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Cancer immunotherapy: Current progress and future perspectives

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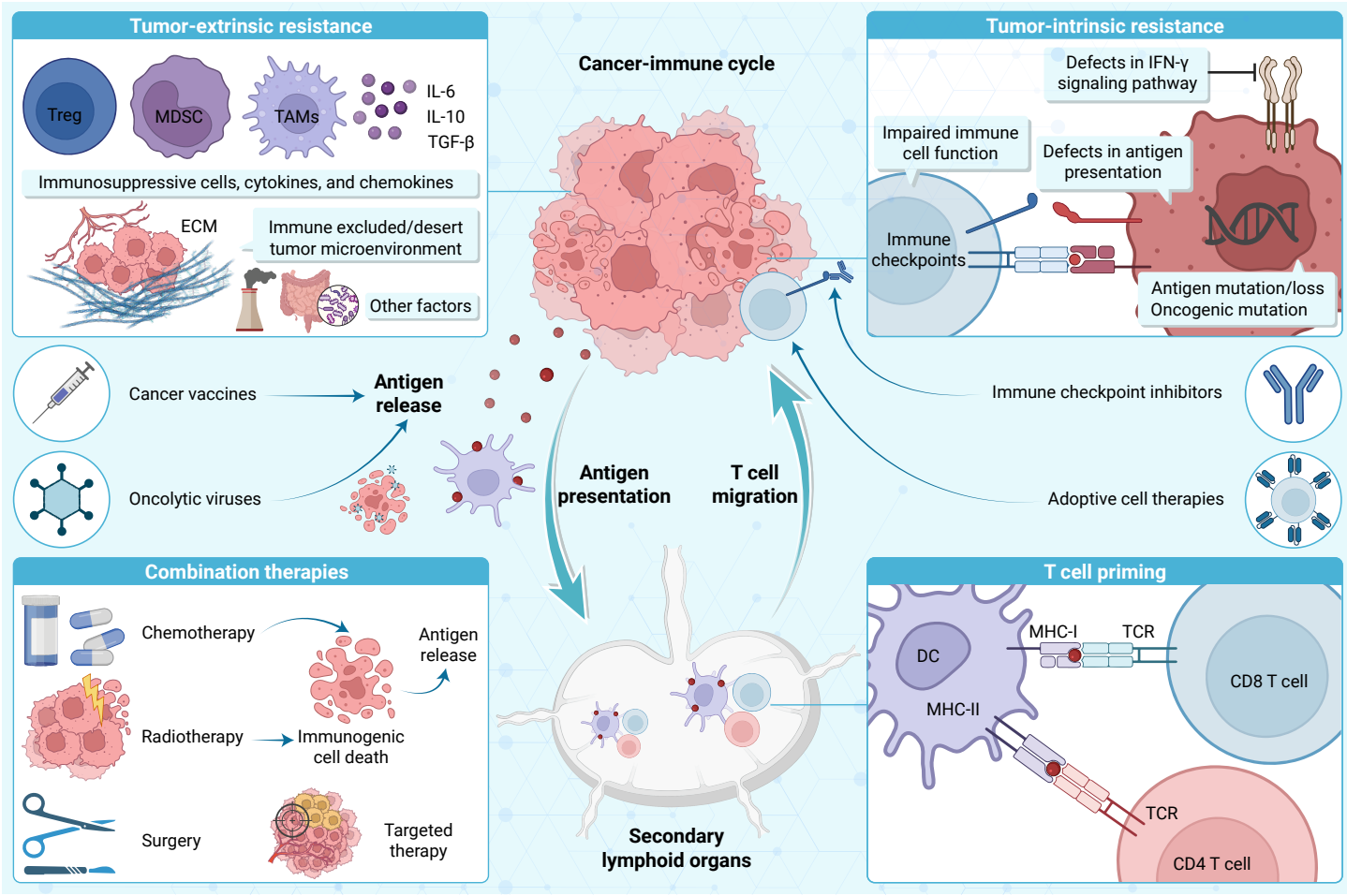
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Cancer immunotherapies exert their effects by targeting different steps of the cancer-immune cycle.
- Significant progress was achieved in immune checkpoint inhibitors, cancer vaccines, oncolytic viruses, and adoptive cell therapies.
- Tumor extrinsic/intrinsic mechanisms hinder antitumor immunity and promote immune evasion and therapeutic resistance.
- Rational combination strategies may enhance immune responses, overcome resistance, and improve therapeutic efficacy.

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Cancer immunotherapy has revolutionized cancer treatment by harnessing the host immune system to recognize and eliminate tumor cells. In recent years, significant progress has been achieved in multiple immunotherapeutic modalities, particularly immune checkpoint inhibitors (ICIs), cancer vaccines, oncolytic virus therapies (OVs), and adoptive cell therapies (ACTs). Extensive clinical trial data proved that immunotherapy brings durable responses and survival benefits across various malignancies, supporting the official approval of numerous immunotherapy agents for cancer treatment. Despite these advances, major challenges remain, including immune-related toxicities, tumor heterogeneity, and treatment resistance, which restrict the therapeutic efficacy and tolerability. To address these limitations, emerging strategies are being actively explored, including rational combination therapies, next-generation immune cell engagers, and engineered innate immune cellular products. In this review, we comprehensively summarize recent progress in the development of cancer immunotherapy and discuss the bottlenecks and potential strategies for each therapeutic approach. Available clinical data are highlighted to provide a more intuitive understanding of the efficacy and safety of these treatments, thereby facilitating future broader application of immunotherapy. Ultimately, such insights may guide the more effective and safer use of current therapies and support the development of next-generation therapeutic alternatives.

INTRODUCTION

Cancer is a multifaceted and heterogeneous disease that remains a substantial global health burden, with high morbidity and mortality. While traditional therapeutic modalities, including surgical resection, radiation, and cytotoxic drugs, have significantly improved clinical outcomes, their efficacy is limited by restricted applicability to certain patient populations, primary or acquired resistance, and dose-limiting systemic toxicities. The emergence of cancer immunotherapy represents a shift in treatment: from directly killing tumor cells toward reinvigorating or enhancing the host immune system. By reactivating immune responses or adoptively transferring immune cells, cancer immunotherapy has demonstrated the potential to induce durable immune responses and establish long-term immune memory.[1]

Although cancer immunotherapy has gained great prominence only in recent decades, its conceptual root can be traced back to the 19th century. Fehleisen and Busch independently reported tumor regression following erysipelas infection in patients.[2] Later, Coley observed the same phenomenon and developed inactivated bacteria known as "Coley's toxins", providing the first evidence of pathogen-induced immune activation against solid tumors and laying the foundation for immune-based cancer therapy.[3] However, difficulties in manufacturing standardization, instability, and safety risks all contributed to its decline in clinical practice. This field re-emerged in the 1970s when Morales demonstrated the effectiveness of intravesical Bacillus Calmette-Guérin (BCG) in superficial bladder cancer, a practice that remains a standard of care.[4] Subsequent decades witnessed significant advances in cytokine therapy, cancer vaccines, and monoclonal antibodies (mAbs). Systemic immune stimulation of high-dose interleukin-2 (IL-2) or interferon (IFN)-α demonstrated their tumor-killing capacity and were approved for clinical use in the 1990s.[5] Sipuleucel-T became the first FDA (Food and Drug Administration)-approved therapeutic cancer vaccine for prostate carcinoma, and the implementation of prophylactic vaccines against oncogenic viruses such as the hepatitis B virus (HBV) and the human papillomavirus (HPV), greatly reduced the incidence of virus-associated malignancies worldwide.[6-8]

A transformative milestone occurred in 2011 with the approval of ipilimumab, the first immune checkpoint inhibitor (ICI) targeting cytotoxic T lymphocyte-associated protein-4 (CTLA-4), establishing ICI as a revolutionary therapeutic strategy. Soon afterward, programmed cell death protein 1 (PD-1) inhibitors pembrolizumab and nivolumab achieved FDA approval for melanoma. In 2015, Talimogene laherparepvec (T-VEC), a genetically modified herpes simplex-1 virus expressing granulocyte-macrophage colony-stimulating factor (GM-CSF), became the first approved oncolytic virus (OV) for advanced melanoma.[9] In parallel, immune cell therapies such as chimeric antigen receptor (CAR)-T cells and advances in genome-editing technologies like CRISPR/Cas9 technique further broadened the immunotherapeutic landscape. To date, anti-CTLA-4, anti PD-1/programmed death-ligand 1 (PD-L1) antibodies, their combinations, and novel ICIs have generated more than 40 approved indications covering 17 different cancer types. CAR-T cell therapy has revolutionized the management of hematological malignancies, with seven CAR-T cell products approved to date, although their efficacy in solid tumors remains limited and is still under active investigation.[10,11] To overcome the limitations of CAR-T cells, novel adoptive cell therapies (ACTs) have attracted considerable attention, including T cell receptor (TCR)-T cells, CAR-natural killer (NK) cells, CAR-macrophages, and engineered γδ T cells, which have shown potential against solid tumors with a lower incidence of cytokine release syndrome (CRS), a lethal but reversible disorder caused by the release of massive cytokines in the serum.[12-14]

Despite these remarkable advances, several challenges continue to limit the broader clinical impact of immunotherapy. A considerable proportion of patients fail to derive clinical benefit, exhibiting primary or acquired resistance. Responses to immunotherapy are shaped by the complex interplay of tumor-intrinsic, tumor-extrinsic, and host-related factors, such as tumor immune profile, gender, microbiome, genetics, and living environment.[15] Evidence-based biomarkers have been developed for predicting therapy responses (predictive biomarkers) and evaluating clinical prognosis (prognostic biomarkers), such as serum lactate dehydrogenase, PD-L1, microsatellite stability, and tumor mutational burden (TMB).[16,17] Promising emergent biomarkers such as IFN-γ related signatures and the presence of tertiary lymphoid structure have entered the stage but need further validation.[18,19] Nevertheless, universally reliable biomarkers for patient stratification remain unavailable. Moreover, immune-related adverse events (irAEs), high treatment costs, and complex manufacturing processes restrict their widespread implementation.[1]

In this review, we first summarize the fundamental mechanisms of antitumor immunity and provide a comprehensive overview of the historical evolution and current landscape of cancer immunotherapy. We focus on ICIs, cancer vaccines, OVs, and ACTs, highlighting both clinically approved therapies and emerging strategies with significant potential. By discussing ongoing challenges and future directions, this review aims to offer an integrated perspective and inspire further progress in the rapidly evolving field of cancer immunotherapy.

UNDERLYING MECHANISMS OF ANTITUMOR IMMUNITY

The rapid development of cancer immunotherapy has been driven by an increasingly sophisticated understanding of the dynamic interplay between cancer and the host immune system. The concept of immune surveillance,

proposed by Burnet and Thomas, postulated that the immune system is capable of recognizing and eliminating nascent transformed cells.[20] This hypothesis was later refined into the framework of cancer immunoediting, which describes tumor-immune interactions as a dynamic process comprising three phases: elimination, equilibrium, and escape, highlighting the dual role of the immune system in both eliminating tumor cells and shaping tumor immunogenicity.[21,22]

Effective antitumor immunity relies on a coordinated transition from innate to adaptive responses (Figure 1). The innate compartment, including dendritic cells (DCs), macrophages, NK cells, neutrophils, and other immune populations, functions as the initial sensor of oncogenic danger signals. The adaptive immune system primarily consists of B cells and T cells, capable of generating antigen-specific responses and long-term immune memory. Among these, DCs (especially the conventional DC1 subset) play a critical role in the antigen presentation process.[23] They internalize and process these antigens into peptides, present them on major histocompatibility complex (MHC) molecules, and migrate to secondary lymphoid organs (SLOs) to activate T cells. Notably, effective T cell activation requires three signals: (1) the specific engagement of the TCR with peptide-MHC complex; (2) co-stimulatory signaling, such as the interaction between CD80/CD86 on antigen-presenting cells (APCs) and CD28 on T cells; (3) a milieu of cytokines that orchestrate T cell differentiation.[24]

Upon activation, T cells proliferate and differentiate into effector subsets, including $CD8^+$ cytotoxic T lymphocytes (CTLs) and $CD4^+$ helper T cells. Effector T cells, guided by chemokines and adhesion molecules, migrate from SLOs to reach the tumor site. CTLs recognize tumor cells through peptide-MHC-I complexes and directly induce tumor cell apoptosis either by releasing perforin and granzyme or activating death receptor pathways.[24] Meanwhile, $CD4^+$ helper T cells amplify immune responses by secreting immunostimulatory cytokines such as IL-2, IFN-γ, and tumor necrosis factor-α (TNF-α).[24] Notably, cytotoxic $CD4^+$ T cells that are capable of directly killing tumor cells have been reported and are considered great prognostic indicators.[25] In addition, B cells contribute to antitumor immunity not only via antibody production but also through the formation of tertiary lymphoid structure, as well as cytokine production and specialized antigen presentation.[26,27]

Importantly, tumors often evade immune surveillance through complex intrinsic and extrinsic mechanisms. Tumor-intrinsic adaptations can disrupt antigen presentation and immune recognition, thereby limiting effective T cell-mediated tumor elimination. Genetic mutations and epigenetic modifications enable immune escape through the loss or downregulation of tumor antigens, defects in antigen-presentation machinery such as β2-microglobulin and transporter associated with antigen processing, and impaired production of type 1 helper T-associated chemokines.[28] In addition, aberrant oncogenic signaling pathways, including WNT/β-catenin activation, mitogen-activated protein kinase alterations, and phosphatase and tensin homolog loss, promote immune exclusion.[29] Moreover, defects in IFN-γ-Janus kinase signaling and adaptive upregulation of inhibitory checkpoints further dampen antitumor immunity.[30]

Tumor-extrinsic resistance mechanisms are largely mediated by the immunosuppressive tumor microenvironment (TIME). Tumor cells actively reshape the immune landscape by secreting immunosuppressive cytokines and chemokines, recruiting regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and immunosuppressive tumor-associated macrophages (TAMs). This cellular suppression is compounded by the accumulation of suppressive metabolites such as lactic acid and adenosine, alongside the enzymatic activity of arginase-1.[31] Physical and structural barriers impede effective antitumor immunity as well. Remodeling of the extracellular matrix (ECM), characterized by increased cancer-associated fibroblasts, elevated matrix metalloproteinases (MMPs), and aberrant composition of collagen and glycosaminoglycans, restricts immune cell infiltration into the tumor and may contribute to the formation of an immunologically cold tumor phenotype.[32] Furthermore, systemic host factors are increasingly recognized as important determinants of therapeutic outcomes. The gut microbiome, baseline immune fitness, environmental exposures, and lifestyle factors can profoundly influence antitumor immunity and contribute to the inter-individual heterogeneity. Collectively, these evasion mechanisms represent the primary hurdles to treatment efficacy but simultaneously serve as focal therapeutic targets for next-generation cancer immunotherapy.

