor core; accumulation of Tregs, myeloid-derived suppressor cells (MDSCs), and M2 macrophages releasing TGF- β and IL-10 and upregulating checkpoint proteins such as PD-L1 and CTLA-4 creates a hostile TME, where CD4⁺ T cells get primed to become Tregs, that in turn function as IL-2 sinks. Created in BioRender. Bratina, M. (2026) <https://BioRender.com/oeyl3n3>.

(Mattiu et al., 2026). This positions cDC1s as key orchestrators and potential therapeutic targets. Clinically, the presence of mature TLS correlates with improved responses to ICIs across multiple cancer types, including melanoma, non-small cell lung cancer (NSCLC), and pancreatic cancer, and has been associated with prolonged overall survival (Vanhersecke et al., 2021).

From an immunological perspective, hot tumors show increased infiltration of CD8⁺ T cells, natural killer (NK) cells, and functional APCs, along with pro-inflammatory cytokines. Elevated IFN- γ , PD-L1, and FOXP3⁺ suggest postinfiltration negative feedback after immune infiltration (Binnewies et al., 2018). Hot tumors often have a high tumor mutational burden (TMB), which generates neoantigens recognized as non-self; consequently, high-TMB tumors (e.g., melanoma, NSCLC) typically respond better to anti-PD-1 therapy (Valero et al., 2021; Sha et al., 2020; Budczies et al., 2024; Rizvi et al., 2015).

Conversely, cold tumors lack or exclude tumor-infiltrating lymphocytes (TILs), have impaired antigen presentation, and feature an immunosuppressive TME. Immune-desert tumors exhibit deficient APC recruitment, limited T cell priming, minimal immune infiltration, low immunogenicity and TMB, and resistance to ICIs (Binnewies et al., 2018; Joyce and Fearon, 2015) (Fig. 1). Unlike immune-desert tumors, which lack significant T cell infiltration altogether, immune-excluded tumors contain activated immune cells that fail to penetrate the tumor parenchyma because of vascular dysfunction, stromal barriers, and other mechanisms such as chemokine dysregulation, suppressive immune populations, and tumor-intrinsic signaling (Binnewies et al., 2018) (Fig. 1). Pioneering work from Dirk Jäger's group systematically defined inflamed (hot), non-inflamed and immune-excluded (cold) patterns across human solid tumors, and showed that a bivariate classification of CD8⁺ and CD163⁺ cell topography can stratify patient prognosis, providing a framework for spatial tumor-immune interactions (Kather et al., 2018).

A major research focus is converting cold tumors into hot, ICI-responsive states (Galon and Bruni, 2019). This conceptual shift recognizes that effective immunotherapy requires not only checkpoint blockade but also a productive intratumoral immune response. Beyond reprogramming the TME by improving antigen presentation, enhancing T cell priming and infiltration, and dismantling immunosuppressive barriers, emerging approaches seek to enrich the quality of tumor neoepitopes, restoring immune visibility to previously non-inflamed tumors (Binnewies et al., 2018; Chen and Mellman, 2013; Hegde and Chen, 2020; Schumacher and Schreiber, 2015).

In this review, we discuss the immunological basis of cold tumor phenotypes and emerging therapeutic strategies aimed at enhancing tumor immunogenicity. By focusing on approaches that promote the transition from cold to hot tumor phenotypes, we aim to highlight key opportunities and challenges in overcoming immunotherapy resistance and improving patient outcomes.

Enhancing tumor antigenicity

Somatic mutations are common in most cancer types; some can be drivers of oncogenesis, but the biological processes generating them remain largely unclear (Alexandrov et al., 2013). Tumor-unique mutations that can be translated into immunogenic proteins presented on MHC class I (MHC-I) are called neoantigens (Xie et al., 2023). Neoantigens are proteins that are acquired rather than being germline encoded, and thus specifically present in cancer cells while being absent in normal healthy tissue. They can arise from post-translational modification, dysregulated RNA splicing, or viral reading frames (Xie et al., 2023). The following sections address strategies to induce neoantigens, improve their presentation, and enhance tumor antigenicity in cold tumors with low TMB and neoantigen load.

Increasing TMB

TMB is defined as the total number of non-synonymous somatic mutations in the cancer genome, with variability across and within cancer types (Budczies et al., 2024). Hence, the TMB reflects the antigen pool available for processing and presentation. Increasing the TMB, and consequently neoantigen incidence, is an important strategy for enhancing tumor antigenicity (Fig. 2). Genomic alterations are the main source of neoantigens; therefore, targeting DNA repair or replication fidelity can broaden the range of tumor-specific mutations that give rise to new immunogenic targets.

In healthy conditions, the mismatch repair (MMR) system corrects single-base substitutions (Kunkel and Erie, 2015). Key components of this pathway, including MutS homolog 2 (MSH2), MutL homolog 1 (MLH1), and MutS homolog 6 (MSH6), are frequently altered in cancers, resulting in MMR deficiency (MMRd). MMRd allows many genetic alterations to accumulate, creating neoantigens (Evensen et al., 2018; Johannet et al., 2025). Both clinical and animal studies have associated impaired tumor growth with MMRd and attributed this to increased CD8⁺ T cell infiltration (Le et al., 2015; Germano et al., 2017). Patients with

