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REVIEW

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Leveraging T cells for cancer immunotherapy

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Abstract

T cells play an essential role in tumour prevention and control, however, avoidance or disruption of anti-tumour T cell responses frequently leads to tumour progression and malignant disease. Immunotherapy aims to address this breakdown in T cell-mediated anti-tumour immunity and restore T cell function to promote the elimination of cancerous cells. Although immunotherapy has led to drastic improvements in patient prognoses across a range of clinical setting, most patients still fail to exhibit a durable therapeutic response.

In this review we discuss the role of T cells in controlling tumour progression, how T cell immunity is avoided or disrupted in the context of malignant disease, and the mechanisms by which soluble, cellular, or vaccine-based immunotherapies aim to restore anti-tumour T cell responses. This review does not aim to provide a comprehensive summary of approved immunotherapies, nor does it focus on the logistical challenges faced during the development or clinical application of immunotherapy. Instead, this review aims to highlight the mechanisms by which different therapeutic approaches address, or fail to address, specific aspects of the breakdown in T cell-mediated anti-tumour immunity. This review will also discuss exciting pre- and early-stage clinical developments that may improve the therapeutic efficacy and applicability of these treatments by more comprehensively addressing the challenges faced by T cells to improve patient prognoses.

Keywords T Cells, Cancer, Immunotherapy, Adoptive cell transfer, Immune checkpoint blockade, Vaccination

A brief introduction to T cells

T cells are a functionally diverse component of the adaptive immune system that recognise diseased cells through their T cell receptor (TCR) binding to peptide-loaded major histocompatibility complex (pMHC) or MHC-like molecules.

The TCR, a polymorphic member of the immunoglobulin (Ig) super-family, functions as an αβ or γδ heterodimer and determines T cell specificity [1–8]. While γδ T cells can exhibit anti-tumour activity [9, 10], this review focuses on canonical αβ T cells restricted to pMHC. The variable antigen-binding region of each chain is formed during thymic development via somatic recombination of variable (V), diversity (D), and joining (J) genes, and the addition of non-template nucleotides at gene junctions [11, 12], yielding an estimated diversity exceeding 10^8 unique TCRs per person [13]. This enables recognition of a wide range of antigenic peptides including those specific to, or enriched in, malignant cells.

Successful activation of T cells requires TCR-pMHC engagement ("signal 1"), alongside co-stimulation ("signal 2"), e.g. engaging cluster of differentiation (CD) 28 with CD80/86 [14] or tumour necrosis factor receptor superfamily member 9 (TNFRSF9 or 4-1BB) with 4-1BB ligand (4-1BBL) [15], and interleukin (IL) 2 signalling [16] triggers a range of functional responses that promote the elimination of diseased cells. The TCR has no inherent signalling ability and relies on CD3, a multimeric εγ-εδ-ζζ- tri-dimer for signal transduction [17, 18]. The degree of T activation and resulting effector function depends on the balance of activatory signalling from the TCR-CD3 complex and co-stimulatory molecules, and inhibitory signalling from co-inhibitory receptors [19] which are acquired

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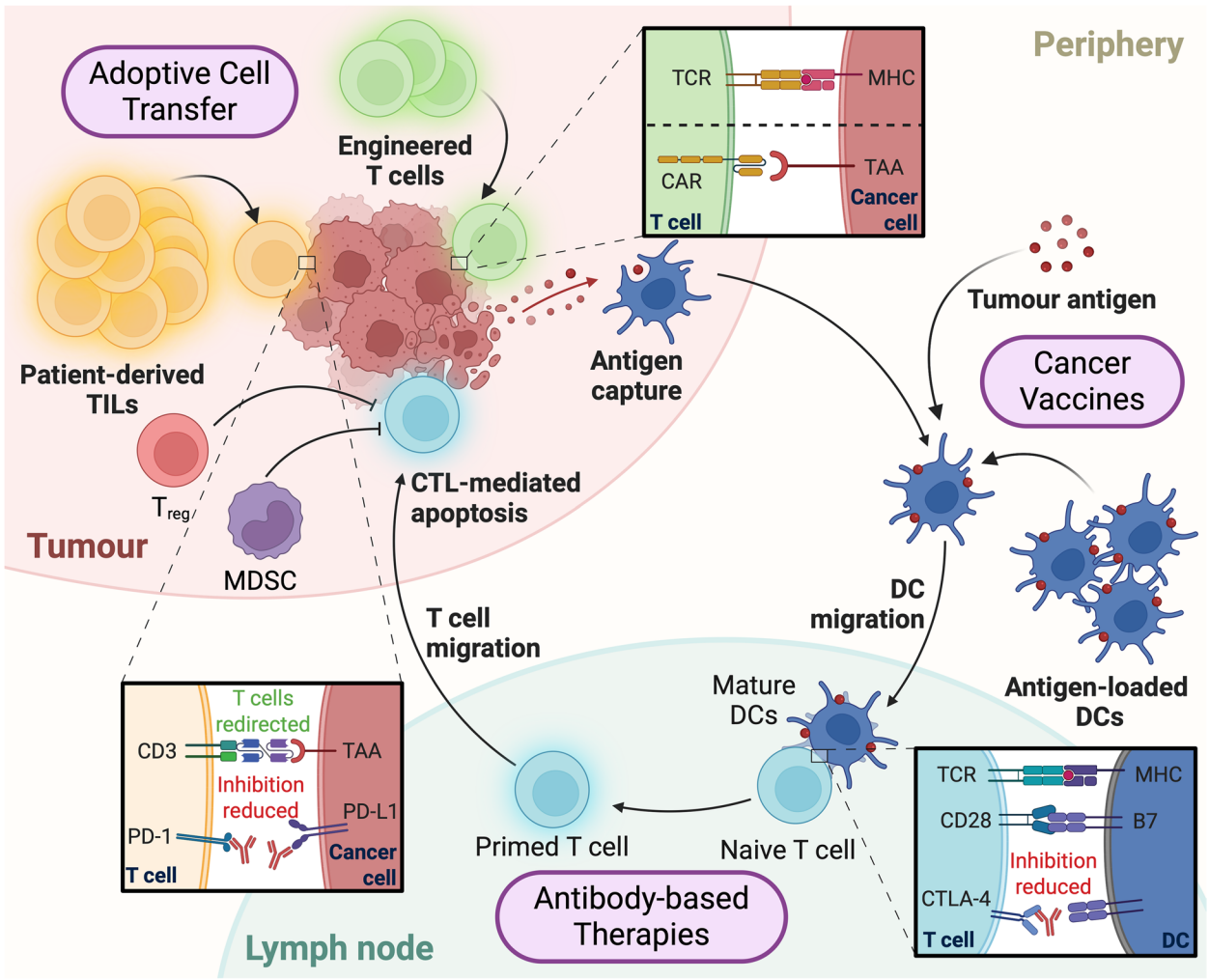
Graphical Abstract