Notably, increasing evidence indicates that antitumor immunity extends beyond the localized tumor microenvironment (TME) and is profoundly influenced by systemic immune compartments, including peripheral blood, bone marrow, and SLOs. On one hand, in tumor-bearing hosts, systemic immune perturbations induced by tumor burden include dysregulated hematopoiesis skewed towards myeloid lineages, expansion of immunosuppressive populations, and reduced circulating TCR diversity, all associated with therapeutic resistance and poor prognosis.[33,34] In particular, the bone marrow has emerged as a critical origin of those immunosuppressive cells that subsequently infiltrate the TME and regulate the local immune landscape.[35] On the other hand, from a therapeutic perspective, the mobilization of systemic immunity is required for effective cancer immunotherapy and also reflects therapeutic responsiveness.[36] A landmark study has underscored that response to ICIs relies heavily on the recruitment of novel, non-exhausted T cell clones from peripheral compartments rather than the invigoration of pre-existing intratumoral T cells.[37] Consequently, preserving the integrity of systemic immunity and harnessing its responses during treatment are critical. For instance, systemic chemotherapy underperforms compared with localized chemotherapy due to its non-selective lymphodepleting effects.[38] Therefore, maintaining and boosting systemic immunity represents a promising avenue to monitor therapeutic efficacy and design rational combination regimens to overcome resistance.[39]

IMMUNE CHECKPOINT INHIBITORS (ICIs)

Immune checkpoints are a variety of molecules that function through inhibitory pathways to help regulate immune responses and prevent off-target damage, essential in maintaining immune homeostasis under normal physiological conditions. In cancer, however, persistent antigen stimulation leads to upregulation of these checkpoints, contributing to T cell exhaustion and dysfunction, which are crucial for tumor immune evasion.[40] ICIs are effective in restoring T cell function and have reshaped cancer treatment paradigms. Over the past decades, a variety of ICIs have been designed and evaluated, especially those targeting PD-1, PD-L1, and CTLA-4, which have provided substantial clinical benefits for patients with previously limited options (Table S1). Novel checkpoints are intensively investigated as well, including lymphocyte activation gene 3 (LAG-3), T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), and T cell immunoreceptor with Ig and ITIM domains (TIGIT), which promotes the development of more ICIs against a wide range of malignant neoplasms.

PD-1/PD-L1 axis

PD-1 (also known as CD279) is an inhibitory checkpoint receptor minimally expressed on naïve T cells but rapidly upregulated following TCR engagement. It becomes highly enriched on chronically stimulated lymphocytes, such as exhausted $CD8^+$ T cells in the context of tumor.[40] Its primary ligand PD-L1 (CD274, B7-H1) is broadly expressed on tumor cells, stromal cells, and tumor-associated myeloid cells, while PD-L2 (CD273, B7-DC) is more restricted and predominantly confined to APCs.[41] The interaction between PD-1 with PD-L1 or PD-L2 delivers signals to attenuate T cell cytokine production, proliferation, and cytotoxic function, which is critical for maintaining peripheral immune tolerance but is frequently co-opted by tumors to facilitate immune evasion. Therapeutic blockade of PD-1/PD-L1 axis unleashes antitumor immunity and represents one of the most transformative advances in cancer immunotherapy. To date, the U.S. FDA has approved multiple PD-1/PD-L1 inhibitors for clinical use, including anti-PD-1 antibodies (nivolumab, pembrolizumab, cemiplimab, dostarlimab, retifanlimab, and tislelizumab), as well as anti-PD-L1 antibodies (atezolizumab, avelumab, durvalumab, and cosibelimab).[42,43] Notably, their clinical utility is often guided by PD-L1 expression, quantified as tumor proportion score (TPS) or combined positive score (CPS), although the predictive value varies among different tumor types and therapeutic contexts.

Pembrolizumab and nivolumab constitute the backbone of PD-1-targeted immunotherapy, with extensive regulatory approvals spanning melanoma, non-small cell lung cancer (NSCLC), head and neck squamous-cell carcinoma, renal cell carcinoma (RCC), and other malignancies.[44-47] For example, in advanced or metastatic NSCLC, pembrolizumab monotherapy is a stan-

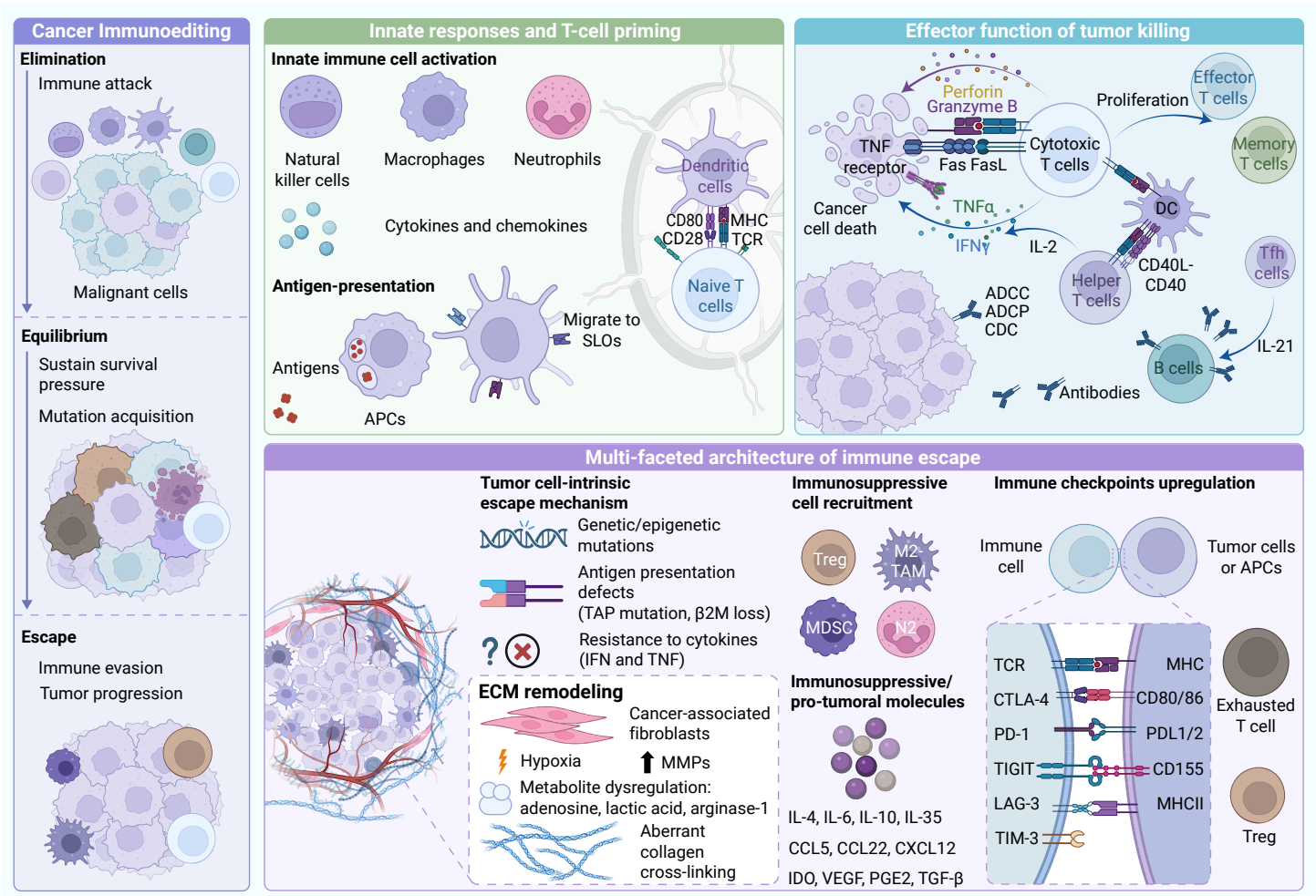

Figure 1. Dynamic interplay between antitumor immunity and tumor immune invasion The cancer immunoediting paradigm comprises three sequential phases: elimination, equilibrium, and escape, during which antitumor immunity continuously exerts selective pressure on tumor evolution. Initially, innate immune cells recognize transformed cells and initiate inflammatory responses. APCs, especially DCs, present tumor antigens and prime T cells in secondary lymph organs (SLOs). Activated CTLs eliminate tumor cells through cytolytic and cytokine-mediated mechanisms, supported by $CD4^+$ T cells and B cells. However, tumors evade immune attack through impaired antigen presentation, recruitment of immunosuppressive cells, ECM remodeling, and upregulation of immune checkpoints, ultimately establishing an immunosuppressive microenvironment that drives tumor progression. FasL: Fas ligand; Tfh: T follicular helper; ADCC: Antibody-dependent cellular cytotoxicity; ADCP: Antibody-dependent cellular phagocytosis; CDC: Complement-dependent cytotoxicity; TAP: Transporter associated with antigen presentation; β2M: Beta 2 microglobulin; VEGF: Vascular endothelial growth factor; CXCL: C-X-C motif chemokine ligand; CCL: CC chemokine ligand; PGE2: Prostaglandin E2; TGF: Tumor growth factor.

dard first-line treatment for PD-L1-postive (TPS≥1%) tumors (particularly those with TPS≥50%), demonstrating superior benefit over platinum-based chemotherapy.[48,49] In the second-line setting for NSCLC, both pembrolizumab and nivolumab outperform docetaxel, with pembrolizumab's efficacy linked to PD-L1 status and nivolumab showing benefit irrespective of histology and PD-L1 expression level.[50,51] Beyond histology-driven strategies, a pivotal advance was the approval of pembrolizumab for adult and pediatric patients with advanced microsatellite-instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors, regardless of tumor types.[52] This marked the first tumor-agnostic immunotherapy based on a common biomarker rather than tumor anatomic location or origin, and its efficacy has been firmly validated in subsequent trials.[53-55] Notably, Cercek et al. reported that neoadjuvant 6-month dostarlimab monotherapy in patients with operative dMMR solid tumors achieved 100% clinical complete response in rectal cancer and 65% across non-rectal tumors, with encouraging 2-year recurrence-free survival (RFS) rate, offering a nonoperative management strategy for early-stage dMMR solid tumors and holding great potential to alter the traditional therapeutic paradigm.[56] Other PD-1 inhibitor monotherapies have also been widely explored and carved out important niches: cemiplimab, for instance, is the first ICI approved for advanced cutaneous squamous-cell carcinoma,[57] metastatic basal cell carcinoma after hedgehog pathway inhibitor,[58] and as first-line monotherapy for advanced PD-L1-high NSCLC (TPS ≥50%),[59] as well as for recurrent cervical cancer.[60]

Combination approaches have substantially expanded the clinical application of PD-1 inhibitors, from late-line to front-line and even curative-intent settings. In untreated metastatic squamous or non-squamous NSCLC, KEYNOTE-189 and KEYNOTE-407 trials showed that adding pembrolizumab to chemotherapy improves long-term survival regardless of PD-L1 level.[61-63] In resected stage III-IV melanoma, adjuvant nivolumab showed superiority over ipilimumab (anti-CTLA-4), offering improved RFS and distant metastasis-free survival, thereby becoming a standard-of-care.[64] In early-stage NSCLC, perioperative pembrolizumab plus chemotherapy greatly enhanced pathological complete response and event-free survival (EFS).[65]

PD-L1 inhibitors have also achieved broad clinical implementation, both as monotherapy and in combination regimens. For instance, atezolizumab is approved as a first-line treatment for metastatic NSCLC with high PD-L1 expression.[66] Avelumab is approved for Merkel cell carcinoma and advanced urothelial carcinoma,[67,68] while cosibelimab is the first PD-L1 targeting mAb approved for metastatic or locally advanced cutaneous squamous cell carcinoma not amenable to curative surgery or radiation.[69] At present, PD-L1 inhibitors are widely used in combination strategies to improve efficacy. Representative examples include the combination of atezolizumab and bevacizumab in unresectable hepatocellular carcinoma (HCC),[70] and the triplet regimen of atezolizumab, vemurafenib, and cobimetinib as a first-line option for previously untreated, *BRAF*^{V600} mutant, advanced melanoma.[71,72] Atezolizumab-based combinations with chemotherapy and/or target therapy

have also been extensively investigated across various tumor types, including NSCLC,[73] cervical cancer,[74] endometrial cancer,[75] and breast cancer;[76] while their clinical utility in RCC requires further evaluation.[77]

CTLA-4

CTLA-4 is another pivotal checkpoint that downregulates immune responses to maintain immune homeostasis. In contrast to PD-1, which primarily impairs effector T cells in peripheral tissues and the TME, CTLA-4 restricts T cell expansion at the priming phase predominantly within SLOs.[78] CTLA-4 is rapidly upregulated on the T cell surface upon antigen activation and is constitutively expressed at high levels on Tregs.[79] Homologous to CD28, CTLA-4 binds the shared ligands CD80 and CD86 with higher affinity, thereby constraining T cell proliferation and effector functions.[80] Due to the central role in controlling immune responses, CTLA-4 inhibition might activate a wide range of T cells, which may explain the high incidence of irAEs after the treatment with CTLA-4-targeted therapies.[81] This is consistent with the observation that germline disruption of CTLA-4 in mice led to rapidly developed lymphoproliferation and fatal tissue destruction.[82]

The therapeutic potential of the CTLA-4 inhibitor was first demonstrated with the development of ipilimumab. Pooled analysis found that ipilimumab achieved durable survival benefits in patients with advanced melanoma, with some responses lasting for up to 10 years.[83]. The second FDA-approved CTLA-4 inhibitor is tremelimumab. However, as monotherapy, neither ipilimumab nor tremelimumab demonstrated better clinical efficacy compared with PD-1 inhibitors or chemotherapy, while both are frequently associated with irAEs, thereby promoting application in combination strategies for synergetic benefits. Notably, next-generation CTLA-4 inhibitors have entered clinical investigations. Gotistobart (ONC-392/BNT316) is a pH-sensitive antibody designed to selectively deplete Tregs within the TME. In the pivotal phase 3 trial, gotistobart monotherapy demonstrated improved overall survival (OS) compared with docetaxel in patients with metastatic squamous NSCLC whose disease progressed after prior PD-1/PD-L1 inhibitor therapy.[84,85] Additionally, botensilimab, an Fc-enhanced CTLA-4 antibody, in combination with balstilimab (anti-PD-1), demonstrated promising efficacy and a manageable safety profile in patients with microsatellite stable metastatic colorectal cancer (CRC) or relapsed/refractory metastatic sarcomas.[86,87] These findings warrant further investigations and underscore the potential of novel CTLA-4 antibodies to extend the reach of ICIs to more "cold" tumors.

Dual CTLA-4 and PD-1/PD-L1 inhibitions

While ICI monotherapies have fundamentally altered the oncological landscape, only approximately 20% patients derive meaningful benefit from single-agent treatment.[40] This therapeutic limitation has prompted the development of dual-checkpoint inhibition, among which anti-PD-1/PD-L1 and anti-CTLA-4 combinations are the most promising. Mechanistically, the PD-1/PD-L1 blockade predominantly reinvigorates the exhausted $CD8^+$ T cell compartment, while CTLA-4 blockade mainly enhances T cell clonal expansion and trafficking.[88,89] The non-redundant spatial and functional roles of PD-1/PD-L1 and CTLA-4 provide a strong biological rationale for their combination.

The clinical efficacy of dual PD-1 and CTLA-4 inhibition has been notably demonstrated by the combination of nivolumab and ipilimumab. In the phase 3 CheckMate 227 trial, this combination as first-line treatment for metastatic NSCLC achieved superior, long-term survival benefits over chemotherapy, independent of PD-L1 expression.[90] A meta-analysis revealed that the addition blockade of CTLA-4 to PD-1/PD-L1 inhibitors may be particularly advantageous for specific subgroups, including those PD-L1 TPS less than 1% or harboring *STK11* mutations, emphasizing the need for biomarker-stratified treatment rather than a general approach.[91] Similarly, in advanced melanoma, nivolumab and ipilimumab have continued to show significant survival benefits compared with monotherapies.[47,92] However, this regimen has been identified with a higher incidence and a broader spectrum of adverse events.[81] Consequently, this toxicity profile necessitates a nuanced risk-benefit assessment and reinforces proactive management of adverse events.[93]

Alternative dual PD-L1 and CTLA-4 blockade has also achieved encouraging results. For example, tremelimumab was approved in combination with durvalumab for unresectable HCC. In the phase 3 trial, the STRIDE (single tremelimumab regular interval durvalumab) regimen demonstrated long-term superiority over the traditional targeted drug sorafenib.[94,95] In metastatic NSCLC, the triplet regimen of tremelimumab, durvalumab, and chemotherapy sustained OS benefit compared with chemotherapy alone, whereas the durvalumab plus chemotherapy doublet failed to reach statistical significance.[96] These data suggest that while dual checkpoint inhibition represents a potent strategy, its application must be tailored to the specific biological context and combination regimens need more testing.