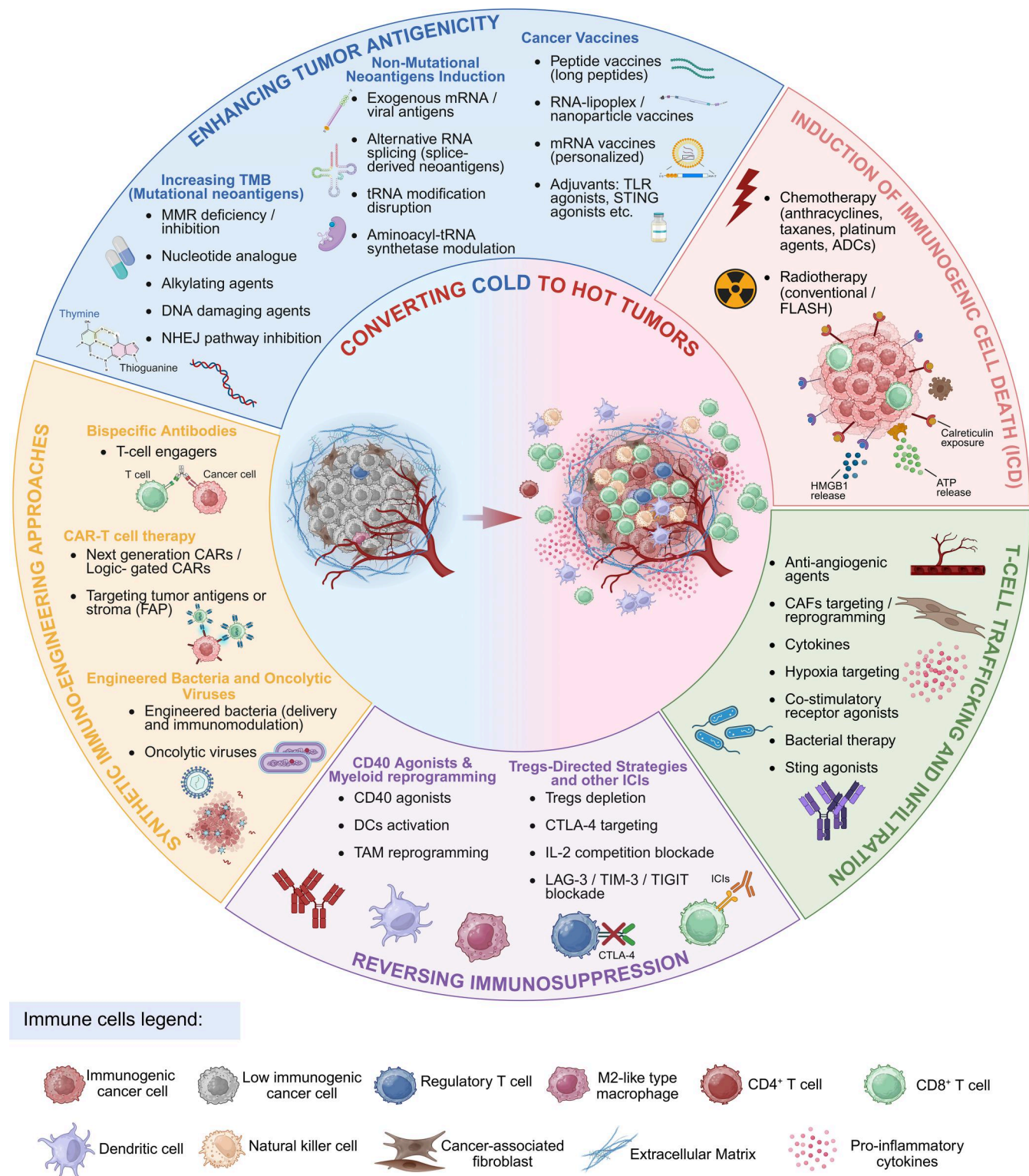


Figure 2. Strategies to enhance tumor immunogenicity and promote cold-to-hot tumor conversion. Schematic overview of complementary therapeutic approaches that remodel the TME to enhance antitumor immunity. Strategies to enhance tumor antigenicity include increasing TMB, induction of neoantigens, and cancer vaccines. ICD, induced by chemotherapy, radiotherapy, and ADCs, promotes release of DAMPs, including ATP, HMGB1, and calreticulin, thereby enhancing antigen presentation and T cell priming. Additional approaches improve T cell trafficking and infiltration through anti-angiogenic therapies, cytokine modulation, stromal re-modeling, STING agonists, and bacterial therapies. Reversal of immunosuppression includes ICIs, Treg depletion, and myeloid-cell reprogramming. Synthetic immuno-engineering approaches, including bispecific antibodies, CAR-T cells, engineered bacteria, and OVs, further enhance immune recognition and local immune activation, collectively promoting conversion of immunologically “cold” tumors into inflamed “hot” tumors. Created in BioRender. Bratina, M. (2026) <https://BioRender.com/mdz1mmy>.

solid MMRd tumors benefit from ICI plus chemotherapy regimens, with 2 years of therapy improving overall survival (Margalit et al., 2024; Johannet et al., 2025). This underscores the critical role of mismatch mutations in sensitizing tumors to immune checkpoint blockade (ICB) and promoting immune infiltration. Furthermore, MMRd tumors can retain sensitivity to ICB even when they lose β 2-microglobulin, suggesting that CD4⁺ T cells, $\gamma\delta$ T cells, and NK cells also contribute to antitumor immunity (de Vries et al., 2023; Germano et al., 2021).

Months to years of treatment with thiopurines such as 6-thioguanine (TG; 6-TG) and 6-mercaptopurine (6-MP) are essential for achieving cure in lymphoblastic leukemia and lymphomas (Larsen et al., 2021; Toksvang et al., 2022). Insertion of TG in DNA is silent, but DNA-TG can become S-methylated, causing nucleotide mismatching, mostly TG-T mismatching. These point mutations trigger repeated but futile MMR activity. Incomplete DNA repair can induce point mutations that accumulate with every cell cycle, or it can lead to an accumulation of double-strand breaks (DSBs) leading to cytotoxicity (Swann et al., 1996; Evensen et al., 2018). MMR-proficient cells are typically more sensitive to 6-TG due to this futile repair cycling (Evensen et al., 2018). In a preclinical model of low-mutation melanoma, 6-TG induced an increase in TMB and neoepitope generation, while also reprogramming the TME with increased TIL infiltration and ICI responsiveness (Nazerai et al., 2023; Nazerai et al., 2025; Yankilevich et al., 2024). Supporting the therapeutic potential of transient MMR disruption, a pharmacological inhibitor of PMS2 (a subunit that partners with MLH1) restores ICI sensitivity and delays tumor growth in preclinical colorectal cancer models (Blagg et al., 2026). Temozolomide (TMZ) transfers methyl groups to DNA, resulting in DNA damage and cell death (Chen et al., 2025e). TMZ also inactivates MSH6, thereby introducing new mismatch mutations and leading to microsatellite instability (Yip et al., 2009). In mouse models, TMZ selects for MMRd tumor cell populations, which show increased neoantigens, TMB, and reduced tumorigenicity, suggesting enhanced immunogenicity (Germano et al., 2017). Building on this concept, combining TMZ-induced mutagenesis with additional DNA-damaging agents may further amplify genomic diversification. Cisplatin forms DNA cross-links, obstructing replication and repair (Dasari and Tchounwou, 2014). The combination of TMZ and cisplatin was shown to induce a hypermutated state enriched for insertion/deletion mutations through the downregulation of MSH2. This acquired MMRd phenotype increased TMB, enhanced neoantigen generation, promoted intratumoral CD8⁺ T cell infiltration, and resensitized tumors to PD-1 blockade (Rousseau et al., 2025). Further characterization of this approach demonstrated that TMZ/cisplatin induced hypermutation can drive CD8⁺ T cell-mediated immune surveillance, immunoediting of treatment-induced neoantigens, and durable immune memory, particularly when combined with ICB (Vitiello et al., 2025).

Alternative ways to increase TMB include inducing DNA polymerase proofreading defects. Intratumoral delivery of cisplatin in a melanoma mouse model activated the DNA damage tolerance pathway (Zhuo et al., 2021). This recruits error-prone translesion synthesis polymerases that bypass damaged DNA

and introduce additional mutations (Sale et al., 2012). Intratumoral cisplatin activates error-prone translesion synthesis polymerases, which, when combined with ICI, led to tumor regression with increased T cell infiltration and granzyme B expression (Zhuo et al., 2021; Gorgun et al., 2021).

Defects in other DNA damage response pathways, such as the non-homologous end joining repair mechanisms, cause insertions, deletions, and translocation errors (Ceccaldi and Cejka, 2025). DNA-dependent protein kinase (DNA-PK) is a serine/threonine kinase composed of the Ku70/80 heterodimer and the DNA-PK catalytic subunit. It functions as a central regulator of the nonhomologous end joining pathway by recognizing and repairing DNA DSBs (Goff et al., 2024). Aberrant DNA-PK catalytic subunit is often a key driver of this dysregulation, contributing to the induction of mutation and tumorigenesis and to increased TMB (Chen et al., 2020). The DNA-PK inhibitor NU7441 increased MHC-I expression and neoantigen load, improving ICI responsiveness in a patient cohort (Nielsen et al., 2024). Homologous recombination deficiency (HRD) results in the inability to repair DSBs (Sung and Klein, 2006). Although many HRD cancers are successfully treated with poly (ADP-ribose) polymerase inhibitors (Mirza et al., 2020; de Bono et al., 2020), ICB may also be effective, as these tumors are often MMRd, TMB-high, PD-L1 positive, and immune-enriched (Moretto et al., 2022). Guanosine diphosphate-mannose (GDP) was identified as a metabolite in triple-negative breast cancer (TNBC) HRD-low that induces DNA repair suppression. In a preclinical HRD-low TNBC model, GDP together with a poly (ADP-ribose) polymerase inhibitor and anti-PD-1 induced strong antitumor immunity (Ding et al., 2024).

Not all neoantigens are equally immunogenic. Clonal neoantigens, derived from mutations shared across tumor cells, elicit stronger clinical responses than subclonal neoantigens restricted to tumor subsets (McGranahan et al., 2016). Tumors with a high clonal neoantigen burden respond better to ICIs (McGranahan et al., 2016; Boll et al., 2023). Conversely, chemotherapy-induced mutagenesis can generate subclonal heterogeneity, which may promote immune escape (Wolf et al., 2019; Westcott et al., 2023), and may paradoxically attenuate rather than enhance antitumor immunity (Wolf et al., 2019; Wu et al., 2022). More broadly, high mutational load can enhance immunogenicity, whereas excessive intratumor heterogeneity can dilute immune recognition and promote immune evasion (McGranahan et al., 2016; Wu et al., 2022).

Non-mutational cancer neoantigens induction

Although DNA mutations are a well-studied source of neoepitopes, RNA-derived neoantigens have recently gained attention for their ability to induce antigen expression and immune activation without altering the host genome (Fig. 2). mRNAs can encode tumor suppressors, tumor antigens, cytokines, or genome-editing tools (Liu et al., 2023a; Lorentzen et al., 2022).

RNA splicing is a naturally occurring process within cells during which RNA sequences are spliced into mature and functional mRNAs; however, it is often hijacked in cancer cells to confer therapy resistance and favor tumor progression (Zhang et al., 2021). The possibility that alternative splicing (AS) in cancer leads to neoantigens is coming into focus, and the idea

that this can be used to predict ICI responsiveness is being explored. For example, the epithelial splicing regulatory protein-1 drives AS and is a biomarker for ICI responsiveness and improved survival in TNBC, linked to increased T cell infiltration (Xiong et al., 2025). In a cohort of metastatic renal cell carcinoma, high splice burden was identified as a biomarker for a more immunogenic TME with enriched neoantigen presentation (Govindarajan et al., 2026). Pharmacological modulation of RNA splicing generated immunogenic splice-derived neoantigens in preclinical models, reducing tumor growth in a CD8⁺ T cell-dependent manner and increasing MHC-I presentation of the splice-derived immunopeptidome (Lv et al., 2025). However, this concept is not universal. AS of FGGY generates the neoantigen FGGY-204 in hepatocellular carcinoma; its expression defines immune-cold tumors and inversely correlates with CD8⁺ T cell infiltration, highlighting the complex relationship between splicing-derived neoantigens and tumor immune states (Zhao and Andersen, 2026).