following antigen stimulation and inflammatory cytokine signalling [20–29].

Activated $CD8^+$ T cells, or cytotoxic lymphocytes (CTLs), release cytotoxic granules containing granzymes (GZM), granulysin, and perforin [30–32], and pro-inflammatory cytokines including interferon (IFN) γ and tumour necrosis factor (TNF) to directly induce target cell death [33]. Although cytotoxic $CD4^+$ T cells have been described [34], activated $CD4^+$ T cells predominantly attract and support other immune cells within tumour draining lymph nodes and the tumour microenvironment (TME) [35]. $CD4^+$ T cells activate Classical type 1 dendritic cells (cDC1s) via CD40L, increasing cDC1 expression of co-stimulatory receptor ligands and stimulatory cytokines, including CD80/86, CD70, IL-12 and IL-15, enhancing $CD8^+$ T cell priming [36–38]. In addition, T helper 1 (T_{H1}) $CD4^+$ T cells release IFN-γ, TNF, and IL-2 which can directly restrict tumour growth [33], enhance innate and adaptive immune cell function [39–42], promote immune infiltration [43], and support the expansion and maintenance of $CD8^+$ T cells [16].

Tumour antigens & the role of T cells in anti-tumour immunity

T cells play key roles in cancer immunosurveillance and tumour control, as evidenced by increased tumour incidence in patients with compromised T cell immunity

[44–46], and the generally positive prognostic implications of T cell infiltration in most cancer types [47–49]. T cells can recognise malignant cells expressing tumour-antigen-derived peptides presented in the context of MHC and elicit effector functions (Fig. 1).

In cancers, non-synonymous mutations in protein coding genes and aberrant transcript splicing generate novel proteins that are processed into antigenic peptides known as neoantigens [50, 51]. Neoantigens are frequently recognised by adaptive immune cells as non-self, promoting anti-tumour immunity, and increased tumour mutational burden (TMB) is associated with increased immune infiltration and improved clinical outcomes [52–55].

The immune system's ability to recognise neoantigens and the restriction of neoantigens to malignant cells makes neoantigens appealing targets for immunotherapy. Certain neoantigens, such as those resulting from tumour-driving hotspot mutations in the Kirsten rat sarcoma virus (*KRAS*) [56–58], B-Raf proto-oncogene (*BRAF*) [59], and tumour protein p53 (*TP53*) [60] genes occur across patients and are termed "public" neoantigens. Furthermore, aberrant splicing can generate public "neo-junctions" that produce antigenic peptides shared across patients, cancer types, and primary and secondary tumours [51]. However, neoantigens are frequently "private" and specific to an individual's tumour, limiting the applicability of neoantigen-specific therapies.

Tumour associated antigens (TAAs) are typically expressed at low levels in healthy tissue but can be overexpressed in tumours. Although TAAs are less tumour-specific than neoantigens, endogenous TAA-specific T cell responses, such as melanoma antigen recognised by T cells 1 (MART-1 or MELAN-A) [61], glycoprotein 100 (gp100) [62], and mucin-1 (MUC-1) [63] have been observed. In the clinic, programmed cell death 1 (PD-1) blockade (discussed below) induced vitiligo, caused by a resurgence in MART-1/MELAN-A specific $CD8^+$ T cells, is a positive prognostic indicator [64]. As TAAs are germline-encoded, conserved, and expressed by multiple patients' tumours, therapies targeting TAAs have broader therapeutic applications than those targeting neoantigens. However, on-target off-tumour toxicity caused by T cells responding to low levels of TAA expression in healthy tissue is an important consideration for TAA-specific immunotherapies.