Other novel immune checkpoints

LAG-3 is an inhibitory receptor expressed among various immune cells and is upregulated on activated T cells, B cells, and NK cells.[97] LAG-3 interacts with MHC-II molecules, as well as other ligands such as galectin-3, α-synuclein, and the fibrinogen-like protein 1, leading to T cell dysfunction.[98,99] Notably, LAG-3 is frequently co-expressed with PD-1 to drive a deeper state of T cell exhaustion, and dual blockade of these pathways has demonstrated synergistic immunological effects.[100] Mechanistically, this combination enhances $CD8^+$ TCR signaling, alters $CD8^+$ T cell differentiation towards heightened cytotoxicity, despite the retention of exhaustion signatures in advanced melanoma.[101]

Opdualag, a combination of relatlimab (anti-LAG-3) and nivolumab (anti-PD-1), was approved by the FDA in 2022, establishing LAG-3 as the third clinically validated immune checkpoint target. This approval was based on a phase 3 trial, in which the addition of relatlimab to nivolumab significantly improved progression-free survival (PFS) compared with nivolumab monotherapy in patients with previously untreated, unresectable melanoma, and also exhibited a more favorable safety profile than PD-1/CTLA-4 combination.[102,103] However, this benefit did not translate to the adjuvant setting for completely resected stage III-IV melanoma.[104] Currently, relatlimab remains the only globally approved LAG-3 inhibitor, and other LAG-3 antibodies such as favezelimab, fianlimab, and leramlimab are under active clinical investigations.[105] The limited efficacy of LAG-3 monotherapy underscores the need for a deeper understanding of LAG-3-mediated immune regulation and supports the development of more rational combination therapies.[97]

TIM-3, also named CD366, is a pleiotropic receptor expressed on immune cells, with particularly high expression on dysfunctional or exhausted T cells.[106] TIM-3 engages a diverse set of ligands such as galectin-9, high-mobility group protein B1, and phosphatidylserine, which mediate different biological effects based on engaged ligands and cellular types.[105] Consequently, TIM-3 acts as a context-dependent immune regulator rather than a canonical inhibitory receptor, and its expression marks a state of T cell dysfunction, often associated with resistance to PD-1-directed immunotherapy.[107,108] Clinically, several TIM-3 mAbs have been evaluated alone or in combination with other ICIs, chemotherapy, or targeted therapy. Early-phase trials exploring combinations such as sabatolimab (anti-TIM-3) with spartalizumab (anti-PD-1) in solid tumors, and cobolimab (anti-TIM-3) and dostarlimab (anti-PD-1) in locally advanced or metastatic NSCLC, showed preliminary positive results.[109,110] However, TIM-3 inhibitors have faced setbacks in late-stage development. The phase 3 trial (NCT04266301) evaluating sabotolimab plus chemotherapy in patients with myelodysplastic syndrome or leukemia was discontinued as it failed to meet its primary OS endpoint.[111] Similarly, the phase 3 COSTAR trial (NCT04655976) assessing cobolimab plus docetaxel in immunotherapy-pretreated NSCLC failed to achieve clinical benefit. These outcomes highlight that the complex, context-dependent biology of TIM-3 poses challenges for clinical translation, necessitating deeper mechanistic insights into ligand-specific signaling and synergy interactions to fully exploit its therapeutic potential.

TIGIT is an inhibitory receptor predominantly expressed on the surface of T cells and NK cells. It competes with the costimulatory receptor CD226 for binding to its ligands CD155 (poliovirus receptor, PVR) and CD112 (PVR-like protein 2, nectin-2), and is able to suppress both innate and adaptive immunity.[112] Notably, TIGIT is found frequently co-expressed with PD-1 on a variety of T cells, including exhausted T cells and Tregs.[113] To date, several mAbs targeting TIGIT, including tiragolumab, vibostolimab, ociperlimab, and domvanalimab, have advanced to clinical evaluation. While TIGIT inhibitor monotherapy has indeed shown limited clinical activity, combination strategies with PD-1 inhibitors have yielded encouraging results.[114] For instance, the combination of tiragolumab with atezolizumab outperformed

atezolizumab monotherapy in patients with NSCLC.[115] Similarly, the synergetic improvements were observed in the combination of triagolumab with atezolizumab and bevacizumab for unresectable HCC.[116] However, a subsequent phase 3 trial evaluating the efficacy of tiragolumab/atezolizumab combination did not meet the primary endpoints.[117] Given that most evidence regarding TIGIT inhibitors comes from early-phase trials, the outcomes of ongoing phase 3 clinical trials, especially those evaluating advanced synergetic strategies across multiple cancers, will be crucial for understanding their therapeutic role.[118,119]

Beyond TIM-3, LAG-3, and TIGIT, additional novel immune checkpoints such as V domain immunoglobulin suppressor of T cell activation, B and T lymphocyte attenuator, CD47, killer immunoglobulin-like receptors, natural killer group 2 member A, and signaling lymphocytic activation molecule 6, are under active investigations and have demonstrated considerable promise as alternative cancer therapies.[31,120]

Challenges and future directions

However, despite encouraging outcomes, two essential challenges, therapeutic resistance and safety concerns, continue to limit the broader clinical application of ICIs. During the past decade, the estimated rate of patients eligible for and respond to ICIs has expanded, but over 40% of patients with advanced or metastatic cancers in the US still demonstrated resistance, with only about 20% achieving an objective response.[121] Furthermore, several novel ICIs have failed in late-stage clinical trials, such as the combination of tiragolumab and atezolizumab in advanced unresectable or metastatic NSCLC,[117] the combination of cobolimab and docetaxel in immunotherapy-pretreated NSCLC (NCT04655976), and domvanalimab plus zimberelimab combined with chemotherapy in metastatic NSCLC (NCT05502237). These disappointing outcomes highlight the substantial gap between promising early clinical activity and clinical validation, which probably results from complex tumor resistance mechanisms, limited predictive performance of current biomarkers, and inadequate patient stratification.

The therapeutic resistance, including primary and acquired resistance, is determined by interconnected tumor-intrinsic and tumor-extrinsic mechanisms (discussed in section 2). Specifically, primary resistance, which prevents patients from ever deriving clinical benefit from checkpoint blockade, is heavily driven by the inherent insensitivity of certain tumor architectures. For example, immunogenic "hot" tumors, such as melanoma and NSCLC, typically demonstrate superior responses owing to high TMB and immune cell infiltration, while "cold" tumors, exemplified by pancreatic ductal adenocarcinoma (PDAC) and microsatellite stable CRC, remain largely restricted to ICIs due to low inherent immunogenicity and a dense stroma environment. Acquired resistance to ICIs (ARI) is another major limitation, occurring in up to 65% of patients who experience an initial period of response but subsequently develop disease progression.[122] This may be attributed to the complex immune evasion mechanisms of cancer under the pressure of immune surveillance, such as antigen mutation or loss, impaired antigen presentation process, and suppressed T cell function.[123] Notably, while a significant mechanistic overlap exists between primary and acquired resistance, they differ in chronological dynamics. Primary resistance reflects a baseline non-responsiveness macro-environment, whereas ARI is more predominantly orchestrated by the selection of resistant subclones under the survival pressure of ongoing treatment.[122] Consequently, defining the dominant, context-specific mechanisms governing ICI responses and resistance is paramount to select more efficient treatments and develop advanced rational regimens.

Given the highly dynamic and co-evolving interactions between cancer and the immune system, substantial efforts have been devoted to identifying predictive biomarkers to guide patient selection and therapeutic decision-making. Several biomarkers have been applied in clinical practice, most notably PD-L1 expression, MSI-H/d-MMR status, and TMB. For example, TMB serves as a surrogate marker of tumor immunogenicity, and a high TMB is generally associated with increased neoantigen load, enhanced immune cell infiltration, and better responsiveness to ICIs. However, current biomarkers exhibit suboptimal predictive performance because of the spatial and temporal heterogeneity of the TME, as well as intratumor and inter-individual heterogeneity.[124] For instance, although PD-L1 expression has been widely used as a predictive biomarker for ICIs, its value varies across tumor types and therapeutic regimens, and no optimal cut-off threshold has yet been established.[125] These observations underscore that therapeutic response is determined by the coordinated interaction of tumor-intrinsic characteristics, disease stage, and the host immune landscape, rather than by a single biomarker. The diverse mechanisms of primary and acquired resistance reflect the dynamic evolving TME and partially explain the limited predictive value of current biomarkers across different tumor types and therapeutic settings.

Consequently, growing attention has been focused on identifying novel predictive biomarkers and developing rational strategies to optimize patient stratification. Rather than relying on individual biomarkers, integrated approaches combining multiple molecular and immune biomarkers are expected to provide a more comprehensive assessment of treatment responsiveness. Exploratory analyses have shown predictive efficacy of other biomarkers such as lactate dehydrogenase levels, specific genomic alterations, IFN-γ-related signatures, and cytokine levels, especially when used in combination.[126–128] Moreover, advances in multi-omics technologies and computational tools are helping to deepen our understanding of dynamic tumor-immune interactions and expand the scope of biomarkers for more precise therapeutic strategies.[129]

Beyond efficacy, adverse effects pose a critical bottleneck that cannot be ignored. As conventional ICIs non-selectively block inhibitory pathways, they inevitably disrupt systemic peripheral self-tolerance. Importantly, immune checkpoints are expressed not only on targeted T cells but also on other immune populations such as Tregs, B cells, and DCs. Therefore, ICIs can induce widespread immune activation beyond tumor sites, resulting in multi-organ irAEs. [130] While systemic glucocorticoids remain the cornerstone of irAEs management, they are not universally effective and may impair antitumor immunity while increasing the risk of infection.[131] These challenges have prompted pivotal exploration toward tissue-specific activation strategies, including probody inhibitors and highly specific checkpoint-targeted inhibitors.[85,132] Moreover, hyper-progression disease has emerged as another concern, characterized by rapid progression following immune checkpoint blockade.[133] Although several associated molecular alterations and dysregulated signaling pathways have been implicated, their underlying mechanisms, predictive biomarkers, and solutions remain poorly defined.[134,135]

Collectively, these findings underscore the need for deciphering resistant mechanisms, refining predictive biomarkers, and developing next-generation strategies to further expand the clinical impact of ICIs, with the goal of improving efficacy while minimizing toxicity.

CANCER VACCINES

Cancer vaccines, encompassing both prophylactic and therapeutic modalities, represent a kind of active immunotherapy designed to activate antigen-specific immune responses. While prophylactic cancer vaccines are mainly designed to prevent virus-related tumorigenesis, therapeutic cancer vaccines, primarily discussed in this review, aim to eliminate established malignancies. Various vaccine platforms, including cells, peptides, nucleic acids, and viruses, have been employed to target tumor-specific antigens (TSAs), tumor-associated antigens (TAAs), viral oncoproteins, and emerging neoantigens.[136] Mechanistically, different vaccine platforms have their own features in initiating antitumor immunity (Figure 2). Whole tumor cell-based vaccines provide a broad array of tumor antigens. DC-based vaccines bypass endogenous antigen uptake by directly transferring *ex vivo*-equipped, antigen-loaded DCs. Peptide-based vaccines deliver defined epitopes to elicit highly specific immune responses, although their efficacy may be limited by MHC restriction. DNA-based vaccines require nuclear entry for transcription before antigen translation, whereas RNA-based vaccines are translated directly in the cytoplasm. Viral vector-based vaccines, in contrast, can elicit robust immune activation, but may be constrained by pre-existing anti-vector immunity and potential safety considerations.

Despite encouraging immunogenicity observed in preclinical studies, cancer vaccines have historically faced challenges in achieving consistent clinical efficacy, particularly when used as monotherapies, which may be attributed to immune tolerance, tumor immune evasion, and immunosuppressive mechanisms.[137] Consequently, extensive efforts have focused on

improving the vaccine's antitumor efficacy through optimized antigen selection, improved adjuvant systems, enhanced delivery platforms, and rational combination strategies with ICIs, surgery, chemoradiotherapy, or targeted therapies.[138]

Cell-based vaccines

Cell-based cancer vaccines include whole tumor cell vaccines and DC-based vaccines. Whole tumor cell vaccines are generally autologous or allogeneic tumor cell lines that have undergone immunogenic cell death. These cells can be genetically manipulated to highly express immune-activating molecules. The most frequently studied genes in whole tumor cell vaccines are cytokines, including GM-CSF, IL-2, and IL-12, in both basic research and clinical studies.[138-140] One typical example is GVAX, which is prepared by genetically modifying cancer cells with GM-CSF and inactivated by irradiation. GVAX has shown promising antitumor effects in pancreatic cancer.[141,142] The highly expressed signals, such as GM-CSF, can promote the maturation of DCs and thereby increase the delivery of TAAs or TSAs to shape the adaptive antitumor immunity.[138] GVAX as monotherapy induces the formation of intratumoral tertiary lymphoid yet also upregulates the expression of immunosuppressive signals such as the PD-1/PD-L1 signaling in pancreatic cancer patients, thereby necessitating its combination with other immunotherapies to activate T cells and improve clinical outcomes. Recently, novel genes have been identified to be involved in innate immunity regulation, such as Tag-7. A Tag-7 gene-modified vaccine exhibited favorable safety and promising disease control of melanoma and RCC in a phase 1/2 clinical trial (NCT04180774).[143] Inactivated cancer cells preserve intact antigens and can stimulate broadly effective antitumor immunity, simplifying the process of identifying tumor antigens in advance. Nevertheless, the intact cellular context is highly complex and comprises unknown components, potentially giving rise to unexpected adverse effects, while robust inflammatory responses may also result in undesirable side effects.

DCs are the most important professional APCs that link innate and adaptive immunity. In the generation of DC-based vaccines, peripheral blood-derived monocytes are first differentiated into DCs using GM-CSF and IL-4, and subsequently pulsed with tumor antigen epitopes, nucleic acids, tumor cell lysates, or immune activators.[138,144,145] Since the approval of Provenge for metastatic prostate cancer by the U.S. FDA in 2010, the development of DC-based vaccines has attracted increasing attention in the market. Provenge, also named Sipuleucel-T, is an autologous DC vaccine that is stimulated *ex vivo* with a recombinant fusion protein PA2024 consisting of a prostate antigen and GM-CSF.[6] It leads to a 4.1-month improvement in the median survival of castration-resistant prostate cancer.[6] Apart from Provenge, many DC-based vaccine candidates have entered different stages of clinical trials with promising clinical outcomes, especially DC vaccines pulsed with inactivated tumor cell lysates, such as DCVAC/OvCa for ovarian cancer,[146,147] TLPLDC for melanoma,[148] AV-GBM-1,[149] and DCvax-L[150,151] for glioblastoma etc. (Table S2) The DCVax-L vaccine is developed by Northwest Biotherapeutics in the U.S., which is composed of autologous DCs loaded with tumor lysates. Recently, results from a phase 3 clinical trial suggested that adding DCVax-L to standard of care temozolomide treatment significantly improved the survival of newly diagnosed and recurrent glioblastoma.[150,151] To improve the efficacy of DC vaccines, a major line of current research focuses on optimizing the sources of DCs, their induction and maturation, and antigen-loading strategies. In parallel, combining DC vaccines with other immunotherapeutic approaches, as well as refining immunization regimens and timing,[137] represents an effective strategy to further enhance therapeutic outcomes.