The nonsense-mediated mRNA decay (NMD) pathway degrades transcripts containing premature stop codons, which can arise from frameshift mutations or aberrant intron retention (Tan et al., 2022). This pathway can also target AS mRNAs, long noncoding RNAs, and aberrant open reading frames (Tan et al., 2022), thereby reducing the pool of potential neoantigens (Kwok et al., 2025). However, tumor antigens are not exclusively derived from mutated sequences, as a substantial immunogenic fraction originates from non-mutated genomic regions (Apavaloaei et al., 2025). Accordingly, pharmacological and genetic inhibition of NMD components can increase neoantigen abundance in situ, independently of mutation burden, offering a strategy to enhance tumor immunogenicity without generating subclonal heterogeneity (Pastor et al., 2010; Vendramin et al., 2026). Inhibition of SMG1 (the key kinase initiating NMD) stabilizes transcripts containing premature termination codons, reshaping the immunopeptidome and enhancing MHC-I presentation to levels comparable with high-TMB tumors. SMG1 inhibition also promoted ex vivo T cell-mediated killing and increased in vivo ICI sensitivity (Vendramin et al., 2026). Other NMD players elicit similar effects. Up-frameshift protein 1 (UPF1), which acts as a binding platform, negatively impacts microsatellite instability, immunogenicity, and anti-PD-1 sensitivity in colorectal cancer. Its pharmacological inhibition using a specific anti-UPF1 antibody restores tumor immunogenicity and ICI sensitivity (Zhu et al., 2025a).

Transfer RNAs (tRNAs) are essential adaptor molecules that decode mRNA codons during translation, a process ensured by aminoacyl-tRNA synthetases and regulated by posttranscriptional modifications that maintain fidelity (Mohler and Ibbá, 2017). The epitranscriptome is heavily perturbed in cancer, suggesting tRNAs as a therapeutic target (Dedon and Begley, 2022). Loss of specific tRNA-modifying enzymes, such as tRNA wybutosine (yW)-synthesizing protein 2 (TYW2), induces ribosomal frameshifting, generating aberrant MHC-I-presented peptides that enhance CD8⁺ T cell infiltration, increase ICI sensitivity, and reduce tumor growth in a preclinical melanoma model. Clinically, TYW2 expression is associated with patient survival and response to ICB (Weller et al., 2025). Although

pharmacological inhibitors are not yet available, these findings highlight tRNA modification pathways as a promising source of non-mutational neoantigens (Weller et al., 2025).

Cancer vaccines

Although not a recent idea, the field of therapeutic cancer vaccines has seen rapid development in recent years. The aim is to trigger a potent tumor-specific CD4⁺ and CD8⁺ T cell response capable of inducing durable immune memory (Mami-Chouaib et al., 2018) (Fig. 2). They do so by delivering tumor-associated antigens (TAAs) or tumor-specific antigens via a variety of mechanisms, including cell-based platforms, peptides, or nucleic acids. A fundamental element in cancer vaccination is the presence of a potent adjuvant that can attract and activate DCs, essential for T cell activation. Commonly used adjuvants belong to the TLR agonist and the stimulator of interferon genes (STING) targeted agonist families (Zaidi et al., 2025; Chandra et al., 2014). Tumor-specific antigens are presented by DCs on MHC-II, enabling T cell priming, activation, and differentiation through TCR recognition and CD28–CD80/CD86 co-stimulation. Following vaccine-mediated priming, activated T cells traffic to tumors, infiltrate the TME, and mediate cancer cell killing (Zaidi et al., 2025). CD4⁺ T cells enhance CD8⁺ activation through CD40/CD40L signaling; therefore, inclusion of CD4⁺ T cell-activating neoantigens strengthens CD8⁺ responses, limits exhaustion, and reduces immunosuppressive M2 macrophages (Huff et al., 2023).

Epitope spreading is the diversification of epitope specificity from an initially focused immune response against a dominant epitope to a secondary epitope. This can occur within the same antigen or extend to a separate one (Vanderlugt and Miller, 2002). As part of the evolving immune response, epitope spreading can contribute to both the amplification phase of the immune response and the later regulatory phase that restores immune homeostasis. In the context of tumor vaccination, epitope spreading has been proposed to enhance the efficacy of peptide-based therapies (Qdaisat et al., 2025). Peptide-based vaccines are most effective when longer than 20–30 amino acids, as opposed to shorter peptides (Melief and van der Burg, 2008). Long synthetic peptides require uptake and processing by APCs, enabling presentation through both MHC-I and -II, thus activating both CD8⁺ and CD4⁺ T cells and reducing the risk of immune tolerance (Ott et al., 2020b; Melief and van der Burg, 2008; Zaidi et al., 2025).

Notably, the SARS-CoV-2 mRNA vaccine sensitized tumors to ICIs. In melanoma and Lewis lung cancer mouse models (typically ICI-nonresponsive), concomitant treatment with SARS-CoV-2 vaccine and anti-PD-1 improved survival via IFN- γ , due to activation of myeloid compartments presenting SARS-CoV-2 viral spike epitopes on tumor MHC, creating a novel immune target and restoring ICI sensitivity (Grippin et al., 2025; Qdaisat et al., 2025). However, a subsequent reanalysis of these clinical findings suggested that the observed survival benefit of peri-ICI vaccination is largely attributable to selection bias, as patients with more favorable prognoses were more likely to receive vaccination, rather than a true biological synergy between vaccination and ICI therapy (Jee et al., 2026).

Nucleic acid neoantigen vaccines, particularly mRNA-based, are the most prominent approach. They are inherently immunogenic, reducing (but not eliminating) the need for additional adjuvants. mRNA vaccines drive robust antitumor immunity through strong antigen-specific T cell responses. Encouraging phase II data suggest that personalized mRNA neoantigen vaccines may improve recurrence-free survival in melanoma and pancreatic cancer, but definitive conclusions await larger randomized trials. Whether these vaccines induce epitope spreading to non-vaccine neoantigens remains unclear; most vaccine targets are passenger mutations and may be subclonal, potentially limiting their impact (Weber et al., 2024; Rojas et al., 2023). Similarly, RNA-lipoplex vaccination targeting shared TAAs elicits potent and durable CD4⁺ and CD8⁺ T cell responses in ICI-experienced melanoma patients (Sahin et al., 2020). Additionally, self-assembling nanoparticle platforms that conjugate tumor-specific antigens with TLR agonists activate DCs, promote CD8⁺ T cell responses against multiple neoantigens, and produce strong systemic antitumor immunity in several cancer models (Shi et al., 2023). Neoantigen vaccines are highly tumor-specific, making manufacturing personalized and costly. However, immunopeptidome analyses show that neoantigens tend to arise from common genomic regions, enabling prediction and shared targeting (Niknafs et al., 2023; Alexandrov et al., 2013). Several neoantigen vaccines in clinical trials have shown high efficacy in targeting shared neoantigens, with strong CD4⁺ and CD8⁺ responses and even more promising results when combined with ICI (Pant et al., 2024; Baretti et al., 2023). While the field is rapidly evolving, manufacturing remains complex and costly (Haanen et al., 2026).

Inducing immunogenic cell death

One of the pivotal steps of antitumor immunogenicity is the induction of immunogenic cell death (ICD). According to consensus guidelines published in 2020, the Nomenclature Committee on Cell Death defines ICD as a form of regulated cell death capable of activating an adaptive immune response in immunocompetent hosts (Galluzzi et al., 2020). The definition emphasizes that ICD is determined not only by the dying cell itself but also by its interaction with the host's immune system. For a dying cell to trigger immunity, two things are necessary: antigenicity and adjuvanticity. The cells must express antigens recognizable by the host's immune system and release danger signals such as damage-associated molecular patterns (DAMPs) to activate immune cells (Galluzzi et al., 2020).

Genetic and cellular alterations can trigger the cancer-immunity cycle, a multistep process required for effective cytotoxic antitumor responses (Mellman et al., 2023). Neoantigens released by dying tumor cells are first captured by DCs in a pro-inflammatory environment, then presented in lymph nodes via MHC-I and -II to prime effector T cells. Activated T cells then traffic to and infiltrate the tumor, where they recognize cancer cells through TCR-MHC interactions and mediate cell killing, further amplifying the cycle through release of additional DAMPs from dying tumor cells (Mellman et al., 2023).