Cancer testis antigens (CTAs) are a subset of TAAs expressed only in the testis, an immune privileged tissue, and malignant cells. As a result, CTA-specific immune responses may cause less on-target off-tumour toxicity than those targeting other TAAs. While CTA-specific T cells have been observed ex vivo, they typically present with lower affinity and cell numbers than neoantigen-specific T cells [65]. As TAAs are self-antigens, high-affinity TAA-specific TCRs are likely removed by negative selection during thymic development.

Virus-associated cancers account for ~ 10-12% of newly diagnosed cancers globally [66, 67]. These include human papilloma virus (HPV) induced cervical cancer [68], hepatitis B virus (HBV) or hepatitis C virus (HCV)

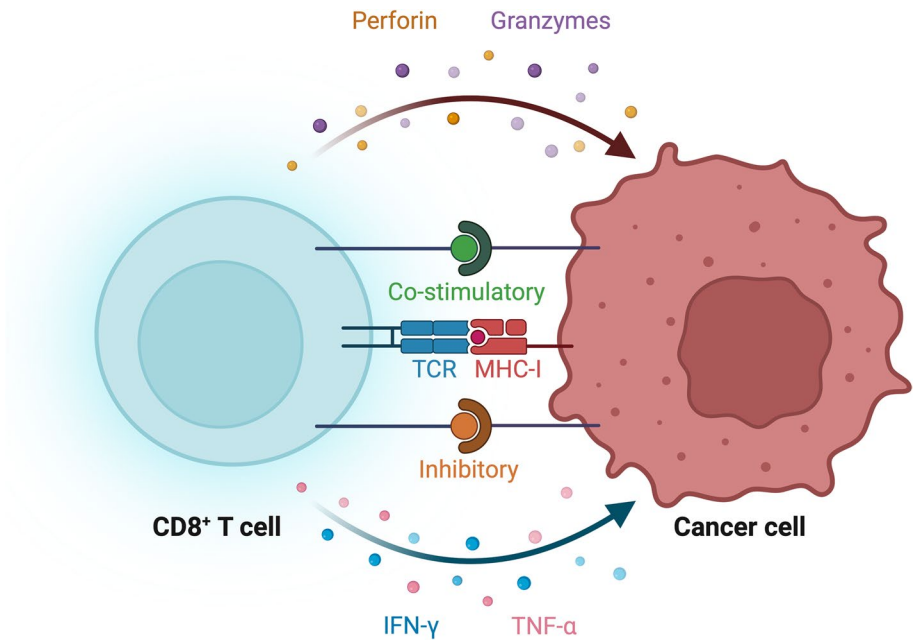


Fig. 1 Recognition of tumour antigens via TCR-pMHC interactions elicits T cell effector functions. TCR: T cell receptor, pMHC: peptide-loaded major histocompatibility complex, TNF: tumour necrosis factor, IFN: interferon

induced hepatocellular carcinoma (HCC) [69, 70], and Epstein-Barr virus (EBV) induced Burkitt's lymphoma [71]. Although mechanisms of viral oncogenesis vary [72], viral antigens can be used to identify infected cells that are at risk of, or have undergone, malignant transformation, and T cell responses against oncogenic viruses have been broadly observed [73–77]. These antigens are decisively non-self and conserved among patients with a common infectious agent. Immunotherapies targeting viral antigens therefore offer minimal on-target off-tumour toxicity, and broader scope for therapeutic translation than "private" neoantigen-targeting therapies.

Breakdown of anti-tumour immunity

Although T cells recognise and eliminate malignant cells expressing tumour antigens, tumours escape anti-tumour immune responses, leading to progressive disease. Key causes of T cell failure are highlighted below and summarised in Fig. 2.

Impaired T cell priming

Effective anti-tumour T cell responses depend on the proper priming of naïve T cells by dendritic cells (DCs) presenting tumour antigens. Tumours often inhibit T cell priming to evade the adaptive immune system.

Malignant cells disrupt DC migration by downregulating chemokine receptor ligands needed for tumour infiltration [78, 79], or by exploiting transforming growth factor (TGF) β signalling to upregulate tissue-retention receptors while suppressing C–C chemokine receptor (CCR) type 7, trapping DCs within the tumour and preventing their migration to tumour-draining lymph nodes for antigen presentation [80].

Tumours also modulate DC phenotype and function. Overexpression of CD47 provides a "don't eat me" signal that reduces tumour antigen uptake [81], and inhibits cyclic guanosine monophosphate-adenosine monophosphate synthase–stimulator of interferon genes (cGAS–STING) activation and type I IFN release [82]. This impairs IFN-dependent cross-presentation of exogenous tumour antigens on MHC-I by tumour-infiltrating DCs which is essential for $CD8^+$ T cell priming [83]. Additionally, tumours block DC maturation into pro-immunogenic cDC1 and classical type 2 DCs (cDC2), instead promoting tolerogenic phenotypes [84–87].