Peptide-based vaccine

Peptide-based vaccines represent a classical and well-established approach in cancer immunotherapy, aiming to elicit antigen-specific immune responses through the presentation of defined epitopes. Their key advantages include high specificity, ease of manufacturing and storage, and favorable safety profiles. However, low immunogenicity remains a major limitation, necessitating the incorporation of adjuvants such as Montanide, CpG oligodeoxynucleotides, and poly-ICLC. Over the past decades, peptide-based cancer vaccines have been investigated to target various antigens, including TAAs[152], TSAs,[153] oncoproteins,[154,155] as well as multi-peptide formulations[156], shared HLA-restricted epitopes, and phosphopeptide antigens,[157] with a substantial number progressing into clinical evaluation. Although many studies have reported limited clinical success, continuous advances in antigen discovery, adjuvants, and delivery systems, especially in combination with other cancer treatments, have renewed interest in this field.

Peptide-based cancer vaccines have demonstrated controversial clinical results. For example, a mucin-1-targeting peptide vaccine reduced the recurrence of colorectal adenoma without significant clinical improvement.[158] Similarly, IMA901, consisting of ten tumor-associated peptides for RCC, and S-588410, five cancer-testis peptides for esophageal squamous cell carcinoma, failed to achieve clinical improvement in phase 3 trials.[159,160] Nevertheless, the addition of OSE2101, targeting five TAAs, to chemotherapy prolonged survival in patients with advanced NSCLC with acquired ICI-resistance.[161] The combination of GV1001, a peptide vaccine targeting human telomerase reverse transcriptase, with chemotherapy extended OS in patients with advanced PDAC.[162] More recently, immunomodulatory peptide-based vaccines such as UCPVax activating polyfunctional Th1 cells,[163] 6MHP stimulating helper T cells,[164] and IO102/IO103 against indoleamine 2,3-dioxygenase and PD-L1 that inhibit immunosuppressive cells,[165] have shown encouraging early-phase clinical results, which support further larger-scale evaluations.

Increasing attention has also been focused on "off-the-shelf" peptide vaccines targeting novel shared antigens. These include vaccines employing computationally identified shared epitopes derived from TAAs, such as PolyPEPI1018 and IMA970A, as well as those targeting tumoral key driver mutations.[166,167] For instance, a vaccine targeting mutant isocitrate dehydrogenase 1 achieved a 3-year progression-free rate of 63% and a death-free rate of 84% in newly diagnosed glioma.[168] Likewise, a lymph node-targeted, mutant KRAS-specific amphiphile vaccine, ELI-002 2P, was immunogenic and improved survival in patients with pancreatic or CRC, accompanied by induced antigen spreading in 67% patients.[169] In parallel, personalized neoantigen-based peptide vaccines have shown encouraging clinical activity, particularly in the adjuvant setting[170,171], but further studies are needed to determine the optimal combination regimens and sequence strategies for better efficacy.[172] These findings also supported a positive association between vaccine-induced neoantigen-specific T cell responses and improved clinical outcomes. Altogether, it is necessary to develop next-generation peptide-based cancer vaccines that are capable of inducing durable and precisely targeted immune responses while effectively overcoming tumor immune evasion.

Nucleic acid-based vaccine

Nucleic acid-based vaccines, comprising both DNA and RNA platforms, are able to elicit robust immune responses owing to their intrinsic immunostimulatory properties. Compared with cell- and peptide-based vaccines, nucleic acid-based vaccines offer a relatively simple and rapid manufacturing process, as well as greater flexibility in modifying target sequences. Recent clinical successes, particularly those involving mRNA neoantigen vaccines in combination with ICIs, have underscored their capacity to induce durable and clinically meaningful antitumor immunity.

Although DNA-based vaccines generally exhibit lower immunogenicity than RNA-based vaccines, they remain important and rapidly evolving due to their favorable safety profile, high stability, and ease of manufacture.[173] SCIB1, a DNA vaccine targeting tyrosinase-related protein 2 and gp100, demonstrated its safety and high immunogenicity in clinical settings, and its combination with ICIs achieved an encouraging response rate in patients with advanced unresectable melanoma.[174,175] GX-188E, a therapeutic HPV E6/7 DNA vaccine, showed clinical efficacy in cervical intraepithelial neoplasia.[176] Latest results from a phase 2 trial showed its combination with pembrolizumab in patients with inoperable cervical cancer achieved an overall response rate (ORR) of 35%, with higher efficacy observed in the PD-L1$^+$ population.[177] In addition, a personalized neoantigen DNA vaccine evaluated in early phase clinical trial achieved an 87.5% RFS at a median follow-up of 36 months in triple-negative breast cancer patients.[178] Moreover, several other DNA vaccines targeting the androgen receptor ligand-binding domain in prostate cancer,[179] insulin-like growth factor binding protein-2 in ovarian cancer,[180] and neoantigens across multiple malignancies[178,181,182] have completed early-phase clinical

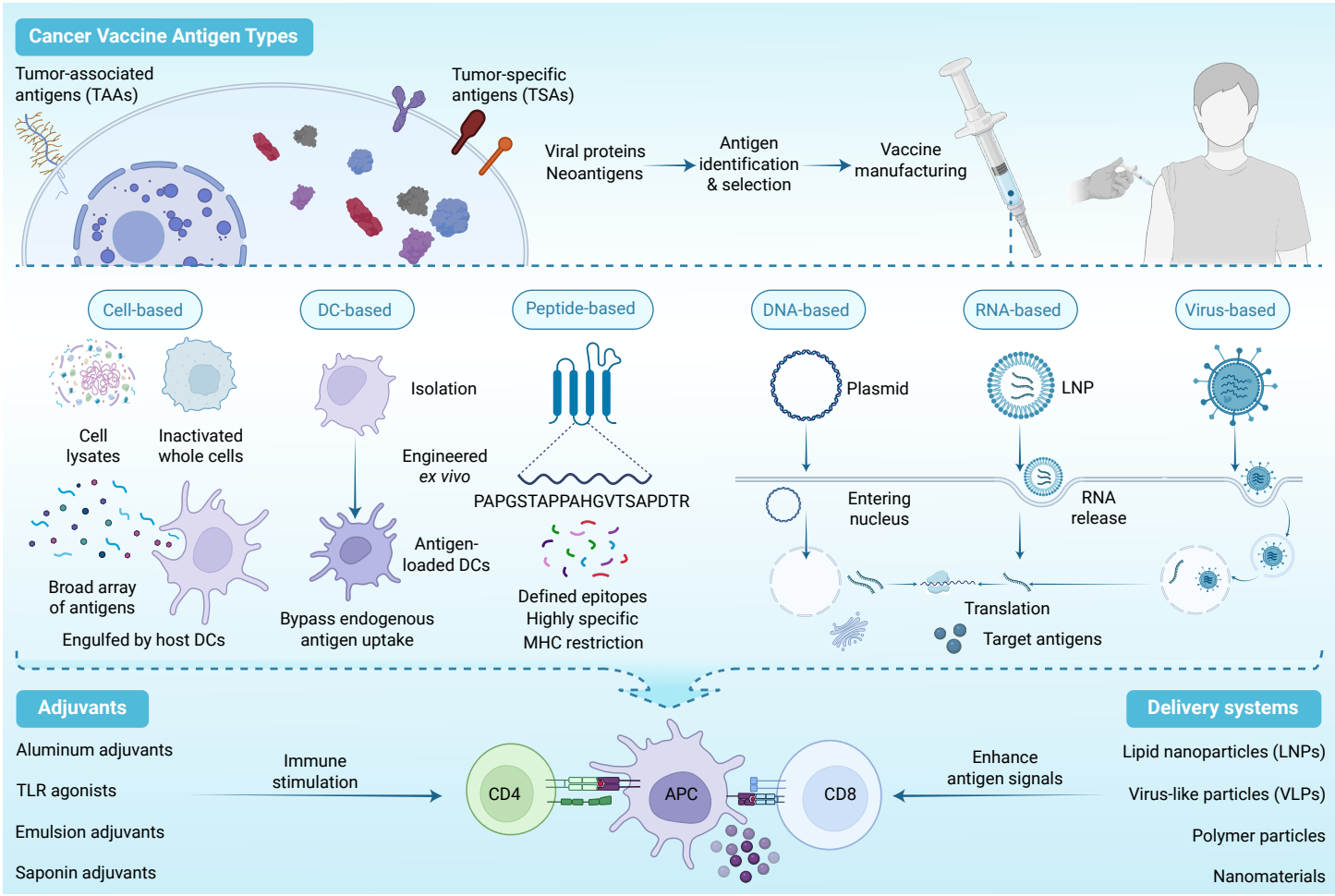

Figure 2. Immune-activation mechanisms of therapeutic cancer vaccines Cancer vaccines are designed to eliminate malignant cells by priming the host immune system against a spectrum of tumor antigens. These vaccines utilize diverse platforms, including tumor cells, DCs, peptides, nucleic acids, and viral vectors, each possessing distinct properties. Ultimately, these heterogeneous platforms converge on APCs as a central hub for antigen presentation, leading to the activation of $CD8^+$ CTLs and $CD4^+$ helper T cells, which collectively mediate durable, antigen-specific antitumor immunity. Moreover, advanced adjuvants and delivery systems are increasingly employed to further enhance the efficiency of antigen presentation and amplify the magnitude of antitumor immunity. TLR: Toll-like receptor.

trials, prompting further optimization and investigations in larger cohorts.

RNA vaccines encompass conventional non-replicating mRNA (nr-RNA) and self-replicating mRNA (sa-RNA), along with emerging platforms such as trans-amplifying mRNA and circular RNA, all of which have exhibited high efficacy and encouraging results in preclinical models and clinical studies[183,184]. The success of mRNA vaccines during the COVID-19 pandemic has accelerated interest in this platform for cancer immunotherapy. A major hurdle for RNA-based vaccines lies in their susceptibility to degradation and inefficient *in vivo* delivery. To address these limitations, advanced delivery systems, most notably lipid nanoparticle (LNP), have been developed to protect RNA from degradation, enhance cellular uptake, and promote immunogenicity. A personalized mRNA neoantigen vaccine mobilized strong antitumor immunity with a broad repertoire of T cell responses and, in combination with pembrolizumab, achieved a complete response in one patient, suggesting the synergistic potential of combining mRNA vaccines with ICIs.[185] Notably, mRNA-4157(V940), an LNP-formulated personalized vaccine encoding up to 34 neoantigens, reduced the recurrence or death event rates and prolonged the RFS compared with pembrolizumab monotherapy in patients with resected IIIB-IV melanoma, leading to its advancement into phase 3 clinical trials.[186] Similarly, another personalized neoantigen mRNA vaccine, autogene cevumeran, demonstrated clinical efficacy in combination with atezolizumab and chemotherapy, with vaccine responders exhibiting prolonged RFS.[187] The study also found this regimen induced long-lived and functional $CD8^+$ memory T cell clones, potentially delaying PDAC recurrence.[188] In contrast, a heterologous chimpanzee adenovirus (Ad) and sa-RNA-based neoantigen vaccine, combined with ICIs, showed limited clinical efficacy but revealed a biased T cell response toward TP53 rather than KRAS neoantigens. This indicates an immunodominance hierarchy that may constrain the effectiveness of multi-antigen vaccines.[189]

Viral vector-based cancer vaccine

Viruses have emerged as a promising platform, which has been developed into two major categories: replication-defective viral vectors and OVs. In this section, we primarily discuss replication-defective viral vector-based vaccines, which are engineered to deliver targeted antigens to initiate specific immune responses while simultaneously leveraging the intrinsic immunogenicity of viral components to activate robust innate immune activation. Commonly used viral vectors include Ad, vaccinia virus (VACV), measles virus, herpes simplex virus (HSV), and poxvirus, each with distinct tropism and immunogenicity profiles.[190] However, several challenges remain, including pre-existing or vector-induced neutralizing antibodies that may impede the efficacy of repeat administration, and potential safety concerns requiring careful evaluation.

Clinically, several replication-defective viral vector-based cancer vaccines have achieved regulatory approval or demonstrated encouraging results in clinical trials, especially as combination strategies. Nadofaragene firadenovec, an Ad vaccine delivering IFNA2B, received FDA approval in 2022 for BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC).[191] Five-year follow-up result of its phase 3 clinical trial demonstrated 49% cystectomy-free survival, 80% 60-month OS rate, and 3.3% rate of muscle-invasive progression, supporting its durable efficacy and safety profile.[192] Several additional phase 3 trials are currently underway to expand the clinical appli-

cation of nadofaragene firadenovec, including its use in intermediate-risk NMIBC, comparisons with standard intravesical chemotherapy, and evaluation of combination strategies with chemotherapy or immunotherapy in high-grade NMIBC and malignant pleural mesothelioma (NCT06510374, NCT06929286, NCT06545955, NCT03710876). TG4010, a modified vaccinia Ankara (MVA) encoding mucin-1 and IL-2, has been evaluated in advanced NSCLC. In a randomized phase 2b trial, its addition to standard chemotherapy extended PFS (5.9 vs 5.1 months) and OS (12.6 vs 10.6 months), laying the foundation for further phase 3 evaluation.[193] Similarly, the combination of MVA vaccine targeting oncofetal antigen 5T4 with low-dose cyclophosphamide improved PFS (5.0 vs 2.5 months) and OS (20.0 vs 10.3 months) in patients with inoperable metastatic CRC.[194]

A heterologous prime-boost strategy has been developed to circumvent neutralizing antibodies and broaden immune responses. In a phase 1 study involving patients with low- and intermediate-risk prostate cancer, sequential immunization with chimpanzee Ad and MVA vectors encoding 5T4 induced strong specific immune responses.[195] Moreover, a combination of chimpanzee Ad and sa-RNA platforms has also been explored (discussed above).[189] Another innovative approach is Nous-209, an off-the-shelf vaccine encoding 209 shared frameshift neoantigens derived from sporadic and hereditary MSI-high tumors and employing heterologous prime-boost administration of multivalent viral vectors, which has the capacity to induce optimal breadth of immune responses.[196] In an ongoing phase 1 trial combining Nous-209 with pembrolizumab in patients with metastatic dMMR gastric, colorectal, and gastroesophageal junction tumors, interim results have demonstrated early signals of clinical efficacy.[197] Correlative analyses found expansion and diversification of TCR, as well as increased tumor-infiltrating T cells in responding patients, providing mechanistic evidence that viral vector-based neoantigen vaccine can remodel the tumor immune landscape and synergize with PD-1 inhibitors.[198] Collectively, these clinical findings illustrate the development of viral vector-based cancer vaccines from single-antigen delivery systems toward advanced versions incorporating neoantigens, heterologous regimens, and combination strategies to overcome resistance and improve therapeutic benefit.