Exploiting the cancer immunity cycle through the induction of ICD has emerged as a clinically relevant therapeutic strategy capable of impacting and changing immunotypes (Fig. 2). ICD overcomes low antigenicity and poor immune priming by providing antigens and adjuvanticity, driving cold-to-hot conversion. The following sections outline the mechanisms through which different therapeutic modalities drive neoantigen generation, initiate ICD, and lead to an antitumor response.

Chemotherapy

Chemotherapy drugs have transformed the landscape of cancer treatment, leading to the development of numerous cytotoxic agents now used clinically. Most chemotherapeutic agents act by inducing acute damage to DNA, the cytoskeleton, or mitochondria in a nonspecific fashion, triggering danger signals that activate programmed cell death pathways (Letai and de The, 2025). Although traditionally viewed primarily as cytotoxic agents targeting proliferating cells due to their heightened basal stress (Letai and de The, 2025), rapidly emerging evidence indicates that the clinical success of many agents depends equally on a substantial immunological component.

Many chemotherapy agents such as anthracyclines, taxanes, and platinum-based drugs can induce ICD and activate antitumor immunity (Liu et al., 2026; Solari et al., 2020; Pol et al., 2015). Specifically, anthracyclines can induce ICD through ATP and HMGB1 release and calreticulin exposure, promoting APC activation and inflammatory remodeling of the TME that can support antitumor immunity (Deng et al., 2025; Ma et al., 2025). Taxanes can promote immunogenic cellular stress and DAMP release through oxidative stress-associated pathways, including ROS-dependent HMGB1 release and subsequent inflammatory signaling via NF- κ B activation (Liu et al., 2026). For example, docetaxel was found to upregulate the expression of the chemokine receptor ligand CXCL11 in NSCLC, leading to CD8⁺ T cell recruitment (Gao et al., 2019). Platinum-based chemotherapies, such as cisplatin and carboplatin can induce immunogenic cellular stress and the release of DAMPs and calreticulin surface exposure, leading to DC recruitment, activation, antigen presentation, and increased tumor cell killing (Solari et al., 2020; Liu et al., 2026; Galsky et al., 2024).

Antibody-drug conjugates (ADCs) are an emerging class of chemotherapy-based therapeutics that combine target-specific antigen recognition and Fc receptor interactions. Their therapeutic advantage lies in selectively delivering highly potent cytotoxic agents to tumor cells, increasing intratumoral drug concentration while limiting systemic exposure (Zippelius et al., 2025). Beyond direct cytotoxicity, ADCs can also modulate antitumor immunity through mechanisms such as ICD in a similar way to the chemotherapy agent they carry. A strong immune microenvironment shift can be achieved with ADCs, resulting in increased CD8⁺ T cell infiltration and activation (Gedik et al., 2024; Kepp and Kroemer, 2025; Dong et al., 2024). With the combined cytotoxic and immunomodulatory properties, ADCs represent particularly promising partners for combination with immunotherapeutic strategies.

Radiotherapy

Radiotherapy is a widely used first-line treatment across most solid malignancies. Over half of all cancer patients receive it (Abdel-Wahab et al., 2024). Radiation induces DNA damage, particularly DSBs, leading to cytosolic DNA that activates the cyclic GMP-AMP synthase (cGAS)–STING pathway, which promotes type I IFN and inflammatory signaling. In parallel, radiation-induced DNA damage activates the DNA damage response, causing cell cycle arrest, senescence, or apoptosis (McLaughlin et al., 2020).

Radiotherapy is recognized for both its therapeutic efficacy and its capacity to induce immunogenic effects through STING-dependent cytosolic nucleic acid sensing, which activates innate immune pathways that induce type I IFNs, IFN β , and other inflammatory cytokines. This creates a state of viral mimicry that triggers ICD (Vanpouille-Box et al., 2017; Deng et al., 2014). In the past decade, it has been established that radiotherapy strongly impacts tumor immunogenicity in a way that induces ICD. Particularly, radiotherapy can enhance T cell trafficking to locally treated tumor sites and amplify preexisting anticancer T cell responses (Dovedi et al., 2017). It also increases MHC-I antigen presentation in a dose-dependent manner (Reits et al., 2006). Additionally, radiation therapy promotes local expansion of T cell subsets, increases CD8⁺ T cell infiltration, and broadens TCR repertoire diversity, thereby strengthening antitumor immunity (Dovedi et al., 2017; Twyman-Saint Victor et al., 2015; Lai et al., 2019). These elements strongly support the idea that radiotherapy-induced remodeling of the TME provides a strong foundation for combining with immunotherapeutic strategies (Liu et al., 2023c; Ni et al., 2022b).

When combined with ICIs or targeted therapy, radiotherapy helps convert cold tumors into inflamed TMEs by promoting IFN signaling, antigen processing, ICD, T cell infiltration, TCR expansion, and abscopal immune responses (Huang et al., 2025; Ni et al., 2022a; Patin et al., 2024; Lhuillier et al., 2021). For example, radiotherapy plus anti-PD-L1 reshaped the suppressive TME in a preclinical model of pancreatic cancer through macrophage repolarization and stromal remodeling (Ni et al., 2022b). Radiotherapy combined with ataxia telangiectasia and Rad3-related protein serine/threonine kinase inhibitors enhanced costimulatory signaling and memory T cell activation (Patin et al., 2024). When used with STAT inhibitors, radiotherapy restored lost interactions between DCs and T cells in CNS tumors (Ott et al., 2020a). Radiotherapy also enhanced expression and presentation of immunogenic targets when used as an adjuvant with neoantigen vaccines, improving vaccine-primed CD4⁺ and CD8⁺ T cell responses (Lhuillier et al., 2021). Notably, clinical trials combining localized radiation with ICIs have induced abscopal responses in only a small subset of patients (Ferdinandus et al., 2025), highlighting the need for better patient selection and combination strategies (Morris et al., 2025).

FLASH radiotherapy is a modern approach that delivers ultrahigh doses of radiation in extremely short timeframes. It improves the therapeutic index of radiation treatment while limiting damage to surrounding tissues (Vozenin et al., 2026). Although the biological explanations for FLASH efficacy remain poorly defined, a leading hypothesis is its increased

immunogenicity compared with conventional radiotherapy (Vozenin et al., 2026). Studies have shown that FLASH therapy induces greater lymphocyte infiltration into tumors while minimizing collateral damage to healthy tissues (Iturri et al., 2023). FLASH may also reverse tumor-associated immune suppression and reduce systemic leukopenia, thereby facilitating the infiltration of endogenous lymphocytes as well as adoptively transferred immune cells such as chimeric antigen receptor T (CAR-T) cells (Ni et al., 2025; Tao et al., 2026).

Beyond external beam radiotherapy, radioligand therapy, which delivers radiation systemically to tumors expressing specific surface markers, can also remodel the TME across disseminated disease (Sathegke et al., 2024; Chen et al., 2025c).

T cell trafficking and infiltration

The successful trafficking of effector T cells from the circulation into the tumor parenchyma represents a major bottleneck in the cancer-immunity cycle and is frequently impaired in cold tumors. Therefore, even successful antigen release, processing, and T cell priming may fail to generate T cells capable of reaching their targets due to physical and chemical barriers within the TME (Mellman et al., 2023). Beyond these barriers, neutrophils, mast cells, and eosinophils also contribute to immune exclusion. Neutrophil extracellular traps drive cold tumor formation and immunotherapy resistance (Li et al., 2026b), while IL-4⁺ and CTSG⁺ mast cells promote fibrotic TME remodeling and T cell exclusion (Guo et al., 2024; Jiang et al., 2026), and eosinophils can modulate the TME toward immune-permissive states (Grisaru-Tal et al., 2022). This section outlines key therapeutic strategies designed to dismantle these barriers and promote T cell infiltration (Fig. 2).

T cell infiltration is regulated by chemokines and adhesion molecules. Tumor-derived chemokines such as CXCL9, CXCL10, and CXCL11 recruit effector T cells via CXCR3, whereas CCL5 and XCL1 are critical for recruiting cDC1s, which cross-present tumor antigens and prime CD8⁺ T cells (Mempel et al., 2024; Böttcher et al., 2018). Conversely, tumors that lack these chemokine axes or downregulate endothelial adhesion molecules exclude immune cells (Spranger et al., 2017; Zhu et al., 2025b). Work from Gajewski's group established that host type I IFN signaling is critical for intratumoral cDC1 accumulation and spontaneous antitumor CD8⁺ T cell responses (Fuentes et al., 2011). The presence of cDC1s within the TME correlates with favorable prognosis and ICI responses (Sánchez-Paulete et al., 2016; Teixeira et al., 2022). Additionally, cDC1 density is associated with clinical benefit from checkpoint inhibitors across multiple tumor types (Lopez-Janeiro et al., 2026), and spatial proximity between cDC1s and CD8⁺ T cells is critical for ICI response in melanoma (Gobbini et al., 2025). Mechanistically, CCR7⁺ activated DCs are essential for T cell priming and immunotherapy responses, with ablation of these activated DCs impairing spontaneous tumor control and ICI efficacy (Koufaki et al., 2026).