T cell dysfunction—exhaustion and the suppressive TME

Chronic antigen stimulation and inflammatory signalling promote T cell exhaustion, an epigenetically stable, dysfunctional phenotype driven by the transcription factors

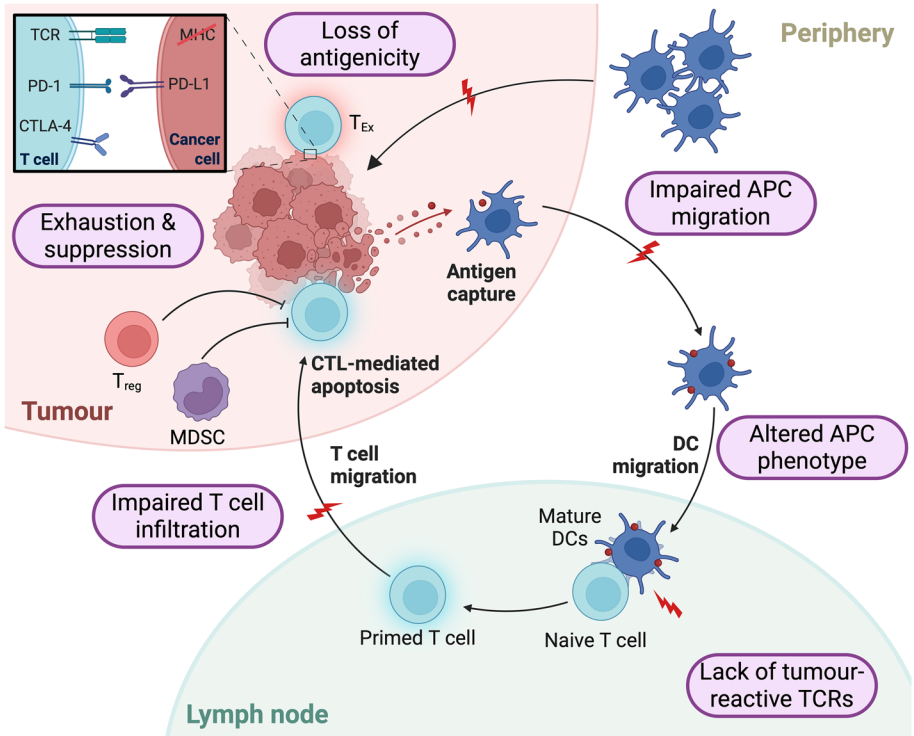


Fig. 2 Cancers utilise multiple mechanisms to impair anti-tumour T cell responses. APC: antigen presenting cell, CTL: cytotoxic lymphocyte, T_{Ex}: exhausted T cell, T_{reg}: regulatory T cell, MDSC: myeloid derived suppressor cell, TCR: T cell receptor

thymocyte selection-associated high mobility group box (TOX) and TOX2 [88–90]. T cell exhaustion is associated with high levels of inhibitory receptor expression, including PD-1 [28, 91, 92], cytotoxic lymphocyte antigen 4 (CTLA-4) [24, 25, 27, 93], lymphocyte activation genes 3 (LAG-3) [22, 94, 95], T cell Ig and mucin-domain containing-3 (TIM-3) [96–98], and T cell immunoreceptor with Ig and ITIM domains (TIGIT) [99] which limit effector function and reduce proliferative capacity [88, 100]. First described in the context of chronic viral infections [101, 102], T cell exhaustion is also a consistent feature of cancer [100].

Malignant cells, especially within solid tumours, remodel their environment to create an immunosuppressive TME that restrains anti-tumour immunity. This conditioning includes the induction of cancer associated fibroblast (CAFs), myeloid derived suppressor cells (MDSCs), regulatory B (B_{reg}) and T (T_{reg}) cells, and M2-macrophages which express inhibitory receptor ligands, anti-inflammatory cytokines, and inhibitory immunomodulators [103, 104], reinforcing T cell exhaustion and preventing the priming of new tumour-reactive clonotypes.

Additionally, hypoxia is common in solid tumours [105] which reduces T cell density, proliferation, and effector molecule secretion [106–108]. Furthermore, cytotoxic T cells are largely dependent on aerobic glycolysis for adenosine triphosphate (ATP) and must compete with tumour cells that upregulate glucose uptake and glycolysis, known as the Warburg effect [109].

Lack of tumour-reactive clonotypes & loss of tumour antigenicity

As neoantigens are frequently the result of germline mutations, patients with lower TMB are expected to exhibit lower neoantigen availability and an increased dependence on TAAs for TCR-mediated tumour recognition. Concordantly, patients with a higher TMB exhibit more favourable outcomes with anti-PD-1 and anti-programmed death ligand 1 (PD-L1) monotherapy (discussed below), demonstrating an enhanced anti-tumour T cell response in high TMB patients [110, 111].

Previous studies have demonstrated the importance of high-affinity TCRs for tumour control [112–114]. However, this topic remains contentious with studies also demonstrating the importance of low-affinity TCRs [115–117], e.g. TAA-specific TCRs. While T cells bearing high-affinity TCRs may be more sensitive and readily activated by tumour cells with low antigenicity, this increased sensitivity may increase the risk of acquiring an exhausted phenotype. T cells with lower affinity TCRs may be less sensitive but possess a greater capacity for durable anti-tumour immune responses. The importance of T cells with high- vs low-affinity TCRs is likely context-specific and dependent on the antigen and immune landscape of an individual's tumour.