Challenges and future perspective

Altogether, cancer vaccines represent a versatile and rapidly advancing class of immunotherapies with substantial translational potential. Cancer vaccines based on different platforms exhibit distinct strengths and limitations, underscoring the need for continued refinement in antigen selection, adjuvant incorporation, and combinational strategies to maximize their efficacy.[136] Although many cancer vaccines have entered clinical evaluation, a majority have not achieved significant clinical efficacy in large phase 3 trials, especially when compared with standard-of-care. For example, DCVAC/PCa, IMA901, and S-588410 all failed to improve survival outcomes in large phase 3 clinical trials.[159,160,199] This discrepancy largely reflects several biological and clinical bottlenecks including suboptimal antigen selection, tumor heterogeneity, tumor immune escape mechanisms, and inappropriate clinical patient selection.[137]

First, optimal antigen selection for vaccines remains a fundamental determinant of therapeutic success, yet its effectiveness can be impaired by immunoediting, antigen evasion, and T cell tolerance. Early-generation vaccines primarily target shared TAAs, which are subject to central and peripheral immune tolerance. High-avidity T cell clones recognizing these self-proteins are largely eliminated during thymic selection, leaving only low-affinity repertoires with limited efficacy.[200] Vaccines targeting TSAs can successfully generate high-affinity antigen-reactive T cell clones, but extensive spatial, temporal, and intratumoral heterogeneity driven by ongoing genomic instability hampers vaccine efficacy. Second, vaccine-induced immune activation does not successfully translate into effective tumor control. Once antigen-specific immune cells are activated, they need to traffic to, infiltrate, and function within tumor sites. This is particularly evident in immunologically "cold" tumors with a dense stromal architecture that restricts T cell penetration or in highly immunosuppressive microenvironments that impair immune cell function. Accordingly, vaccine therapeutic efficacy varies across tumor types, reflecting differences in mutation burden, immune landscape, and stromal architecture. Another key determinant of clinical success for therapeutic cancer vaccines is optimal patient selection. Most cancer vaccines evaluated in clinical trials enrolling heavily pretreated patients with advanced or metastatic disease, who exhibit profound immune dysfunction, including systemic immune exhaustion, impaired antigen presentation, and expansion of immunosuppressive populations, all of which impair the capacity of cancer vaccines to generate durable antitumor responses. In contrast, preclinical studies are typically conducted in immunocompetent animals, which may partially account for the gap between promising preclinical findings and clinical translation.

Notably, recent advances in RNA-based vaccines and neoantigen-targeted approaches have revitalized the field of cancer vaccines. In particular, as neoantigen-based vaccines attract growing attention, optimization of computational pipelines for antigen identification and the establishment of efficient vaccine manufacturing workflow remain important challenges.[172] Looking forward, continued innovation in multi-omics-guided antigen discovery, next-generation adjuvant and delivery systems, and rational combination strategies with ICIs and other therapies will be essential to fully unlock the clinical potential of cancer vaccines.[201]

ONCOLYTIV VIRUS THERAPIES (OVs)

OVs selectively replicate within tumor cells while sparing normal tissues, leading to direct tumor cell lysis and the concomitant release of TAAs and danger-associated molecular patterns (DAMPs). This form of cell death is classified as immunogenic cell death, which can effectively potentiate antitumor immune responses, thereby positioning OVs as in situ cancer vaccines (Figure 3).[202] To date, four OVs have been approved globally for cancer therapy, including T-VEC, H101, Teserpaturev, and the discontinued ECHO-7 (Table S3).[203] The development of ECHO-7 has been discontinued in 2019 because of manufacturing problems. OVs consist of natural viruses and genetically engineered viruses that showed elevated tumor targeting, replication efficiency, and immunogenicity with less pathogenicity. Both DNA and RNA viruses can be engineered as OVs. However, the majority of OVs that have advanced to clinical evaluation are based on DNA viruses, largely because their molecular biology and life cycles are better characterized at present.[204] HSV, Ad, and VACV are the most commonly used viral platforms for OV development, whereas other viruses, such as reovirus and measles virus, are also being actively investigated.[202]

Monotherapy with OVs

Currently approved OVs. T-VEC is based on an attenuated HSV-1 strain and was engineered to replicate in tumor cells and express GM-CSF.[203] Administered by intratumor injection, T-VEC exhibited a higher durable response rate (DRR, 16.3% vs 2.1%) and (ORR, 26.4% vs 5.7%) than GM-CSF in patients with stage III-IV melanomas in the randomized open-label phase 3 OPTiM trial. Meanwhile, the median OS of patients receiving T-VEC reached 23.3 months, significantly longer than those injected with GM-CSF (18.9 months).[9] This promoted the FDA approval of T-VEC for the local treatment of melanoma, which is also the first approval of OV products for cancer treatment globally. Real-world studies of T-VEC in clinical practice have confirmed its safety and efficacy in patients with advanced melanoma, with some even showing a higher response rate than that reported in the OPTiM trial.[205-207] The promising anticancer effects of T-VEC in melanoma strongly encouraged the expanded exploration of T-VEC against other cancer types, including but not limited to breast cancer, head and neck cancer, pancreatic cancer. and peritoneal malignancies.[203,208,209]

H101 is an Ad-based OV whose *E1B* gene was deleted. In a phase 3 clinical trial enrolling 160 patients with head and neck or esophageal squamous cell carcinoma, intratumor administration of H101 in combination with cisplatin and 5-fluorouracil (5-FU) achieved an objective response rate of 78.8%, compared with 39.6% in patients treated with cisplatin and 5-FU alone.[210] These results led to the approval of H101 in China in 2005 for use in combination with chemotherapy for the treatment of nasopharyngeal carcinoma. In a phase 2 study investigating malignant ascites, H101 treatment prolonged the median time to repeat paracentesis to 45 days in comparison to the control of 13 days.[211] A combination of H101 and radiofrequency ablation (RFA) shows potential therapeutic advantages over 3-year disease-free survival (DFS) rates in HCC patients in a phase 3 clinical study compared with

pure RFA.[212] H101 is now under clinical evaluation in the treatment of other malignancies such as gynecological malignancies (NCT05051696), bladder cancer (NCT05564897), and HCC (NCT03790059).

Teserpaturev, also named G47Δ, is a third-generation HSV-1-based OV in which the *α47* and *γ34.5* genes are deleted, and the *infected cell protein 6* (*ICP6*) gene is inactivated.[213] Teserpaturev showed a one-year OS of 84.2% in Japanese patients with recurrent and/or residual glioblastomas after radiation therapy and temozolomide.[214] Teserpaturev received its approval in Japan in 2021 for the treatment of R/R glioblastomas.

Promising novel OVs. Plenty of OVs are currently being evaluated in clinical trials, and comprehensive discussions have been provided in previous reviews.[215,216] Here we focus specifically on OVs that have demonstrated promising clinical outcomes over the past five years or have advanced to late-stage clinical trials, thereby offering readers a more intuitive and up-to-date overview of the field.

(1) Central nervous system tumor. Numerous OVs are being assessed for the treatment of glioma and glioblastoma. DNX-2401, also named Delta24-RGD or tasadenoturev, is a replication-competent oncolytic Ad. In phase 1 trials, DNX-2401 treatment contributed to tumor size control and long-term survival in recurrent glioma patients[217] and newly diagnosed pediatric diffuse intrinsic pontine glioma (DIPG) patients.[218,219] DNX-2401 treatment also leads to changes in TME and T cell repertoire in DIPG patients.[219] However, DNX-2401 is associated with adverse events such as headache, nausea, and vomiting.[219] Putten et al. used convection-enhanced delivery as a local delivery strategy to increase the safety of DNX-2401 in recurrent glioblastoma.[220] CAN-3110 is an HSV-1-derived OV that preserved the viral neurovirulence *ICP34.5* gene and showed more efficient tumor replication.[221] In a phase 1 clinical trial involving 41 patients with recurrent glioblastoma, CAN-3110 promoted the activation of antitumor immunity and prolonged patient survival, especially in those with positive HSV-1 serology.[221] Ad-TD-nsIL12 is an oncolytic Ad producing non-secreting IL-12. It leads to improved median OS (11.3 months for primary DIPG and 12.7 months for progressive DIPG versus 8.3 months) in two phase 1 clinical trials.[222] Similar results were observed in a dose-escalation study of 8 recurrent high-grade glioma patients, with 1×10^{10} viral particles of Ad-TD-nsIL12 being the maximum tolerated dose that showed acceptable safety and preliminary antitumor efficacy.[223]

Treatment with rQnestin34.5, an oncolytic HSV, may activate NOTCH signaling and promote the infiltration of MDSCs. Pharmacologic inhibition of NOTCH signaling reversed the immunosuppressive TME and induced $CD8^+$ T cell antitumor memory immunity, promoting the therapeutic effect of rQnestin34.5 in grade IV glioma.[224] Most currently developed OVs are administered via intratumor injection. To enhance their clinical applicability, novel delivery strategies utilizing stem cells have been explored. Fares et al. developed a neural stem cell-delivered oncolytic Ad NSC-CRAd-S-pk7, which resulted in a median PFS of 9.1 months and a median OS of 18.4 months in 12 patients with newly diagnosed gliomas in a phase 1 dose-escalation study.[225] Similarly, Shimizu et al. used patient-derived bone marrow mesenchymal stem cells to deliver DNX-2401, which homed to brain glioma xenografts after intravascular injection and prolonged survival in tumor-bearing mice.[226] This enables the systemic administration of OVs, particularly for tumors that are difficult to access via local delivery, such as those developing in the brain.

(2) Melanoma. OH2 is an HSV-2-based OVs similar to T-VEC, whose *ICP34.5* and *ICP47* genes were deleted. OH2 is also engineered to express GM-CSF to promote the immune responses. In a phase 1a/1b trial involving 44 patients with stage III or advanced stage IV melanoma, OH2 treatment exhibited a favorable tolerability profile without dose-limiting toxicities and produced durable antitumor effects, particularly in patients who had progressed following prior PD-1 antibody therapy.[227] Given the promising results, a multicenter phase 3 study is ongoing to evaluate the efficacy of injected OH2 in 340 patients with unresectable or metastatic melanoma (NCT05868707). Apart from melanoma, OH2 treatment also displayed promising tolerability and efficacy in other solid tumors in early phase clinical trials, including metastatic sarcoma,[228] metastatic esophageal and rectal cancers.[229] OrienX010 is an HSV-1-derived OV engineered to express GM-CSF. Intratumor injection of OrienX010 resulted in an ORR of 19.2% and a disease control rate (DCR) of 53.8% in 26 patients with unresectable stage IIIC-IV melanoma. The median PFS was 2.9 months, and the OS was 19.2 months in patients receiving OrienX010. Meanwhile, no dose-limiting toxicities were observed.[230] These encouraging results supported the further evaluation of OrienX010 in a larger phase 2 study involving 165 patients with unresectable melanoma (NCT04200040). The coxsackievirus-derived oncolytic virus V937 is another OV candidate against advanced melanoma, which showed 12-month PFS and OS of 32.9% and 75.4%, respectively, without treatment-related serious side effects in a phase 2 clinical study.[231]

(3) Other malignancies. Liang's team developed an HSV-originated OVs named VG161, which is engineered to express multiple cytokines (IL-12, IL-15, and IL-15Rα) and a PD-1/PD-L1-blocking fusion protein. VG161 successfully remodeled the immunosuppressive TME and promoted the infiltration of $CD8^+$ T cells and NK cells in a preclinical study.[232] In a phase 1 multicenter clinical study enrolling 44 patients with advanced liver cancer, VG161 showed acceptable safety profiles and exhibited promising efficacy by reshaping the TME and re-sensitizing tumors to ICI therapy.[233] OBP-301, also called Telomelysin, is a live-attenuated type 5 Ad (Ad5) that utilizes an *hTERT* promoter to improve cancer-specific viral replication. It enhanced the local recruitment of $CD8^+$ T cells and decreased PD-L1 expression with good tolerance at doses of up to 6×10^{12} viral particles in a phase 1 clinical trial.[234] In seven PDAC patients with liver metastasis, ParvOryx, an oncolytic parvovirus, prolonged patient survival and modulated immune responses with excellent tolerability in a phase 2 study.[235]

In addition, many other OVs have advanced into phase 1 clinical trials. For instance, oncolytic measles virus (MV-NIS) demonstrated tolerability and promising anticancer effects with immune-regulating capacity in pediatric patients with recurrent medulloblastoma or atypical teratoid/rhabdoid tumor[236] and multiple myeloma (MM).[237] OVV-01,[238] TILT-123,[239,240] SKV-012,[241] and YSCH-01[242] are other promising OVs that showed good tolerability and preliminary efficacy in advanced solid tumors and warrant further evaluation.

Combination treatment with OVs

Combination with other immunotherapies. The combination of OVs with ICIs or T cell-based therapies can leverage complementary mechanisms to synergistically enhance antitumor immunity. OVs treatment can increase cancer immunogenicity and promote immune cell infiltration, whereas ICIs sustain the cytotoxic potential of T cells by inhibiting exhaustion.[243] OVs and ICIs synergistically remodel immunologically "cold" tumors into "hot" tumors, which overcome treatment resistance and improve immunotherapy response. Various ICIs have been explored as combination partners for OVs in recent years, including antibodies targeting PD-1, PD-L1, and CTLA-4. In a phase 1b study of 21 patients with metastatic melanoma, a combination of T-VEC with pembrolizumab promoted intratumoral $CD8^+$ T cell infiltration and resulted in an ORR and a complete response rate (CRR) of 62% and 33%, respectively.[244] Robert et al. further reported that T-VEC plus pembrolizumab showed antitumor efficacy and tolerability in PD-1-refractory melanoma in a phase 2 clinical trial.[245] In another phase 2 study, Cretostimogene grenadenorepvec (an Ad5-based OV) combined with pembrolizumab led to a CRR of 51.4% at 24 months in BCG-unresponsive NMIBC patients.[246] Pembrolizumab has also been evaluated in combination with other OVs, including TILT-123,[247] CVA21,[248] and DNX-2401,[249] for the treatment of ovarian cancer, advanced NSCLC, and recurrent glioblastoma, respectively. These studies have demonstrated promising survival benefits and acceptable safety, accompanied by enhanced tumor immunogenicity and modulation of the TME. In a phase 1b trial involving patients with resectable stage III/IV acral melanoma, neoadjuvant therapy with OrienX010 combined with Toripalimab improved post-surgical response rates, achieving 2-year EFS and RFS rates of 81.5% and 73%, respectively.[250] In advanced HCC, treatment with OV M1-c6v1 in combination with Camrelizumab and Apatinib achieved an ORR of 70%, with a median OS of 15.4 months and a median PFS of 8.9 months.[251] Thus, OVs have demonstrated promising efficacy and tolerability when combined with PD-1 antibodies across multiple tumor types.