Anti-angiogenic agents

One major barrier is the abnormal, dysfunctional vasculature characteristic of solid tumors. The vascular endothelial growth

factor (VEGF) pathway is a central driver of aberrant angiogenesis, leading to leaky, tortuous vessels lined with adhesion molecules that are poorly permissive for T cell extravasation (Lee et al., 2025). Furthermore, VEGF directly contributes to an immunosuppressive TME by upregulating immune checkpoints like PD-L1 on endothelial cells (Wang et al., 2023). Anti-angiogenic agents, such as VEGF-receptor tyrosine kinase inhibitors, are a cornerstone strategy for vascular normalization. By pruning immature vessels and improving pericyte coverage, these agents can restructure the vasculature to be more organized and less permeable, facilitating T cell homing and infiltration (Zheng et al., 2022). Beyond improving perfusion, vascular normalization can also promote the formation of HEVs, which facilitate T cell infiltration and TLS formation (Johansson-Percival et al., 2017; Chen et al., 2026). Mathematical models help determine optimal dosing and timing of these agents to achieve a “normalization window” that maximizes T cell delivery while minimizing hypoxia (Hadjigeorgiou and Stylianopoulos, 2024; Ansar et al., 2023).

Combining anti-angiogenic therapy with ICIs has shown clinical benefit, with VEGF-targeted agents among the few strategies proven to enhance immunotherapy efficacy with positive phase III trials in renal-cell carcinoma (Rini et al., 2019; Motzer et al., 2021; Choueiri et al., 2021), hepatocellular carcinoma (Finn et al., 2020; Ren et al., 2021; Qin et al., 2025) and cervical cancer (Oaknin et al., 2024). However, many trials have also yielded negative results, reflecting the challenge of balancing VEGF-driven immunosuppression with its physiological role in vascular integrity (Kuo et al., 2024). Clinical data in glioblastoma and breast cancer support this strategy, as single-agent ICIs or VEGF inhibitors have shown limited efficacy, though their combination improved immune infiltration and antitumor responses (Jain et al., 2021; Chen et al., 2021). Newer strategies are advancing this concept further, including the development of bispecific antibodies that co-target VEGF and PD-L1, directly linking vascular normalization with checkpoint blockade (Álvarez-Vallina and Sanz, 2026).

Cancer-associated fibroblast targeting

Beyond the vasculature, the tumor stroma also restricts T cell infiltration, with cancer-associated fibroblasts (CAFs) playing a key role (CAFs). CAFs are a highly heterogeneous population of cells that deposit dense extracellular matrix, creating a physical wall that can exclude T cells (Yang et al., 2023). While specific markers like fibroblast activation protein (FAP), α -smooth muscle actin, and platelet-derived growth factor receptor α have been used to identify CAFs, the lack of a single, universal biomarker emphasizes their functional diversity, with some subtypes being pro-tumorigenic and others potentially anti-tumorigenic (Lavie et al., 2022). This heterogeneity is a key reason why many CAF-targeting strategies have yet to yield positive clinical results (Flynn et al., 2025; Yang et al., 2023). TGF- β signaling in CAFs drives T cell exclusion via stromal fibrosis and direct CD8⁺ T cell suppression, yet direct inhibition has shown limited clinical efficacy, underscoring the need for more selective approaches (Derynck et al., 2021). Beyond its role

in CAF-mediated stromal fibrosis, TGF- β directly promotes Treg differentiation and function in the TME (Chen et al., 2003). Preclinical attempts to target CAFs by depleting them or inhibiting their matrix-producing functions (e.g., by targeting FAP, TGF- β , or IL-6R) have often been limited by toxicity or lack of efficacy (Sato et al., 2024; Chen et al., 2025a; Anouti et al., 2024). The emerging consensus is that successful intervention will not involve indiscriminate CAF depletion, but rather the reprogramming of specific CAF subtypes or the “normalization” of their pro-tumorigenic phenotype into a quiescent or tumor-suppressive state (Yang et al., 2023). For future directions, a deeper understanding of organ-specific CAF phenotypes and their distinct functions (Lavie et al., 2022) will be critical for designing targeted therapies that avoid the significant drawbacks seen in early trials.

Cytokines

A more direct approach to improving T cell trafficking involves the use of cytokines to stimulate and guide effector cells. The IL-2 pathway is a key target because IL-2 regulates T cell expansion, survival, differentiation into effector cells, and tissue trafficking (Spolski et al., 2018). While high-dose IL-2 therapy can potentially activate CD8⁺ T cells, its clinical utility is limited by severe toxicity and the expansion of Tregs, which can suppress the antitumor response (Shouse et al., 2024). To overcome this, next-generation strategies focus on engineering IL-2 variants with improved specificity for the intermediate-affinity IL-2 receptor (IL-2R $\beta\gamma$) on memory CD8⁺ T cells and NK cells, while minimizing engagement with the high-affinity IL-2R α (CD25) on Tregs (Ma et al., 2024; Murer et al., 2025). This can be achieved through IL-2 muteins or conjugating IL-2 to antibodies targeting TME proteins such as PD-1 (creating a PD-1-IL2v bispecific fusion protein) (Piper et al., 2023; Wu et al., 2024b). Preclinically, these PD-1-targeted IL-2 variants have shown the ability to induce a “better” effector CD8⁺ T cell phenotype, reversing exhaustion and promoting cytotoxicity (Codarri Deak et al., 2022; Tichet et al., 2023). However, the clinical data have been mixed, with two major trials of BEMPEG (a PEGylated IL-2) combined with PD-1 blockade failing to show benefits compared with nivolumab alone in first-line melanoma (Diab et al., 2023) and renal cell carcinoma (NCT03729245).

The related cytokine, IL-15, is also being explored as an alternative T cell activator that may avoid some of the pitfalls of IL-2. IL-15 shares the IL-2R $\beta\gamma$ receptor chain with IL-2 but does not bind the high-affinity IL-2R α , thereby preferentially expanding memory CD8⁺ T cells and NK cells without driving Treg expansion or activation-induced cell death (Spolski et al., 2018). Accordingly, IL-15 superagonists have entered clinical trials for both hematologic and solid malignancies (Ma et al., 2022a; Waldmann et al., 2020). Immunocytokines (cytokine-antibody fusions) deliver cytokine activity to the TME and reduce systemic toxicity (Agliardi et al., 2025). Immunocytokines such as anti-PD-L1/IL-15 (Shi et al., 2024) and anti-CD73/IL-2v (Shin et al., 2025) are in development for cold tumors. Beyond direct T cell stimulation, cytokines such as FLT3L can promote cDC1 differentiation and infiltration, particularly when combined with CXCR3/CCR5 ligands (Gorline et al., 2025).

Hypoxia

Hypoxia is a master regulator of immunosuppression and a critical barrier to T cell infiltration. Hypoxia-inducible factors (HIFs) drive PD-L1 expression on cancer cells and myeloid cells, suppressing cytotoxic T lymphocyte activity (Shi et al., 2025; Ma et al., 2022b). Hypoxia also promotes the accumulation of immunosuppressive adenosine via the CD39-CD73 axis (Vignali et al., 2023) and recruits Tregs through CCL28 induction (Facciabene et al., 2011), while downregulating chemokines required for effector cell recruitment (Tian et al., 2017). Physical abnormalities of the tumor cause vascular compression and hypoperfusion, directly perpetuating hypoxia (Mpekris et al., 2024b). Therapeutic strategies targeting hypoxia to overcome ICI resistance include hypoxia-activated prodrugs (HAPs) (Li et al., 2021), HIF inhibitors (Shi et al., 2025), and oxygen-delivering nanomaterials (Halpin-Veszeleiova et al., 2025). HAPs selectively release cytotoxins under low oxygen (Li et al., 2021), with optimal timing dependent on hypoxia dynamics (Mathur et al., 2024). HIF-1 α inhibitors such as acriflavine (blocks HIF-1 α / β dimerization) and vorinostat (downregulates HIF-1 α) enhance immune infiltration and improve ICI efficacy when combined with checkpoint blockade (Lequeux et al., 2021). HAPs are moving into the clinic, with CP-506 currently in a phase 1/2 trial both as a monotherapy and in combination with carboplatin or ICI (NCT04954599). Oxygen-delivering nanomaterials, such as closed-loop nano-tanks, relieve hypoxia in preclinical models with favorable pharmacokinetics and on-demand oxygen release (Yang et al., 2024). Alleviating vascular compression by targeting tumor mechanopathology restores perfusion and reduces hypoxia, thereby promoting T cell infiltration, as shown preclinically with mechanotherapeutics such as tranilast (Mpekris et al., 2024a; Mpekris et al., 2024b). Additionally, hypoxia upregulates GDF15, a cytokine that promotes immunosuppression and immunotherapy resistance; preclinical and early clinical data suggest that targeting GDF15 can overcome this resistance, making it an emerging target for cold tumor conversion (Melero et al., 2025).