Additionally, anti-tumour T cells exert a significant selection pressure on tumours, which are often highly heterogeneous [118], leading to clonal selection of malignant sub-clones with increased resistance to T cell-mediated killing in a process known as immunoediting [119]. This can include the elimination of tumour clones expressing specific antigens [120–122], a broad loss of tumour antigenicity via the downregulation of MHC and/or β2-microglobulin (b2M) [123–126], and the selection of tumour clones with reduced sensitivity to IFNs [127, 128] or increased expression of anti-apoptotic molecules [129]. A broad tumour-reactive TCR repertoire with a range of TCR affinities is likely important for reducing the risk of immune escape via the loss of specific antigens and would provide a balance between highly sensitive and durable T cell responses.

Immune exclusion & impaired T cell migration

In solid tumours, T cells must migrate from their priming site to the tumour body before mediating tumour rejection [130]. In addition to promoting an immunosuppressive TME that is not amenable to anti-tumour immune responses, malignant and co-opted cells remodel the extracellular matrix of the TME and fail to secrete chemo-attractants to exclude T cells, preventing T cell mediated tumour clearance [104].

A paired single-cell RNA sequencing (scRNA-seq) and spatial transcriptomic analysis of nonimmune stromal cells across 16 cancer types identified an enrichment in placental growth factor $(PGF)^+$ endothelial tip cells that interact with fatty acid-binding protein 4 $(FABP4)^+$ pericytes and produce an excess of extracellular matrix at the tumour boundary, excluding immune cells [131]. Furthermore, intra-tumoral enrichment of monocyte-derived anti-inflammatory macrophages, type 2 DCs, and stabilin 1 $(STAB1)^+$ macrophages, has been associated with reduced T cell infiltration [132].

Leveraging endogenous T cells with antibody-based therapies

Immune checkpoint blockade – approved targets

Immune checkpoint blockade (ICB) re-invigorates anti-tumour T cells by blocking inhibitory receptor-ligand interactions (Fig. 3). To date, clinically approved ICB is restricted to the blockade of the PD-1/PD-L1 axis, CTLA-4 and LAG-3. While ICB has transformed cancer treatment and improved patient outcomes, the proportion of patients achieving a durable response remains low [133, 134]. Though often manageable with monitoring and corticosteroids, systemic T cell disinhibition

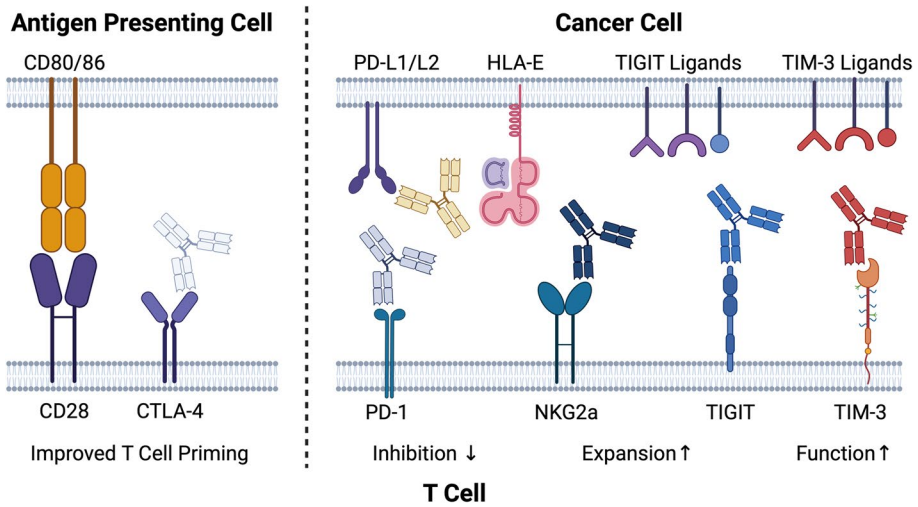


Fig. 3 Immune checkpoint blockade reduces inhibitory signalling by preventing engagement of inhibitory receptors with their ligand(s) to improve T cell function. CTLA-4: cytotoxic T lymphocyte antigen 4, HLA-E: human leukocyte antigen E, NKG2a: natural killer cell group 2 member A, PD-L: programmed death ligand, TIGIT: T-cell immunoreceptor with immunoglobulin and ITIM domains, TIM-3: T-cell immunoglobulin and mucin-domain containing-3

can trigger immune-related adverse events (irAEs) [135] including gastrointestinal, endocrine and neurological toxicity, which are more common with anti-CTLA-4 blockade and multiple checkpoint blockade, limiting combination ICB [135].

Anti-PD-1/PD-L1 ICB is widely used in tumours with high PD-L1 expression, alone or in combination with anti-CTLA-4 or anti-LAG3 blockade. scRNA-seq has helped identify predictors of response across disease contexts [65, 136–138]. Studies of tumour infiltrating lymphocytes (TILs) have demonstrated that anti-PD-1/PD-L1 ICB is unable to rescue terminally exhausted PD-1^{high} T cells, likely due to the co-expression of multiple inhibitory receptors. Instead, anti-PD-1/PD-L1 ICB facilitates intra-tumoral and peripheral expansion of tumour-reactive PD-1^{low} "progenitor-exhausted" cells, leading to an increase in anti-tumour T cells with a functional effector-like phenotype [65, 136, 139, 140]. A pre-existing tumour-reactive "progenitor-exhausted" population is therefore essential for a productive response to anti-PD-1/PD-L1 ICB but may not be present due to a patient's lack of tumour-reactive clonotypes or exhaustion of the "progenitor-exhausted" population.