PD-L1 inhibitors such as durvalumab and avelumab, as well as CTLA-4 blockade with ipilimumab, can also enhance the therapeutic potential of OVs. In a phase 1 study, MEDI5395, an attenuated Newcastle disease virus-

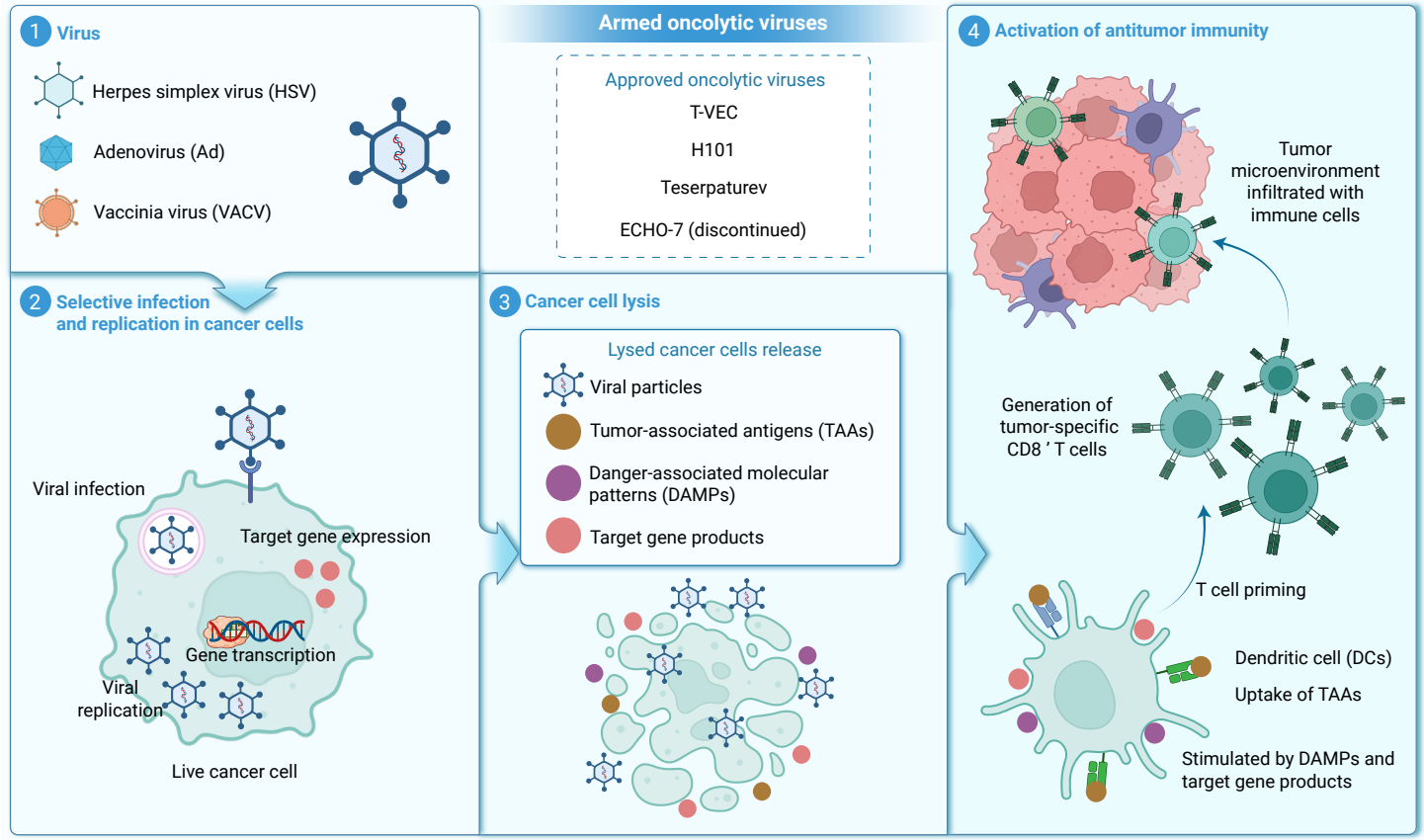

Figure 3. The cancer-killing mechanisms of oncolytic viruses (OVs) OVs selectively replicate within tumor cells, leading to direct tumor cell lysis and the concomitant release of viral particles, TAAs and DAMPs. OVs can also be engineered to express immunomodulatory molecules such as GM-CSF. The released molecules can subsequently activate specific antitumor immunity, positioning OVs as in situ cancer vaccines. Four OVs have been approved globally for cancer therapy, including T-VEC, H101, Teserpaturev, and the discontinued ECHO-7.

derived OV engineered to overexpress GM-CSF, demonstrated synergistic effects in combination with durvalumab, achieving a partial response (PR) rate of 10.4% and increased $CD8^+$ T cell infiltration in patients with advanced solid tumors.[252] Similarly, combining the OV JX-594 with Avelumab and low-dose cyclophosphamide reshaped the immunosuppressive TME in soft-tissue sarcomas, as evidenced by an increased proportion of $CD8^+$ T cells and upregulation of immune-related biomarkers such as C-X-C motif chemokine ligand 10 (CXCL10).[253] Head-to-head comparisons have demonstrated that T-VEC combined with ipilimumab provides superior efficacy compared with either T-VEC or ipilimumab alone, while maintaining a tolerable safety profile in patients with advanced melanoma.[254] 5-year follow-up statistics indicated that T-VEC plus ipilimumab confers durable efficacy, showing a median duration of response (DOR) of 69.2 months and 5-year OS of 54.7%.[255] Ipilimumab combined with V937 also demonstrated promising efficacy in patients with advanced melanoma, including those who had progressed after prior PD-1 therapy,[256] indicating its potential to overcome resistance to previous immune checkpoint blockade. More than one ICI can be combined with OVs treatment. Notably, the addition of tremelimumab (an anti-CTLA-4 antibody) to the JX-594/durvalumab regimen showed a trend toward improved median PFS, although the increase was modest (from 2.1 to 2.3 months).[257] Therefore, the therapeutic efficacy of OVs/ICIs combination strategies may be further enhanced by optimizing the type, number, and timing of ICI therapeutics.

Apart from ICIs, OVs are being evaluated when combined with other immunotherapies. Recently, tumor-infiltrating lymphocyte (TIL) therapy has been approved by the U.S. FDA for the treatment of unresectable or metastatic melanoma-resistant to PD-1 antibodies.[258] In a phase 1 study involving 17 patients with ICI-resistant metastatic melanoma, Monberg et al. found that a combination of TIL and TILT-123 showed well tolerability and preliminary efficacy with a DCR of 35% and 47% base on computed tomography (CT) and positron emission tomography (PET), respectively.[259]

Chemotherapy. As the mainstay of conventional cancer therapies, chemotherapy has been considered for combination with OV treatment. Chemotherapy exerts its effects by killing highly proliferative cancer cells, whereas efficient viral replication within tumor cells is required for OVs to induce cancer cell lysis.[215] There remains controversy regarding the optimal sequencing of chemotherapy and oncolytic OVs. On the one hand, early administration of chemotherapy may eliminate a large number of cancer cells, thereby leaving an insufficient niche for OV infection and replication. On the other hand, late administration of chemotherapy may impair OV-induced antitumor immune responses by depleting activated immune cells. In addition, chemotherapy itself may exert antiviral effects within the TME, thereby further limiting the therapeutic efficacy of both chemotherapy and OVs.[215] Hence, careful optimization of the chemotherapeutic agents, dosing, and scheduling is essential to maximize the efficacy of chemotherapy-OV combination regimens while maintaining acceptable safety profiles. A growing number of combination strategies have demonstrated synergistic antitumor effects in preclinical xenograft tumor models,[232,260,261], and several have progressed to clinical evaluation.

In a phase 2 clinical trial, the addition of oncolytic T-VEC to neoadjuvant chemotherapy (paclitaxel, doxorubicin, and cyclophosphamide) increased the residual cancer burden 0-1 (RCB0-1) rate from 44% to 65% in patients with nonmetastatic triple-negative breast cancer,[262] a response associated with favorable clinical outcomes.[263,264] Several other chemotherapy-OV combination regimens have demonstrated acceptable safety profiles and immunomodulatory effects, such as enhanced $CD8^+$ T cell infiltration and cytokine production, at injected tumor sites in phase 2 clinical trials.[265-267] However, further studies are needed to establish the superior therapeutic benefit of these combination strategies compared with monotherapy.

Other treatment strategies. In certain settings, OVs are also employed in combination with other treatment strategies such as radiotherapy and surgical intervention. In a phase 2 clinical study, a combination of T-VEC with

preoperative external beam radiation therapy resulted in 2-year PFS and OS of 57% and 88%, respectively, in soft-tissue sarcoma patients after surgery.[268] The combination of OVs and stereotactic body radiotherapy (SBRT) has also been shown to increase the antitumor efficacy of pembrolizumab in metastatic NSCLC patients.[269] In esophageal cancer patients unfit for standard therapy, OBP-301 combined with radiotherapy brought clinical benefits with ORR of 91.7%, accompanied by massive $CD8^+$ T cell infiltration and elevated PD-L1 expression.[270] As a neoadjuvant therapy, T-VEC activates antitumor immunity and improves outcomes in patients with difficult-to-resect basal cell carcinoma, thereby facilitating subsequent surgical resection.[271] In resectable stage IIIB-IVM1a melanoma patients, adding T-VEC to surgery results in an estimated 25% decrease in the risk of disease recurrence compared to surgery alone.[272] Overall, when combined with radiotherapy or applied as neoadjuvant agents before surgery, OVs demonstrate promising potential to enhance antitumor efficacy, modulate the TME, and improve tumor resectability, highlighting their expanding role in multimodal cancer therapy.

Challenges and future directions

Effective oncolytic virotherapy requires that OVs reach tumor tissues, infect tumor cells, replicate, lyse infected cells, and subsequently spread to neighboring tumor cells. To improve viral invasion, most OVs are currently administered via intratumor injection. However, physiological barriers such as the ECM can hinder the interaction between OVs and tumor cells and limit viral dissemination within tumors.[202] For metastatic tumors or those not amenable to intratumor injection (e.g., ovarian and pancreatic cancers), intravenous administration is frequently used. Nevertheless, a large proportion of OVs are cleared from the circulation before reaching tumor sites, partly due to preexisting antiviral immunity. For instance, the phase III PHOCUS trial of JX-594 in advanced hepatocellular carcinoma failed to demonstrate a survival benefit in combination with sorafenib, potentially due to insufficient intratumoral viral replication, inefficient systemic delivery, and rapid antiviral immune clearance that limited sustained antitumor activity.[273] Similar translational challenges may also contribute to the limited clinical efficacy of Reolysin, a reovirus-based oncolytic virus, in several advanced solid tumors.[274-276] To address these limitations, several strategies have been developed. First, OVs can be genetically engineered to express molecules that degrade the ECM components (e.g., hyaluronidase[260] and relaxin[277]) or enhance tumor penetration (e.g., E-cadherin[278]). In addition, novel delivery approaches have been explored, including the use of cell carriers such as stem cells[225,226] and immune cells (e.g. DCs,[279] T cells,[280] and mast cells[281]), as well as alternative administration routes such as intraperitoneal, intramuscular, or intranasal delivery, both in preclinical and clinical studies.[202] More importantly, modulation of antiviral immune responses before OV administration has also been investigated to reduce viral clearance and enhance therapeutic efficacy, especially for HSV-based OVs.[202] For example, it is reported that NK cells can infiltrate the TME within 2 hours after viral infection and rapidly eliminate virus-infected tumor cells, thereby limiting OVs activity.[282,283] Pre-treatment with histone deacetylase inhibitors has been shown to suppress NK cell function and enhance the antitumor efficacy of oncolytic HSV (oHSV).[284]

The therapeutic efficacy of OVs is also influenced by tumor type, grade, intratumoral heterogeneity, and patient-specific characteristics. Notably, many patients possess naturally circulating neutralizing antibodies against HSV, which may affect treatment outcomes. Therefore, elucidating the relationship between preexisting antiviral immune responses and OV efficacy and identifying predictive biomarkers for patient stratification will be critical for optimizing OVs-based therapies. In addition, because OVs are replication-competent viruses, their safe handling and clinical application require careful management to avoid unintended transmission to healthy individuals or the environment. Currently, most clinically approved or investigated OVs rely on intratumor injection, which requires substantial technical expertise and may increase the risk of tumor dissemination during injection. Thus, improving clinical training and developing more convenient and effective delivery strategies remain important for advancing OVs-based cancer therapy.

ADOPTIVE CELL THERAPIES (ACTs)

ACTs have attracted considerable attention following the remarkable success of CAR-T cell therapy in the treatment of hematological malignancies. At present, seven CAR-T products has received FDA approval for treating leukemia, lymphoma, and MM.[10] Generally, CAR-T cell therapy involves isolating patient T cells, genetically engineering them to express CARs, *ex vivo* expanding, and reinfusing them into the patient to selectively and effectively kill tumor cells.[10] In solid tumors, the efficacy of CAR-T cells has been limited by tumor heterogeneity and the immunosuppressive nature of TME.[285] Nevertheless, scientists are exploring overcoming strategies by increasing T cell retention and cytotoxicity, recognizing multiple antigens, using novel allogeneic CAR-T cell manufacturing and combination treatment.[285] The success of CAR-T cell therapy has highlighted the great potential of adoptive T cell therapy in cancer treatment. Based on this, several novel ACTs have been developed for oncology, including TIL therapy and TCR-engineered T cells. In addition, the application of genetic engineering technology to innate immune cells, such as NK cells, myeloid cells, natural killer T (NKT) cells, and γδ T cells, has also demonstrated promising antitumor efficacy (Figure 4). TIL therapy involves isolating lymphocytes infiltrating resected tumors (such as T cells and NK cells), expanding them *ex vivo*, and reinfusing them into patients to mediate antitumor responses.[10] In 2024, based on the results of the C-144-01 trial, the U.S. FDA approved the first TIL therapy, Lifileucel, for patients with unresectable or metastatic melanoma who had previously received PD-1 antibody therapy.[286] Five-year follow-up results showed that Lifileucel achieved an ORR of 31.4% and a 5-year OS rate of 19.7%.[287] The advances in CAR-T and TIL therapies have been comprehensively reviewed in previous high-quality papers.[10,288-290] Therefore, this review focuses on the recent progress and challenges in the development of TCR-T cells and CAR-engineered innate immune cells.