Co-stimulatory receptor agonists

Co-stimulatory receptors provide secondary signals that determine T cell activation, proliferation, differentiation, and memory formation, acting as a crucial checkpoint after TCR engagement (Chen and Flies, 2013). CD28 provides an essential co-stimulatory signal by binding to CD80/CD86 on APCs, triggering PI3K-AKT and the CBM signalosome to activate NF- κ B, driving T cell proliferation, survival, and effector differentiation, while also lowering the activation threshold by accelerating ZAP70 recruitment to the TCR complex (Chen and Flies, 2013; Raychaudhuri et al., 2024). A PD-L1-dependent CD28 bispecific antibody (NI-3201) selectively co-stimulates PD-L1+ tumors with promising preclinical activity (Majocchi et al., 2025). Next-generation CD28 agonists with tumor-restricted activation are in early clinical development, including Nectin-4 $\times$ CD28, PD-L1 $\times$ CD28, PSMA $\times$ CD28 and B7-H3 $\times$ CD28 bispecific antibodies (Lotze et al., 2024).

Prosurvival tumor necrosis factor receptor superfamily members (4-1BB, CD27, glucocorticoid-induced TNFR-related

protein [GITR] and OX40) support T cell accumulation during clonal expansion and memory formation (Watts et al., 2025). Specifically, OX40 enhances memory via NF- κ B, 4-1BB promotes CD8⁺ T and NK cell function, and GITR reduces Treg-mediated suppression (Postel-Vinay et al., 2023). ICOS (inducible T cell co-stimulator) is a CD28 family member expressed on activated T cells and Tregs. Its dual role in promoting effector T cell activation and Treg expansion has limited the clinical efficacy of ICOS agonists (Habibzadeh and Davar, 2026; Cragg et al., 2026). First-generation 4-1BB agonists were limited by hepatotoxicity or lack of efficacy, and bispecific formats remain dependent on tumor antigen expression (Claus et al., 2019; You et al., 2026). Next-generation 4-1BB agonists, including Fc-engineered and tumor-conditioned formats, are in clinical development with published evidence of activity (Cragg et al., 2026). Clinical data support combining 4-1BB agonists with T cell engagers in MSS CRC and B cell lymphoma, with manageable safety and enhanced activity (Melero et al., 2026; Hutchings et al., 2026). Tumor-anchored 4-1BB agonism requires Treg depletion for curative responses (Xu et al., 2025). GITR selectively converts intra-tumoral Tregs into IFN- γ ⁺ effectors (Galvez-Cancino et al., 2025). CD27 agonist enhances T cell cytotoxicity and synergizes with PD-1 blockade (Altıntaş et al., 2025). Despite robust pre-clinical activity, agonistic antibodies against GITR, CD27, 4-1BB, and OX40 have shown limited clinical efficacy as monotherapy or in combination with PD-1 blockade, and none have reached registrational trials (Cragg et al., 2026).

Bacterial therapy

Bacterial therapy exploits the ability of certain bacteria to colonize the hypoxic, necrotic, immunosuppressive TME (Kwon et al., 2024). This tropism is driven by multiple mechanisms: obligate anaerobes germinate only in anoxic/necrotic tumor regions (Lambin et al., 1998; Minton, 2003), whereas facultative anaerobes exploit abnormal vasculature (Forbes et al., 2003), tumor-derived metabolites chemotaxis (Kasinskas and Forbes, 2006; Kasinskas and Forbes, 2007), nutrient availability within the TME to achieve up to 1,000-fold greater accumulation than in healthy organs (Forbes et al., 2003; Clairmont et al., 2000). Once localized, bacteria act as potent in situ immune activators through direct cytotoxicity, nutrient competition, and pathogen-associated molecular pattern (PAMP)-mediated stimulation.

Their PAMPs trigger TLRs, releasing pro-inflammatory cytokines (TNF- α , IL-1 β) and recruiting innate immune cells (neutrophils, macrophages, and NK cells) (Akbariqomi et al., 2025), an effect also mediated by bacterial outer membrane vesicles (Kim et al., 2017). This suggests that cold tumors can be converted into inflamed, T cell-permissive states, as demonstrated by objective responses to intratumoral *Clostridium novyi*-NT plus pembrolizumab in a phase I study of refractory solid tumors (Nelson et al., 2025). Preclinically, engineered *Salmonella* reversed T cell exhaustion (Wu et al., 2024c), and *Lactobacillus reuteri* delivered α PD-L1 to reprogram the TME (Zhang et al., 2026a).

The gut microbiome plays a major role in modulating the TIME. Dysbiosis causing a leaky gut can lead to chronic

inflammation, promoting tumor growth. On the other hand, a healthy gut microbiome can modulate antitumor immunity through multiple mechanisms, including the translocation of microbial MAMPs and PAMPs to tumor sites (Paulos et al., 2007), antigen cross-reactivity between microbial epitopes and tumor neoantigens that activates CD4⁺ and CD8⁺ T cells (Balachandran et al., 2017), systemic regulation of cytokines such as TNF- α / β , IL-12, and IL-10 altering the TME, and the production of microbial metabolites that regulate macrophages, DCs, Tregs, Th1/Th17, and plasma cell functions in the tumor lesions and their draining lymph nodes (Simpson et al., 2023). These characteristics can also modulate ICI responsiveness. Specific commensals are enriched in responders and produce immunostimulatory metabolites such as inosine, which activates antitumor T cells (Mager et al., 2020). Segmented filamentous bacteria promote molecular mimicry by inducing Th17 cells that cross-react with tumor antigens upon PD-1 blockade (Najar et al., 2026). Zitvogel's group established that antibiotic-induced dysbiosis compromises ICI efficacy and that fecal microbiota transfer can restore sensitivity (Routy et al., 2018). Long-distance microbial mechanisms impacting cancer immunosurveillance provide a conceptual framework for these effects (Zitvogel et al., 2024). Clinical evidence from a meta-analysis confirmed that pre-ICI antibiotic exposure impairs outcomes (Crespin et al., 2023), and early clinical trials have shown that fecal microbiota transfer from ICI responders can overcome ICI resistance in melanoma and NSCLC (Duttgupta et al., 2026). Emerging strategies include low-dose intestinal irradiation (Chen et al., 2025b) and microbiota-centered interventions such as dietary modifications and beneficial microbes (Almonte et al., 2025).

Collectively, bacteria-based strategies, whether acting directly within the TME or systemically via the gut-immune axis, have the potential to promote cold tumors toward a more inflamed, therapy-responsive environment (Kwon et al., 2024), though confirmation with randomized phase III trials is still pending.

STING agonists

The cGAS-STING pathway senses cytosolic dsDNA, producing 2'3'-cGAMP that activates STING, leading to TBK1/IRF3-dependent type-I IFN induction and downstream DC maturation, facilitating CD8⁺ T cell and NK cell infiltration (Ishikawa and Barber, 2008). This makes cGAS-STING a prime target for converting cold tumors into hot ones (Chen et al., 2016). Rather than being used as stand-alone agents, STING agonists are emerging as immune primers that should be combined with interventions that further boost antigen presentation and T cell priming (Woo et al., 2014). A particularly synergistic partner is DNA-PK inhibition (discussed in Increasing TMB). Pharmacological DNA-PK inhibition not only increases neoantigen diversity and MHC-I expression but also sustains STING activation via the mitochondrial adaptor MAVS, thereby amplifying IFN-I responses and T cell priming (Nielsen et al., 2024; De Rosa et al., 2025). Co-administration of STING ligand, CD40 agonist, and DNA-PK inhibitor increases the number and clonal diversity of TILs and sensitizes resistant tumors to ICB (Nielsen et al., 2024).

Clinically, STING agonists have shown mixed results (Cooper et al., 2025; Harrington et al., 2025; Luke et al., 2025; Meric-Bernstam et al., 2023), and nanotechnologies delivering DNA activate both STING and AIM2 to enhance T cell recruitment (Yum et al., 2026). However, the efficacy of STING agonists may be limited by frequent epigenetic silencing or chronic activation, which can paradoxically promote tumor growth, highlighting the need for careful dosing and patient selection (Falahat et al., 2021; Li et al., 2026a; Wang et al., 2026).