In contrast to anti-PD-1/PD-L1 ICB, anti-CTLA-4 ICB acts earlier in the immune response by enhancing T cell priming in lymph nodes where blocking CTLA-4 – CD80/86 interaction during early activation improves the expansion of tumour-reactive clonotypes [141, 142]. Anti-CTLA-4 ICB also promotes the depletion of CTLA-4^{+} T_{regs} within the TME, which helps promote tumour tolerance [141, 142].

In 2022, the anti-LAG-3/PD-1 combination therapy, Opdualag, was approved for unresectable or metastatic melanoma [143]. Although the full range of LAG-3 ligands and inhibitory mechanisms remain unclear, LAG-3 expression is rapidly induced following TCR stimulation and marks exhausted cells. LAG-3 impairs $CD8^{+}$ T cell function in the presence of galectin-3, liver and lymph node sinusoidal endothelial cell C-type lectin (LSECtin), or fibrinogen-like protein 1 (FGL1), and contributes to immunosuppression when expressed by T_{regs} [144–150].

Next-generation checkpoint blockade and co-stimulatory receptor agonists

Efforts are underway to diversify ICB targets and expand treatment options. Although not yet approved for routine clinical use, several emerging checkpoints are under active investigation (clinicaltrials.gov, clinicaltrialsregister.eu) [151].

T cells can express killer cell lectin like receptor C1 (KLRC1 or NKG2A) following repeated antigen stimulation. NKG2A binds human leukocyte antigen (HLA)-E to inhibit cytotoxicity, contributing to immune evasion, and NKG2A blockade restores $CD8^{+}$ T cell and NK cell activity, enhancing tumour rejection in preclinical and clinical settings [152–155].

TIM-3 marks terminally exhausted T cells and impairs function via ligands such as galectin-9 and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), disrupting the immunological synapse,

promoting anergy, and triggering cell death [96, 97, 156–158]. Its blockade, particularly in combination with PD-1, CD39, or CTLA-4 inhibition, has been shown to enhance T cell cytotoxicity and tumour control in mice [137].

TIGIT, acquired early in T cell exhaustion, inhibits effector function in part by disrupting CD226 co-stimulation [99, 159–162]. Circulating TIGIT$^+$ PD-1$^+$ CD8$^+$ T cells following anti-PD-1 ICB have been highlighted as a positive prognostic marker [163], and co-blockade of PD-1 and TIGIT enhances tumour control in pre-clinical models [99].

V-domain immunoglobulin suppressor of T cell activation (VISTA) has gathered significant attention as a next-generation ICB target due to its role in the regulation of myeloid and lymphoid lineages [164]. Engagement of T cell-expressed VISTA promotes quiescence and peripheral tolerance [165] while VISTA on the surface of tumour cells or APCs reduces T cell proliferation and cytokine production in vitro and interferes with anti-tumour immunity in vivo [166]. VISTA can also indirectly inhibit T cell responses by negatively regulating innate inflammation, reducing Toll-like receptor mediated cytokine release, antigen presentation, and T cell support [167, 168].

As these targets are not yet part of routine clinical care, mechanistic insights in humans remain limited. Co-blockade of PD-1 with late checkpoints (e.g. TIM-3) may restore function to or protect exhausted T cells, while targeting early checkpoints (e.g. TIGIT) may expand progenitor-exhausted populations. Since TIM-3, TIGIT, and VISTA are also expressed on T_{regs} and associated with increased T_{reg} function [169–171], their inhibition may additionally relieve T_{reg}-mediated suppression. VISTA blockade is particularly promising due to its ability to enhance innate inflammation, restore antigen presentation, and directly relieve T cell suppression, thereby supporting the expansion and function of tumour-reactive clones.

Although less established than ICB, efforts are also being made to enhance anti-tumour T cell responses via the use of co-stimulatory receptor agonists. Agonists of tumour necrosis factor receptor superfamily member 4 (TNFRSF4 or OX40), Inducible T cell co-stimulator (ICOS), and 4-1BB have demonstrated capacity to improve T cell proliferation, survival, and function in pre-clinical models, and have demonstrated generally tolerable safety profiles in early trials [172–174]. Ongoing trials will clarify how targeting these and other novel receptors rescues anti-tumour immunity, particularly in combination with, and in tumours resistant to, current therapies where tolerable. Additionally, longitudinal- and meta-analyses of patient samples will help identify new biomarkers to improve patient stratification [175–178]. Finally, better understanding of how immune cells interact with the tumour and other cells within the TME through in vitro whole-genome functional screens will help identify additional targets of therapeutic relevance [179].

T cell redirecting therapies

An alternative antibody-based approach that utilises endogenous T cells is T cell redirection. T cell redirection therapy has several context-specificadvantages over ICB depending on the immunological needs of the patient (Table 1) and uses bispecific antibodies or antibody-based molecules to re-direct patients' T cells towards the tumour [180, 181].