TCR-T

TCR-T cells are antigen-specific T cells generated by genetically engineering natural T cells to express cancer-specific TCR α and β chains, followed by *ex vivo* expansion before reinfusion into patients with cancer.[291] By preserving the natural TCR structure, TCR-T cells mediate strong TCR signaling and recognize diverse antigens even at low density, resulting in potent antitumor activity.[291] Compared with CAR-T cell therapy, which only recognizes tumor surface antigens, TCR-T cells can recognize both intracellular and cell-surface antigens presented by MHC molecules.[289] Besides, TCR-T cell therapy has several advantages, including a broader range of targetable antigens, easier manufacturing, improved safety, and longer cellular persistence. Moreover, TCR-T cells are capable of infiltrating solid tumors, making them a promising therapeutic strategy for both hematological malignancies and solid tumors.[292,293] In 2024, the U.S. FDA approved the first TCR-T cell therapy, afamitresgene autoleucel (Tecelra), for the treatment of HLA-A02-positive patients with melanoma-associated antigen A4 (MAGE-A4)-positive synovial sarcoma who had previously received chemotherapy.[294,295] The approval was based on the results of the phase 2 SPEARHEAD-1 study involving 44 patients with synovial sarcoma, where afamitresgene autoleucel induced an ORR of 39% (17/44) and a PFS of 3.8 months.[296,297]

Beyond afamitresgene autoleucel, hundreds of TCR-T products have launched into clinical trials, although most of them still remain phase 1 and 2. Cancer testis antigens, including the MAGE-A family and New York esophageal squamous cell carcinoma-1 (NY-ESO-1), are the most well-investigated targets of TCR-T cells in clinical trials. IMA202 is an autologous $CD8^+$ T cell product engineered to express a TCR specific for MAGE-A1. In a dose-escalation study enrolling 16 patients with MAGE-A1-positive solid tumors, including liver cancer and melanoma, treatment with IMA202 resulted in 11 cases of stable disease and tumor shrinkage in 5 patients.[298] TBI-1301 is a TCR-T cell therapy in which endogenous TCR expression is knocked down with an affinity-enhanced NY-ESO-1-specific TCR introduced. It mediated an ORR of 50% in synovial sarcoma in a phase 1/2 clinical trial,[299] which promoted further evaluation of TBI-1301 against synovial sarcoma in a multicenter phase 3 clinical trial (NCT07174427). However, it should be noted that TBI-1301 is associated with treatment-related side effects, including CRS.[299,300] Close monitoring and timely intervention are crucial for the management of the adverse events. Meanwhile, NY-ESO-1-specific TCR-T therapy showed promising anticancer effects in advanced soft tissue sarcoma.[301,302]

TCR-T cells can also be designed to target tumor-associated viral antigens. Wang's team developed HBV-specific TCR-T cells (HBV-TCR-T), which significantly reduced circulating HBV DNA titers and induced a PR lasting 27.7 months in one of eight patients with HBV-related HCC.[303] Comparable clinical efficacy has also been reported for another HBV-TCR-T product, SCG101.[304] Zhao et al demonstrated that repeated infusions of HBV-TCR-T cell therapy showed good tolerability in HBV-HCC patients after liver transplantation.[305] Additional targets are being extensively investigated for TCR-T cell therapy and have demonstrated promising antitumor activity with acceptable safety profiles in solid tumors, including but not limited to KRAS G12V,[306] PRAME,[307] and AFP-targeting ADP-A2AFP.[308]

Similar to CAR-T cell therapy, TCR-T cell therapy shows great potential in the treatment of hematological malignancies. Minor histocompatibility antigens (MiHAs) represent common targets for TCR-T cells, as they can be presented by the HLA-A*02:01 molecule. Krakow et al. developed an HA-1-targeted TCR-T cell therapy directed against a polymorphic peptide derived from minor MiHAs, which induced complete remission in 4 of 9 patients with recurrent leukemia upon hematopoietic stem cell (HSC) transplantation, with one remission lasting for more than 2 years.[309]

Although TCR-T cell therapy shows promising potential, the repertoire of validated peptide antigens for its design remains very limited, making the identification of novel targets a critical challenge in the development of TCR-T therapies. The utilization of widely shared neoantigens may provide feasible targets for future TCR-T approaches. Additionally, the advancement of high-throughput tumor antigen screening platforms and technologies has further facilitated the development of novel TCR-T strategies.[14,310] On the other hand, TCR-T cell activation depends on MHC molecules, and the extensive MHC diversity among individuals renders these therapies highly personalized,[1,311] making it difficult to develop broadly applicable TCR-T products similar to CAR-T therapies.

Engineered innate immune cells

To overcome the challenges of CAR-T and TCR-T cell therapies, increasing attention has been directed toward engineering innate immune cells for ACTs. Various innate immune cell-based strategies, including CAR-NK cells, CAR-NKT cells, CAR-macrophages, and engineered γδ T cells, have been developed and are being actively investigated. These approaches leverage the unique biological properties of innate immune cells, such as MHC-independent recognition and favorable safety profiles, and have demonstrated promising therapeutic potential.

CAR-NK. NK cells can eliminate cancer cells through multiple mechanisms independent of prior antigen stimulation.[312] Similar to T cells, NK cells can be genetically engineered to express CAR, thereby generating CAR-NK cells. The innate multi-target-specific anticancer activity of NK cells renders CAR-NK cells to kill both target-specific (CAR-mediated) and target-lacking (CAR-independent) tumor cells, which is essential for overcoming the heterogeneity and immune evasion of solid tumors.[313] Meanwhile, the absence of TCR expression in NK cells decreases the incidence of graft-versus-host disease (GvHD).[13] Compared to CAR-T cells, CAR-NK cell therapy is associated with a lower risk of CRS.[314,315] The development of baboon-enveloped pseudotyped lentiviral vectors enables efficient genetic modification of hard-to-transduce NK cells with CAR constructs.[13] NK cells used for therapeutic applications can be derived from multiple sources, including peripheral or cord blood, as well as stem cell sources such as induced pluripotent stem cells (iPSCs) and HSCs.[13] Generally, CAR-NK cells can be designed to target a multitude of antigens on the surface of cancer cells, including CD19,[316] CD38,[317] CD70,[318] CD123,[319] mesothelin,[320] HER2[321] et al. Intracellular signaling domains used in CAR-NK cells include NK cell-specific molecules such as DNAM-1, 2B4, and NKG2D, as well as costimulatory domains commonly used in CAR-T cells, including 4-1BB, CD3ζ, CD28, and OX40, among which 4-1BB/CD3ζ is used most frequently.[322,323]

Currently, approximately 100 phase 1/2 clinical trials are evaluating the safety and efficacy of CAR-NK cell therapy in various malignancies, including hematological cancers (B-cell lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and MM) and solid tumors expressing targets such as HER2, EGFR, and PD-L1. CD19-positive CAR-NK cells have shown safety and promising preliminary efficacy in CD19$^+$ B cell malignancies. In a phase 1/2 clinical trial enrolling 11 patients with relapsed or refractory CD19$^+$ non-Hodgkin's lymphoma or chronic lymphocytic leukemia (CLL), cord blood-originated NK cells expressing anti-CD19 CAR, IL-15, and inducible caspase 9 (CAR19/IL-15) showed a response rate of 73% with no signs of CRS, GvHD, and neurotoxicity.[324] These results promoted further evaluation of CAR19/IL-15 NK cells in 37 patients with CD19$^+$ B cell neoplasms, which achieved ORR of 48.6% at day 100, one-year PFS and OS of 32% and 68%, respectively.[325] Similarly, a CD19-specific CAR-NK cells stimulated with 4-1BB/CD3ζ resulted in an ORR of 62.5% at day 30 and a median PFS of 9.5 months in 8 patients with relapsed/refractory large B cell lymphoma in a phase 1 clinical trial.[326] FT596 is an iPSC-derived NK cells engineered with anti-CD19 CAR, IL-15, and CD16 Fc receptor. It induced durable and deep antitumor efficacy in patients with indolent and aggressive B-cell lymphomas as monotherapy or combined with anti-CD20 rituximab in a phase 1 study.[327] CAR-NK cells also displayed a promising antitumor effect in solid tumors. It is reported that intraperitoneal injection of NKG2D-modified CAR-NK cells leads to a DCR of 33.3% and increases the recruitment of activated CD8$^+$ T cells in CRC with peritoneal metastasis.[328] Combining NKG2D CAR-NK cells with PD-1 blockade also showed tolerability and promising clinical benefit in advanced CRC patients.[329]

CAR-NKT. NKT cells belong to innate T cells that possess the properties of NK cells.[330] Both T cell and NK cell receptors are present on NKT cells, enabling them to eliminate cancer cells both specifically and non-specifically.[291,330] CAR-engineered NKT cells are becoming a new platform for ACTs. Arming with CAR increased the selectivity of NKT cells. Meanwhile, CAR-NKT cells kill cancer cells with their innate receptor directly and by stimulating other immune cell responses indirectly.[331] Although showing promising efficacy in treating hematological tumors, CAR-NK cell therapy displayed superior antitumor efficacy in solid tumors, which may be related to their high infiltration into tumor tissues.[331] At present, seven phase 1 clinical trials have been registered against neuroblastoma, RCC, advanced solid cancer, and B-cell malignancies. Heczey et al. reported the first-in-human phase 1 study of a CAR-NKT cell therapy, GD2-CAR.15, which co-expresses a GD2 CAR and the cytokine IL-5.[332,333] In 12 children with neuroblastoma, treatment with GD2-CAR.15 achieved an ORR of 25% without dose-limiting toxicities, highlighting its potential as a promising immunotherapeutic strategy for neuroblastoma. Similar to CAR-NK cells, CAR-NKT cells show several advantages, including low cost, high safety with a limited risk of CRS and GvHD, and reduced individual dependency due to their MHC-independent recognition.

CAR-macrophages. Macrophages are key innate immune cells that play essential roles in phagocytosis, proinflammatory responses, TME activation, and antigen presentation, thereby bridging innate and adaptive immune responses.[334] Following the success of CAR-T and CAR-NK cell therapies, engineering macrophages to express CARs has emerged as a promising strategy to enhance antitumor activity against antigen-expressing cancer cells, particularly in solid tumors. The structure of CAR in macrophages includes a scFV component for antigen binding and an intracellular signaling domain.[13,335] CAR-macrophages can be designed against antigens of hematological neoplasms (e.g. CD19[336]) and solid tumors (e.g. HER2,[337,338] CEA[339] etc.). Intracellular signaling domains include CD147, CD3ζ, 4-1BB, FcRγ et al., which can increase the functions of macrophages.[13] To increase tumor infiltration, CAR-macrophages can be engineered to remodel the ECM by producing molecules such as MMPs.[340] Several CAR-macrophages has been evaluated in phase 1 clinical trials against solid tumor specific for HER2, PSMA and FAP (NCT07409766, NCT06224738, and NCT04660929). In the phase 1 study assessing the application of CAR-macrophages (CT-0508) in HER2-positive advanced breast cancer and gastroesophageal cancer, CT-0508 remodels the TME and elevated the expansion of CD8$^+$ T cells. Meanwhile, CT-0508 treatment achieved stable disease in 44% of patients with HER3$^+$ tumors at 8 weeks after treatment, without dose-limiting toxicities or severe adverse events (NCT04660929).[341] Further evaluation in larger patient cohorts is warranted to facilitate the clinical translation of CAR-macrophage therapy.

Engineered γδ T cells. Unlike conventional αβ T cells, γδ T cells are considered innate-like immune cells that possess unique mechanisms for tumor antigen recognition and can bridge innate and adaptive immunity.[342] γδ T cells express distinct TCRs and high levels of NK-like receptors, which

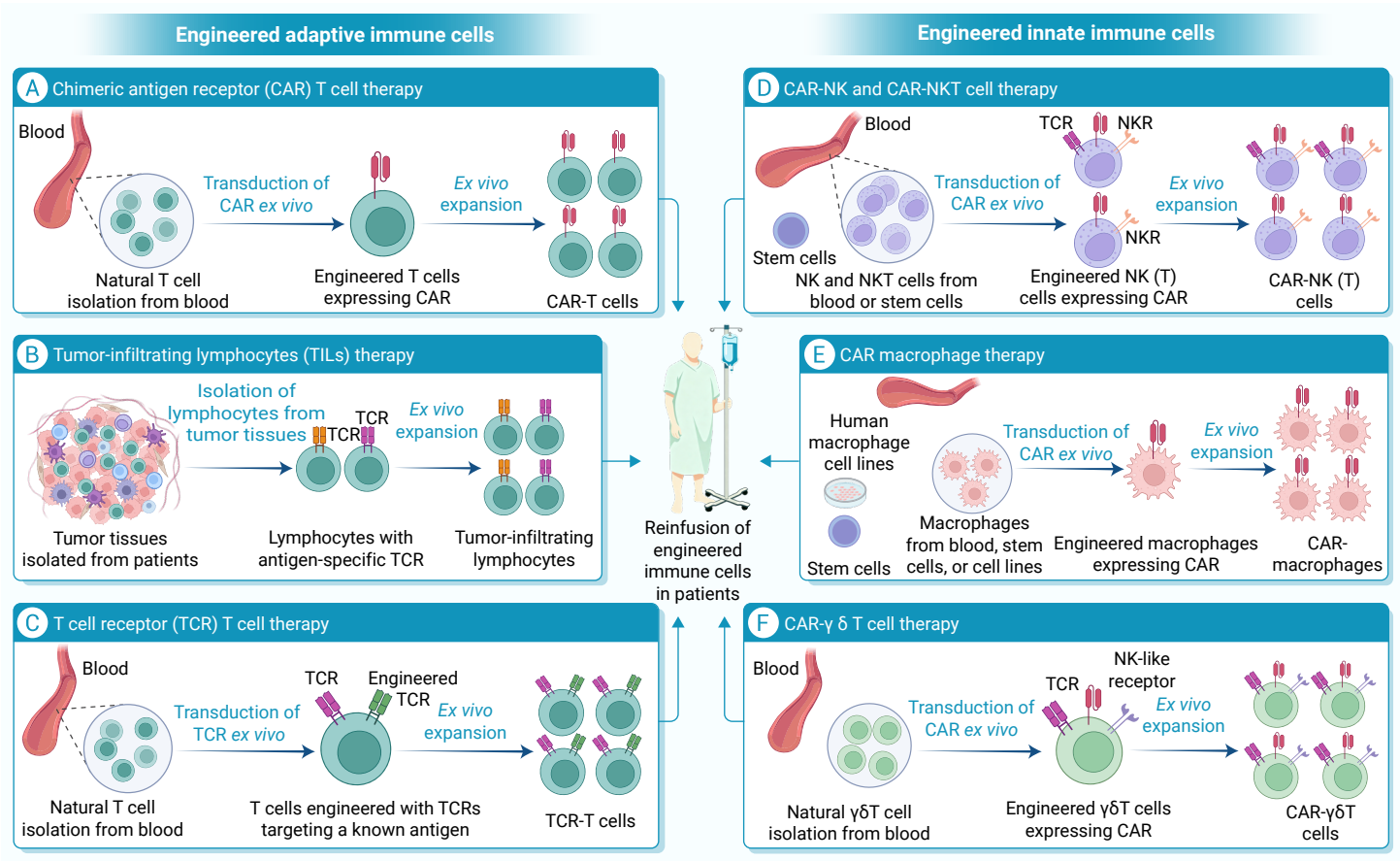

Figure 4. Cancer immunotherapy with adoptive immune cell therapy ACTs are mainly composed of six categories, including adaptive (CAR-T cell therapy, TIL therapy, TCR-T cell therapy) and innate (CAR-NK(T) cell therapy, CAR-macrophage therapy, and CAR-γδT cell therapy) immune cell therapy. TIL therapy involves isolating lymphocytes infiltrating resected tumors, expanding them *ex vivo*, and reinfusing them into patients to mediate antitumor responses. Other treatment strategies involve isolating natural immune cells and *ex vivo* engineering with cancer antigen-specific TCRs or CARs and expansion before reinfusing into patients.

enable MHC-unrestricted recognition of tumor cells and consequently reduce the risk of GvHD following adoptive transfer.[13] γδ T cells possess several unique advantages in cancer immunotherapy, including diverse cytotoxic mechanisms, broad antitumor activity, and the capacity to infiltrate the hypoxic TME and promote a pro-inflammatory immune milieu.[291] Adoptive transfer of unmodified γδ T cells has demonstrated clinical activity in liver and lung cancers,[343] and this approach is currently being evaluated in dozens of clinical trials against both hematological and solid tumors.[342] To enhance therapeutic efficacy, γδ T cells can be engineered to express CARs. Currently, more than 20 studies are evaluating the antitumor activity and safety of CAR-γδ T cells in clinical settings, as summarized in previous reviews.[13,342] Nevertheless, clinical outcome data on CAR-γδ T cells remain limited, highlighting the need for additional studies to assess their safety and efficacy as cancer immunotherapy.