Reversing immunosuppression in cold tumors

Several recurrent genetic alterations directly promote immune escape and exclusion, making some tumor types intrinsically cold (Fig. 1). Among these, KEAP1 (regulator of NRF2, which regulates oxidative stress) loss-of-function mutations have been associated with reduced T cell cytotoxicity and impaired infiltration of DC and T cells in lung cancer (Paredes et al., 2025; Zavitsanou et al., 2023). Likewise, PTEN loss promotes the production of immunosuppressive cytokines and the accumulation of Tregs, Th2 cells, and M2 macrophages in the TIME (Chen and Guo, 2017). Similarly, KRAS mutations (such as KRAS^{G12D}) foster immune exclusion by recruiting myeloid-derived suppressor cells and Tregs, promoting CAF activation, and limiting CD8⁺ T cell infiltration (Watterson and Coelho, 2023). Activation of the WNT/ β -catenin pathway also promotes immune exclusion by impairing CCL4 production and DC recruitment, thereby preventing effective CD8⁺ T cell priming and infiltration (Spranger et al., 2015). These genetic alterations actively establish immune-cold, immunosuppressive, and immune-excluded microenvironments, highlighting the need for therapeutic strategies that overcome immunosuppression. Furthermore, tumor immune evasion in cold tumors is sustained by poor or defective antigen presentation, impaired priming, persistent suppressive signaling from Tregs and myeloid cell populations, and insufficient effector T cell recruitment, all of which limit effective antitumor immune responses (Wang et al., 2020; Wu et al., 2024a; Spranger and Gajewski, 2018) (Fig. 1). Reversing these states requires both T cell reinvigoration and TME remodeling to enhance DC function, reprogram TAMs, and reduce Treg-mediated suppression. In this context, Treg-directed therapies, CD40 agonists, and combinatorial immune checkpoint inhibition can represent complementary strategies that can convert immune-excluded or immune-desert tumors into inflamed, therapy-responsive tumors (Navarrete et al., 2026; Vonderheide, 2020) (Fig. 2).

CD40 agonists and myeloid reprogramming

CD40 signaling plays an essential role by connecting innate and adaptive immunity through the activation of DCs, enhancing antigen presentation, and promoting a pro-inflammatory myeloid program (Vonderheide, 2020). CD40 agonism promotes DC maturation, enhances antigen presentation, and facilitates cross-presentation via cDC1s, with antitumor efficacy being cDC1- and CD8⁺ T cell dependent (Ferris et al., 2020; Vonderheide, 2020; Lam et al., 2026). CD40 antibodies can overcome defective priming by enhancing co-stimulation, cytokine production,

and cross-presentation, thereby fostering de novo antitumor T cell responses (Vonderheide, 2020; McVey and Beatty, 2025). In murine models of cholangiocarcinoma, CD40-mediated immune cell activation has been shown to enhance responses to anti-PD-1 therapy, supporting the principle that innate immune activation can sensitize otherwise resistant tumors to ICB (Diggs et al., 2021).

In the context of TAMs, which are central orchestrators of the suppressive niche in cold tumors, CD40 engagement induces metabolic reprogramming that supports inflammatory and antitumor functions through enhanced fatty acid oxidation, glutamine utilization, and epigenetic remodeling (Liu et al., 2023b). Importantly, disruption of these pathways abolishes the therapeutic efficacy of CD40 agonists and TAM reeducation (Liu et al., 2023b). Single-cell analyses in colon cancer reinforced the concept that myeloid-targeted therapies reshape the TME by altering myeloid states linked to T cell activation (Zhang et al., 2020). CD40 agonism therefore acts as a myeloid reprogramming strategy rather than a simple immune stimulant.

Despite encouraging preclinical data, CD40 agonists have not shown sufficient activity as monotherapy or with PD-1 blockade to advance to registrational trials (Li and Wang, 2020; Padrón et al., 2022; Steeghs et al., 2026). Fc-optimized CD40 agonists in development induce TLS formation and systemic antitumor immunity in preclinical models (Osorio et al., 2025), suggesting that this target may yet be realized.

Tregs: Directed strategies

Tregs represent another key immunosuppressive barrier to effective antitumor immunity in immunologically cold tumors, where they enforce local immune tolerance through CTLA-4 (Navarrete et al., 2026; Zhou et al., 2024). Chemokine receptor CCR5 is expressed by Tregs and recruits them to the TME, contributing to immune exclusion. CCR5 inhibition may help overcome this barrier (Halama et al., 2016) and is being evaluated in combination with ICIs in phase I/II trials. Quezada and colleagues have developed multiple antibody-mediated Treg depletion strategies: Fc-engineered anti-CTLA-4 (Simpson et al., 2013; Arce Vargas et al., 2018), selective anti-CD25 preserving IL-2 signaling on effector T cells (Solomon et al., 2020), and Fc-optimized anti-CTLA-4/CCR8 antibodies with improved selectivity and tolerability, advancing the latter to phase II/III trials (Navarrete et al., 2026). Selective targeting of intratumoral Tregs restores CD8⁺ T cell function through IL-2 competition blockade and TOX pathway uncoupling, supporting local or subset-specific Treg modulation over systemic depletion. This is particularly important because systemic Treg depletion carries a high risk of autoimmunity, whereas selective approaches may provide a better balance between efficacy and safety (Zhou et al., 2024). Furthermore, Gálvez-Cancino and colleagues demonstrated that Treg depletion promotes myeloid activation (Galvez-Cancino et al., 2025). Indiscriminate pan-Treg depletion disrupts peripheral tolerance, whereas tumor-selective approaches, such as gp96/LFA-1-mediated Treg trafficking or CCR8-restricted expression, have been explored (Chen et al., 2025d). In addition, more translational studies have emphasized several Treg-directed modalities, including anti-CCR4 antibodies, modified CTLA-4

antibodies that preferentially deplete CTLA-4-high cells, and combination regimens using low-dose cytotoxic or hormonal interventions to reduce intratumoral Tregs (Galvez-Cancino et al., 2025; Wang et al., 2025; Cao et al., 2025).

Other ICIs

Beyond PD-1/PD-L1 and CTLA-4, a growing number of next-generation ICIs have emerged as key mediators of immunosuppression, particularly in immunologically cold tumors that exhibit poor T cell infiltration and resistance to conventional ICB (Topalian et al., 2023; Joller et al., 2024). Among the most extensively studied are lymphocyte-activation gene 3 (LAG-3), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), and T cell immunoreceptor with Ig and ITIM domains (TIGIT), which are frequently co-expressed with PD-1 on exhausted TILs and collectively reinforce dysfunctional T cell states (Joller et al., 2024). It is widely believed that LAG-3, TIM-3, and TIGIT represent a “second wave” of checkpoint targets with nonredundant roles across multiple immune cell subsets, extending beyond T cells to shape broader immune regulation (Joller et al., 2024). Importantly, studies have demonstrated that combinatorial blockades can restore clonal expansion and effector function of tumor-specific CD8⁺ T cells, overcoming resistance mechanisms characteristic of cold tumors (Nutsch et al., 2024; Guan et al., 2024). However, trials combining TIM-3, TIGIT or LAG-3 blockade with anti-PD-1 have largely failed to improve efficacy over PD-1 alone (NCT04655976, NCT04513925, and NCT03470922), except for LAG-3 plus PD-1 in melanoma, where the benefit is reduced toxicity rather than superior efficacy over CTLA-4 plus PD-1 (Tawbi et al., 2022; Wolchok et al., 2025).

Indoleamine 2,3-dioxygenase 1 (IDO) is a metabolic checkpoint that degrades tryptophan into kynurenine, suppressing effector T cells while expanding Tregs (Puccetti and Grohmann, 2007). Its upregulation following ICI therapy contributes to acquired resistance, and IDO inhibitors combined with ICIs have shown clinical responses (Lemos et al., 2019; Wu et al., 2023). Prodrug-tethered lipid nanoparticles co-delivering IL-12 mRNA and an IDO inhibitor drove complete tumor regression in a colon cancer model by enhancing T cell infiltration and reducing exhaustion (Shi et al., 2026). However, IDO1 blockade plus anti-PD-1 failed in phase III melanoma trials, leading to termination of other phase III studies and underscoring the need for better biomarkers (Long et al., 2019).

Synthetic approaches

Advanced synthetic approaches can overcome physical and chemical barriers in the TME that limit effector T cell function; they aim at reengineering immune cell trafficking, activation, and persistence at the molecular level (Liu et al., 2025). This section outlines key synthetic platforms that are moving beyond traditional biologics, including bispecific antibodies and engineered cellular therapies (Fig. 2).