T cell redirection therapies use a CD3-binding domain to non-specifically capture T cells, and a tumour antigen-binding domain to direct T cells towards malignant cells. The bridging of T cells and tumour cells via CD3 triggers the formation of an immunological synapse leading to the release of cytotoxic granules and pro-inflammatory cytokines, as well as T cell proliferation [182]. Importantly, T cell redirection introduces tumour specificity and therefore does not require pre-existing tumour-reactive T cells. Additionally, T cell redirection circumvents T cells' dependence on MHC for antigen presentation making it a viable treatment option for MHC-deficient tumours.

Table 1 Advantages and disadvantages of antibody-based immunotherapy strategies

	Advantages	Disadvantages
ICB	Reduces inhibitory signalling and the onset of exhaustion	Dependent on endogenous tumour-reactivity
	Lower risk of immunoediting and antigen escape	Dependent on presence of specific T cell phenotypes
	No need to define specific antigen(s)	
T Cell Redirection	Introduces de novo specificity	Does not address immunosuppression or T cell exhaustion
	MHC-independent T cell activation	High risk of immunoediting and escape
		T_{reg} activation
		On-target off-tumour toxicity

MHC: major histocompatibility complex, T_{reg}: regulatory T cell, ICB: immune checkpoint blockade

T cell redirection therapies have been especially efficacious in the treatment of B cell malignancies where targeting lineage-specific antigens facilitates T cell mediated depletion of the B cell lineage. Once malignant B cells have been eliminated, healthy B cells are replenished post-treatment from patients' hematopoietic stem cells.

Blincyto, a bi-specific T cell engager (BiTE®) formed of an anti-CD19 single-chain fragment variable (scFv) and an anti-CD3 scFv was approved by the Food and Drug Administration (FDA) in 2014 for relapsed or refractory B cell precursor acute lymphoblastic leukaemia (B-ALL) and minimal residual disease (MRD)-positive B-ALL [183]. The portfolio of approved bi-specific antibody-based therapies for the treatment of haematological malignancies has since expanded to include full length CD20-CD3 bispecific IgG1 [184, 185], tri-valent bi-specific $CD20^2$-CD3 IgG1 [186], bi-specific B cell maturation antigen (BCMA)-CD3 IgG4 [187], and bi-specific G protein-coupled receptor class C group 5 member D (GPRC5D)-CD3 IgG4 [188] (Fig. 4).

Conversely, T cell redirection therapies have struggled in the context of solid tumours. This is largely thought to be due to the failure of these therapies to address the immunosuppressive nature of the TME: the onset of T cell exhaustion, toxicity, tumour immunoediting, loss of the targeted antigen, poor T cell infiltration, activation of T_{regs}, and difficulties in defining tumour-reactive antigens in a setting where targeting lineage-specific antigens is not viable [181]. Despite these challenges, T cell redirecting antibodies for the treatment of solid tumours remain a topic of great interest with numerous ongoing clinical trials investigating novel TAA-targets, antibody formats, and combination therapies [181].

Promisingly, there have been several recent breakthroughs in T cell redirecting therapies for solid tumours. Tebentafusp, an immune-mobilizing monoclonal TCR against cancer (ImmTAC) targeting CD3 and a gp100 peptide presented by HLA-A*02:01, was approved for the treatment of HLA-A*02:01$^+$ uveal melanoma in 2022 [189]. More recently, Tarlatamab, a BiTE-like molecule targeting CD3 and the small-cell lung cancer (SCLC) associated notch-receptor ligand delta-like ligand 3 (DLL3), was approved in May 2024 for the treatment of extensive-stage SCLC (ES-SCLC) [190].

T cell-based cellular therapy

Cell-based therapies, especially T cell-based adoptive cell transfer (ACT), have emerged as a promising strategy for the treatment of cancers with several mechanistic strengths. Firstly, ACT enables the generation of supra-physiological cell numbers through expansion [191]. Secondly, the ex vivo expansion process maintains T cell functionality at the point of therapy by circumventing the immunosuppressive TME. Thirdly, ACT provides an opportunity to pre-select and expand non-exhausted T cell populations, such as stem-like memory T (T_{scm}) cells, for reinfusion, which exhibit enhanced persistence and therapeutic efficacy compared to terminally differentiated or exhausted T cells [192]. These features ensured a sustained and robust anti-tumour response, positioning ACT as a transformative approach in the ongoing battle against cancer. Below we discuss the distinctions and contextual advantages of TIL, CAR-T cell, and TCR-T cell therapies (Fig. 5).