Except for the CAR-engineering approach, innate immune cells can also be armed with cytokines or chemokines to increase their tumor trafficking, persistence, expansion and antitumor responses. For instance, IL-15 is an essential cytokine that promotes the development, survival, and cytotoxic effect of NK cells and γδ T cells without impacting Treg cells.[344,345] This promoted the addition of IL-15 when producing (CAR-transduced) NK cells and γδ T cells to express IL-15Rα/IL-15 fusion protein.[325,346] Myeloid cells can also be designed to overexpress and deliver cytokines to the TME. IL-12 is a typical cytokine that induces type 1 helper T cell polarization and promotes $CD8^+$ T cell and NK cell-mediated tumor suppression.[347] It is reported that IL-12-armed myeloid cells[348] and DC progenitors[349] reversed the suppressive TME and inhibited tumor growth and metastasis in mouse models. Meanwhile, ACTs face the challenges of poor tumor infiltration, mainly owing to the lack of chemotactic signaling and the dense ECM barrier. Hence, innate immune cells can be engineered to express key chemokine receptors, including C-C chemokine receptor 2 (CCR2), CCR5, and C-X-C chemokine receptor type 1 (CXCR1), or to strengthen endothelial adhesion signaling, thereby enhancing the homing, tumor infiltration, and antitumor activity of adoptively transferred cells.[13] CAR-NK cells engineered to overexpress CXCR4 exhibited enhanced trafficking to CXCL12-rich bone marrow niches and demonstrated improved antitumor efficacy against MM.[350] In summary, engineering immune cells to express cytokines and other immunomodulatory factors represents an important complementary strategy for enhancing the antitumor efficacy of ACTs.

Challenges and future directions

Despite the remarkable clinical success of ACTs, particularly CAR-T cell therapies in hematological malignancies, their broader application remains constrained by several biological, technical, and logistical obstacles. One of the most significant limitations is the comparatively modest efficacy observed in solid tumors. Unlike hematological malignancies, solid tumors are characterized by substantial antigen heterogeneity, which promotes immune escape through antigen loss or downregulation. In addition, the dense stromal architecture and abnormal vasculature of solid tumors impede immune cell trafficking and infiltration, preventing sufficient penetration of therapeutic immune cells within tumor sites. Even when ACT-derived effector cells successfully infiltrate tumors, their functionality is often compromised by the TIME, which is enriched with Tregs, MDSCs, TAMs, immunosuppressive cytokines, and metabolically unfavorable conditions such as hypoxia, nutrient deprivation, and lactate accumulation.[351,352] Together, these factors contribute to T cell dysfunction and exhaustion, ultimately limiting therapeutic durability. For instance, mesothelin- or EGFRvIII-targeted CAR-T cell therapies failed to achieve durable clinical responses in solid tumors and glioblastoma, respectively, mainly due to poor tumor infiltration, antigen heterogeneity, limited persistence, and TIME.[353,354]

Treatment-related toxicity is another limitation to the broader application of

ACTs, especially immune-mediated adverse events. CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) remain among the most common and potentially severe adverse events following ACTs.[352] Off-target effects and insertional mutagenesis should also be noticed.[355] The clinical development of affinity-enhanced MAGE-A3-specific TCR-T cells was discontinued after the occurrence of severe and fatal cardiotoxicity occurred, owing to unintended cross-recognition of a titin-derived peptide in cardiac tissue, underscoring the vital importance of comprehensive antigen specificity assessment to avoid off-target immune toxicities.[356,357] Although advances in patient monitoring and toxicity management have significantly improved safety profiles, reducing systemic toxicities without compromising antitumor efficacy remains an important unmet need. Furthermore, most currently approved ACT products rely on individualized manufacturing processes involving patient-specific cell collection, *ex vivo* expansion, and genetic engineering, resulting in prolonged production timelines, high costs, and limited scalability.

To overcome these obstacles, increasing efforts are focused on developing next-generation ACT platforms with enhanced specificity, persistence, controllability, and safety. CAR-engineered immune cells can be manipulated to express metabolic factors or cytokines to prevent immunosuppressive signals.[358,359] ACT products can also be engineered to knock out the exhaustion signals (such as the immune checkpoint) to sustain the tumor-killing activities.[352] In addition, multi-specific CAR/TCR constructs targeting multiple tumor antigens have been developed to enhance tumor recognition, reduce antigen escape, and improve the overall efficacy of ACTs against heterogeneous malignancies.[352,360] In parallel, engineered innate immune cells offer potential advantages in safety and tumor infiltration as discussed before. Logic-gated and conditionally activated cellular therapies are also emerging as promising strategies to improve tumor specificity while minimizing off-target toxicity. Notably, the EVEREST-2 trial (NCT06051695) of the logic-gated Tmod™ CAR-T therapy A2B694 has shown encouraging safety and antitumor activity in patients with solid tumors expressing mesothelin (MSLN) with HLA-A*02 loss of heterozygosity.[361] Moreover, allogeneic "off-the-shelf" cell products may substantially reduce manufacturing complexity and broaden patient accessibility. Meanwhile, locoregional delivery of ACT products avoid the incidence of T cell entrapment in the lungs occurred during intravenous delivery, including intrapleural,[362] intracerebroventricular,[363] intratumor[364] administration etc. Future integration of ACTs with ICIs, cancer vaccines, OVs, and metabolic or microbiome-targeted interventions may further enhance therapeutic efficacy and help overcome resistance in solid tumors.

OTHER IMMUNOTHERAPEUTIC STRATEGIES

Immune cell engagers

Immune cell engagers are antibodies designed to redirect immune cells to recognize and eliminate cancer cells.[365] They have demonstrated remarkable antitumor efficacy in hematological malignancies and are currently being intensively investigated for solid tumors. Most immune cell engagers consist of bifunctional or multifunctional molecules that simultaneously bind to TAAs on cancer cells and activating receptors on immune effector cells, the latter of which can activate the effector signaling pathways and trigger the antitumor effect of immune cells. T cell engagers represent the most frequently investigated class of immune cell engagers, with 10 products already approved for the management of hematological and solid tumors.[365,366] Blinatumomab is a bispecific T cell engager (BiTE) that targets CD3 on T cells and CD19 on cancer cells. It was the first approved T cell engager for the treatment of relapsed or refractory precursor B cell ALL in 2014. BiTE antibodies are small in size and are rapidly cleared following infusion into cancer patients, which limits their therapeutic efficacy. Addition of Fc fragment or albumin may help increase the half-life of BiTE molecules without interfering with their binding capacities.[365] Other tumor antigens of hematological cancers can be targeted by T cell engagers. For instance, glofitamab,[367] epcoritamab,[368] and mosunetuzumab[369] are CD3×CD20 bispecific antibodies engineered for treating B-cell malignancies. B-cell maturation antigen (BCMA), a member of the TNF receptor superfamily that is selectively expressed on plasma cells and MM cells, has emerged as an attractive therapeutic target for MM.[370] CD3×BCMA bispecific antibodies are under intensive investigation for MM, including the approved teclistamab,[371] elranatamab,[372] and linvoseltamab.[373] As for solid tumors, the approved T cell engagers have been designed to target antigens of gp100-MHC$^+$ uveal melanoma (Tebentafusp[374]), EpCAM$^+$ carcinomas with malignant ascites (Catumaxomab[375]), and delta-like ligand 3 (DLL3) small cell lung cancer (Tarlatamab[376]).

Head-to-head comparisons have demonstrated that the approved T cell engagers, such as tarlatamab,[366] blinatumomab,[377,378] and tebentafusp,[379] provide superior clinical outcomes compared with conventional chemotherapy or immunotherapy, including improved survival and a reduced incidence of severe adverse events. These encouraging results have markedly accelerated the development of T cell engagers. Existing agents are being explored across a wider spectrum of malignancies as monotherapies or in combination with other treatments.[380-383] Meanwhile, the discovery of new TAAs has driven the generation of next-generation T cell engagers, many of which have demonstrated promising antitumor activity, including obrixtamig,[384] acimtamig,[385] pasritamig[386], IMCnyeso[387] et al. In addition, innate immune cells, such as NK cells, γδ T cells, and macrophages, can also be exploited for the development of immune cell engagers.[365] For instance, Gauthier et al. developed trispecific NK cell engagers that simultaneously target two NK cell activators (CD16A and NKG2D) and a tumor antigen on cancer cells (such as HER2, EGFR, CD33, and BCMA).[388] These trispecific engagers demonstrated stronger NK cell activation compared with bispecific engagers targeting only CD16A and tumor antigens and are currently being evaluated in phase 1/2 clinical trials for the treatment of multiple solid tumors (NCT04143711, NCT05597839, NCT04789655, and NCT04975399).

Despite the great progress, several challenges still limit the broader clinical application of immune cell engagers. One major bottleneck is on-target, off-tumor toxicity, caused by the recognition of low levels of target antigens on normal tissues. Another limitation of immune cell engagers is the risk of CRS and other irAEs due to excessive immune activation.[389-391] To overcome these challenges, several strategies are being explored, including the identification of more TSAs, the design of multi-specific engagers, and the targeting of presented antigen peptide-MHC complexes to improve targeting precision[392]. Meanwhile, reducing CD3-binding affinity in T cell engagers,[393,394] along with expanding the targeting to other immune cells with intrinsic tumoricidal capacity, may further improve the safety profile of immune cell engagers.

Cytokines

Cytokines are small secreted proteins that regulate immune responses and enhance antitumor immunity by increasing the recognition and killing of cancer cells. Cytokines can directly activate immune cells and enhance intercellular communication to mediate antitumor responses. Numerous cytokines have demonstrated anticancer activity, including GM-CSF, IL-2, IL-12, IL-15, and IFN-α. However, only a limited number have advanced into clinical evaluation. ALT-803 is a super-agonist of IL-15. In a phase 1b study, ALT-803 plus nivolumab displayed safety and promising clinical activity in 21 patients with metastatic SCLC.[395] In the development of cancer vaccines, cytokines are commonly employed as adjuvants, where they can enhance antigen presentation, promote effector T cell and NK cell responses, modulate the TME, and support the formation of long-term antitumor immune memory.[1,396] However, cytokines are short-lived *in vivo* and possess a relatively narrow therapeutic window, which increases the risk of severe adverse effects and substantially limits their clinical application.

CONCLUSION AND FUTURE PERSPECTIVES

Cancer immunotherapy has revolutionized the landscape of oncology over the past decade, with substantial clinical successes particularly in ICIs, cancer vaccines, OVs, and ACTs. Extensive clinical trials have demonstrated that these modalities can induce durable responses in a subset of patients and, in some cases, achieve long-term survival benefits that surpass conventional therapies, either as monotherapy or in combination with other therapies. While ICIs, ACTs, and OVs have progressed to clinical application with several approved products, cancer vaccines remain primarily under clinical investigation but hold great promise owing to their specificity, safety, and potential for personalized and durable antitumor immunity. Most currently available immunotherapies aim to induce robust CTL responses. The remarkable success of these therapies has driven the development of novel

strategies, including those targeting innate immune cells such as NK cells, NKT cells, macrophages, and γδ T cells, to fully exploit their intrinsic tumor-killing potential. Despite these advances, different immunotherapy modalities possess distinct advantages and limitations. ICIs can induce durable responses but benefit only a subset of patients with high expression of immune checkpoints, whereas cancer vaccines provide highly specific immune priming yet often suffer from limited immunogenicity and antigenicity. OVs can convert immunologically "cold" tumors into "hot" tumors but face challenges in systemic delivery and antiviral immunity. ACTs exhibit potent cytotoxic activity but are frequently restricted by poor trafficking, limited persistence, and T cell exhaustion in solid tumors. ACTs exhibit potent cytotoxic activity and can induce durable clinical responses, particularly in hematological malignancies. However, their efficacy in solid tumors is often limited and their broader clinical application is constrained by limited *in vivo* persistence, on-target off-tumor toxicities, complex manufacturing processes, high costs, and limited scalability. Recognition of these overlapping challenges has promoted the development of rational combination strategies. For instance, cancer vaccines and OVs as in situ vaccines can enhance cancer immunogenicity and T cell recruitment and priming, thereby sensitizing tumors to ICIs, while ICIs can reinvigorate the adoptively transferred T cells. Such complementary mechanisms suggest that future immunotherapy is likely to rely increasingly on personalized, multimodal treatment strategies rather than single-agent approaches.

It is noteworthy that different immunotherapy strategies share common challenges. First, tumor heterogeneity, both inter- and intra-patient, along with the TIME, poses a significant challenge to the consistency of therapeutic efficacy and the broad application of immunotherapy. Second, tumors can evolve a range of mechanisms to develop immune evasion and treatment resistance to immunotherapy. Multiple factors contribute to treatment resistance, including aberrant expression of immune checkpoints, antigen loss or defective antigen presentation, the establishment of a TIME driven by infiltrating suppressive cells (e.g., Tregs, MDSCs, and TAMs) and immunosuppressive cytokines, T cell exhaustion, dysregulated IFN signaling, metabolic disturbances in both cancer and immune cells, alterations in gut microbiota, and epigenetic modifications.[397,398] Third, irAEs may hamper the development and clinical application of immunotherapy, such as CRS and GvHD. Additionally, the translation of promising preclinical findings to clinical success remains constrained by differences in the tumor biology and immune contexture between human and animals.

Looking forward, several strategies are poised to advance cancer immunotherapy. Rational combination therapies represent a key strategy to enhance efficacy while reducing toxicity by optimizing the dosage of each component and leveraging complementary mechanisms of action. In addition, overcoming resistance to immunotherapy remains a central challenge in cancer treatment. With the growing understanding of both tumor-intrinsic and tumor-extrinsic mechanisms of resistance, current efforts to overcome immunotherapy failure increasingly focus on remodeling the TIME. Achieving this goal requires detailed insights into the dynamic changes of the TME before and after treatment, which can be deciphered through high-resolution technologies such as spatial transcriptomics and single-cell sequencing to map the cellular interactome. Increasing efforts are focused on metabolically reprogramming the TME by targeting key metabolic vulnerabilities that drive immune suppression. Such approaches aim to restore T cell fitness and alleviate myeloid-cell-mediated immunosuppression, thereby enhancing the efficacy of current immunotherapies and overcoming therapeutic resistance. Notably, encouraging clinical progress has been achieved with agents targeting metabolites such as arginine (e.g., OATD-02), lactate, and adenosine (e.g., Etrumadenant and Ciforadenant).[399] Modulation of the gut microbiome represents another promising strategy to overcome immunotherapy resistance. Approaches including fecal microbiota transplantation, live biotherapeutic products, and microbiome-directed dietary interventions have demonstrated the potential to restore antitumor immunity, reshape the TME, and enhance responses to immunotherapy, with several candidates already displaying encouraging results in early-phase clinical trials (e.g. ADXS-503 and CRS-207)[400,401] Additionally, therapeutic strategies targeting post-translational modifications, such as acetylation, and lactylation, methylation[402], small molecule inhibitors and novel technologies (e.g., targeted protein degraders (PROTACs) and cell-penetrating peptides)[403] offer promising opportunities to overcome resistance and optimize combination modalities.

The development of genomic and proteomic sequencing guided personalized immunotherapies, such as neoantigen-based cancer vaccines or patient-tailored ACTs, which are expected to improve response rates by targeting TSAs with high precision. Furthermore, emerging technologies and integrative approaches are likely to accelerate the development of immunotherapy. Biomarker-driven patient selection and stratification, informed by TMB, immune cell infiltration, or multi-omics data, can optimize therapy choice and timing. The application of computational modeling and artificial intelligence (AI) tools holds promise to revolutionize cancer treatment and significantly promote the development of precision oncology. AI models can be used to optimize the present treatment strategies through screening response biomarkers, predicting treatment efficacy, treatment planning/monitoring, designing clinical trials, and promoting the development of novel treatments by assist in designing combination regimens, designing personalized neoantigens, and identifying novel targets.[404,405] Finally, advances in delivery technologies, especially nanotechnology-based delivery systems, have been highlighted to improve therapeutic precision and reduce systemic toxicity. By overcoming these obstacles, the next generation of immunotherapies has the potential to expand durable benefits to a broader patient population and transform cancer treatment paradigms.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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