Bispecific antibodies

Bispecific antibodies are engineered engagers that forcibly bridge immune effector cells to tumor antigens, bypassing

endogenous T cell priming (Goebeler et al., 2024). By binding a TAA to CD3, they induce an artificial immunological synapse, driving polyclonal T cell activation and tumor-specific cytotoxicity independent of MHC-restricted antigen presentation (Goebeler et al., 2024). This forced engagement creates an inflammatory “beachhead” within the tumor, promoting immune infiltration even in previously cold microenvironments (Goebeler et al., 2024). Protein engineering has yielded more than 200 bispecific agents in preclinical or clinical evaluation, including bispecific T cell engagers, dual-affinity retargeting, and IgG-like bispecific antibodies, with improved stability, reduced immunogenicity, and tailored pharmacokinetics (Goebeler et al., 2024). A modular “Catch-and-Play” platform enables rapid assembly of personalized T cell engagers with neonatal Fc receptor-driven half-life extension (Xi et al., 2026). To reduce off-tumor toxicity, the B7-H3/EGFR-bispecific IBI334 exploits B7-H3 upregulation in EGFR-positive tumors, achieving cis-inhibition of EGFR and potent downstream suppression, as confirmed by cryo-EM (Guan et al., 2026).

T cell exhaustion limits bispecific antibody efficacy in solid tumors. Two complementary strategies have emerged to overcome this barrier: vaccine-primed T cells recruited by a CD3 bispecific antibody establish a Th1-inflamed microenvironment and achieve tumor eradication, indicating that insufficient T cell infiltration is a primary limitation (Middelburg et al., 2024). Alternatively, a bispecific DC-T cell engager targeting TIM3 on exhausted TILs and activating DCs via IFNAR directly reactivates exhausted T cells within the TME by preventing apoptosis and enhancing DC-mediated co-stimulation (Zhang X. et al., 2026b). Together, these findings highlight that both insufficient infiltration and intratumoral exhaustion limit bispecific antibody efficacy, highlighting the need for combination strategies that either boost T cell entry or directly reverse exhaustion within the TME.

Clinical translation of bispecific antibodies has yielded notable successes. Approved agents include blinatumomab in B-ALL (Litzow et al., 2024), tebentafusp in uveal melanoma (Nathan et al., 2021), zenocutuzumab in NRG1-fusion cancers (Schram et al., 2025), and cadonilimab in cervical cancer (Gao et al., 2023). However, solid-tumor translation remains challenging due to poor tumor penetration, on-target/off-tumor toxicity, and cytokine release syndrome (Goebeler et al., 2024; Shui et al., 2025), though DLL3 × CD3 and STEAP1 × CD3 agents have shown success in small cell lung cancer after chemotherapy and metastatic prostate cancer, respectively, both in typically cold tumor settings with limited ICI responses (Mountzios et al., 2025; Kelly et al., 2024).

CAR-T cell therapy

CAR-T cells are generated by isolating autologous T cells and engineering them to express a CAR. This synthetic receptor consists of an extracellular single-chain variable fragment (scFv) that recognizes a tumor surface antigen, linked via a transmembrane domain to the intracellular CD3ζ chain (providing the primary activation signal), and one or more co-stimulatory domains (e.g., CD28 or 4-1BB) that drive T cell activation, proliferation, and persistence. Upon antigen binding, the CAR triggers

a signaling cascade leading to T cell activation, cytokine release, and direct cytotoxicity of the target cancer cell (Zugasti et al., 2025). However, efficacy in solid tumors has been limited by poor trafficking, rapid exhaustion, and antigen-escape heterogeneity (Escobar et al., 2025).

A recent study of allogeneic CAR-T cells in high-risk neuroblastoma showed feasibility and provided mechanistic insights to improve functionality (Willyard, 2025). An IL-15-autocrine CAR-T design sustains trafficking and persistence by promoting a stem memory T cell subset in the TME. A new CAR design avoids dangerous side effects by releasing immune-stimulating cytokines only when tumor cells express two antigens simultaneously, creating focused local inflammation in resistant cancers (Fieldhouse, 2026; Cohen et al., 2026). Furthermore, targeting the tumor stroma itself represents a complementary approach. FAP-targeted CAR-T cells selectively deplete CAFs, alleviating the desmoplastic barrier and improving immune infiltration (Niu et al., 2024).

Logic-gated CARs integrate Boolean operations: “AND” gates activate only when two tumor antigens are present, “AND-NOT” gates activate only when a tumor antigen is present without a healthy marker, and OR gates activate when either of two antigens is present. These designs improve tumor specificity and reduce off-tumor toxicity (Liu et al., 2025; Du et al., 2025). Tandem and split CAR designs further refine antigen recognition, requiring dual antigen engagement for full activation (Kloss et al., 2013; Roybal et al., 2016). Beyond antigen-based gating, synthetic transcription factors provide drug-inducible control of therapeutic gene expression, enabling precise CAR-T cell regulation (Li et al., 2022).

Clinically, CAR-T cells have transformed hematological malignancies, with six FDA-approved products for B cell malignancies and multiple myeloma (Brudno et al., 2024), though progress in solid tumors has been slower. Recent advances include allogeneic CAR-T cells in neuroblastoma (Quintarelli et al., 2025), with many ongoing phase I/II trials, including in glioblastoma, ovarian, and pancreatic cancer (NCT04003649, NCT06158139, and NCT06051695). The field is now exploring combinations with ICIs (NCT04995003) or oncolytic viruses (OVs) (NCT05057715) to overcome the immunosuppressive TME.

Engineered bacteria and OVs

Beyond their natural immunostimulatory properties discussed in Bacterial therapy, bacteria can be engineered as precision delivery platforms. Engineered bacteria selectively colonize hypoxic tumor cores, overcoming poor perfusion that excludes immune cells. These living therapeutics function as localized factories to produce chemokines, immunomodulators, and checkpoint inhibitors directly at the tumor site (Kwon et al., 2024). The natural tropism of certain bacteria for the immunosuppressed, hypoxic TME allows them to serve as targeted delivery vehicles. One example is nonpathogenic anaerobic sulfate-reducing bacteria that have been engineered to biosynthesize intratumoral nanoparticles, achieving >50% tumor delivery efficiency in preclinical models (Dong et al., 2025).

Similarly, OVs are engineered as multi-transgene delivery platforms to remodel the TME and promote T cell trafficking. In

the *Nature Reviews Cancer* opinion piece (Twumasi-Boateng et al., 2018), it is proposed that OV may serve as multiplexed immune-modulating platforms expressing ICIs, tumor antigens, cytokines, and T cell engagers. Mechanistically, OV unify direct tumor cytotoxicity with the stimulation of antitumor immunity; through the induction of ICD and the release of TAAs, they remodel the TME into an inflamed and immune-permissive niche that enables systemic immune activation (Lin et al., 2023). More recently, engineered OV and cytokine-based gene therapies have been shown to reprogram the TME, converting cold tumors into immune-responsive states and amplifying antitumor immunity (Bernstock et al., 2026). A leading clinical example is VG161, an engineered herpes simplex virus expressing IL-12, IL-15, IL-15R α , and a PD-1–PD-L1 blocking fusion protein, which was well tolerated with no dose-limiting toxicities in a phase I trial for advanced hepatocellular carcinoma (NCT04806464). The virus reshaped the TME to resensitize treatment-resistant tumors to prior therapies (Shen et al., 2025; Giovannoni et al., 2025). However, T-VEC (GM-CSF-encoding oncolytic herpes virus) plus PD-1 blockade failed to improve efficacy over PD-1 blockade alone in a phase III trial for metastatic melanoma, highlighting the challenge of intratumoral injections to elicit systemic responses against non-infiltrated metastases (Chesney et al., 2023).

Concluding remarks

Converting cold tumors into hot, ICI-responsive lesions requires a coordinated approach that enhances tumor antigenicity through neoantigen generation and supports immune priming with additional interventions. The future of immunotherapy lies in personalized combination regimens integrating multiple strategies. Effective synergy likely requires combinations that address distinct bottlenecks in the cancer-immunity cycle: for example, antigenicity-enhancing strategies (mutagenesis, vaccines, and NMD inhibition) can be paired with T cell trafficking facilitators (anti-angiogenics, cytokines, and STING agonists) and immunosuppression reversal (Treg targeting, myeloid reprogramming, and next-generation ICIs). Selecting these combinations requires matching therapy to the dominant resistance mechanism of each tumor, highlighting the need for biomarker-guided treatment rather than universal regimens.

However, despite the advances discussed in this review, significant challenges remain before these approaches can achieve meaningful clinical impact, including predicting effective combinations for individual patients, managing toxicity from dual or triple therapies, and overcoming the heterogeneity and plasticity of cold tumors.

Addressing these challenges will require biomarker-driven patient selection, spatial and single-cell profiling to map resistance mechanisms, and adaptive trial designs that evaluate rationally sequenced rather than simultaneous combinations.

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