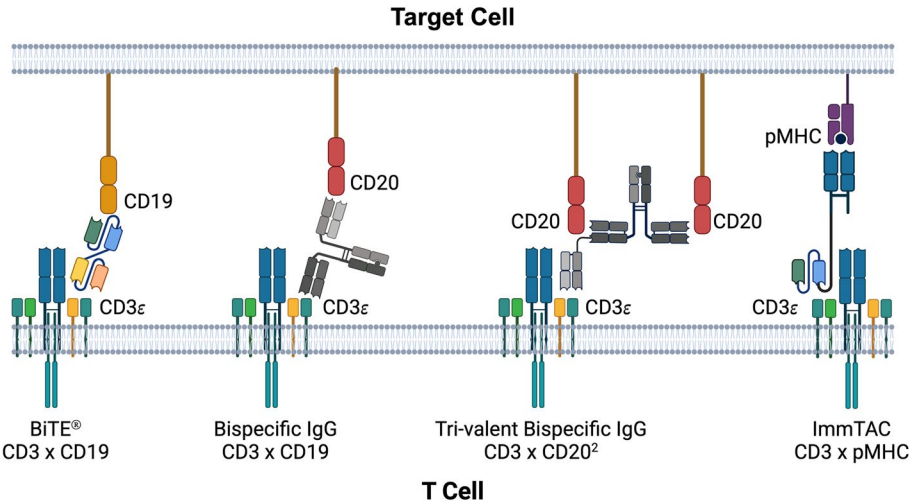


Fig. 4 Examples of T cell redirecting antibodies and antibody-based formats. BiTE®: bi-specific T cell engager, ImmTAC: immune-mobilising monoclonal TCR against cancer, pMHC: peptide-loaded major histocompatability complex

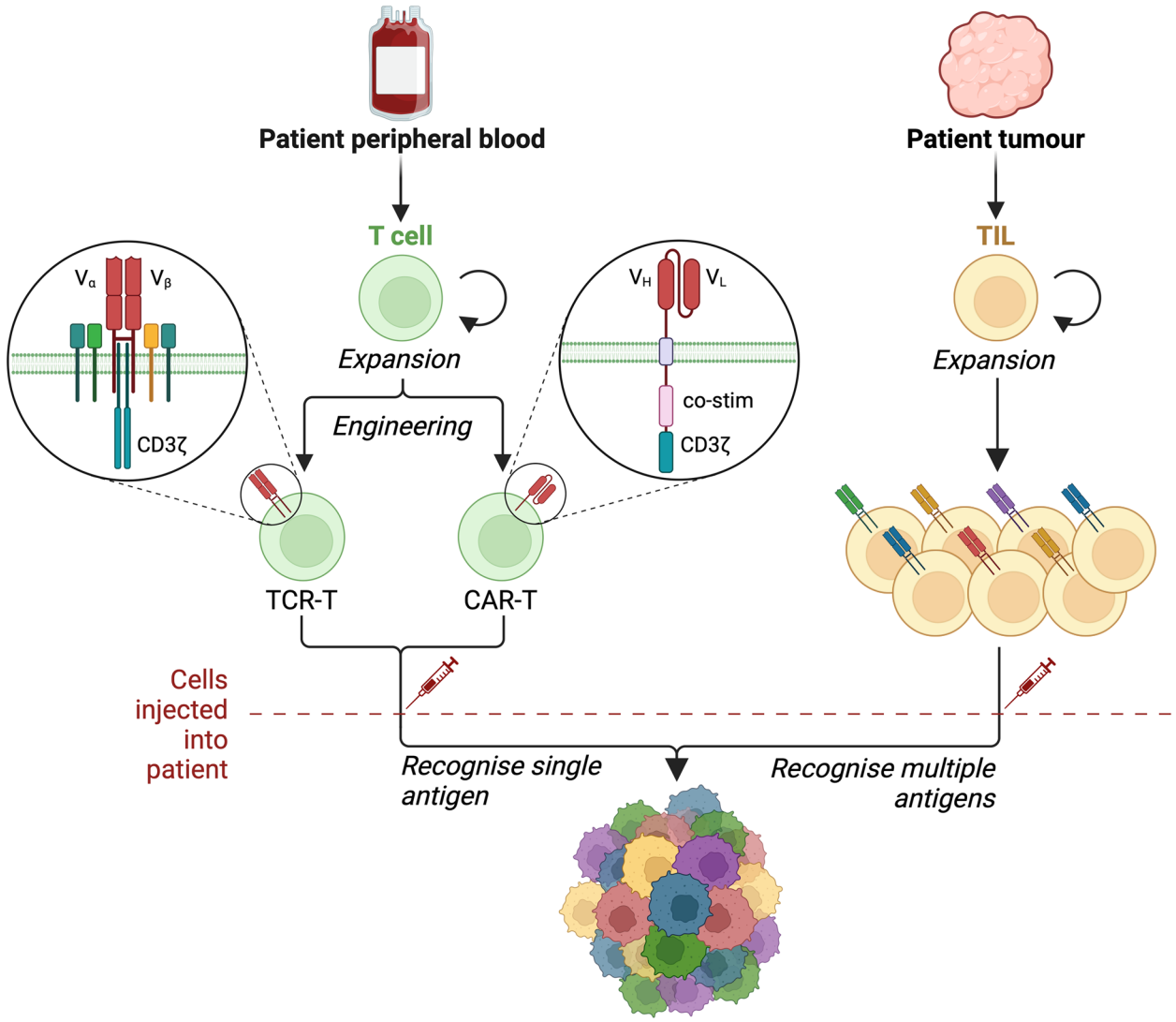


Fig. 5 Patient-derived T cells can be used for the generation of autologous cellular therapies with the capacity to provide long-term tumour protection. TCR-T: TCR-transduced T cell, CAR-T: chimeric antigen receptor T cell, TIL: tumour infiltrating lymphocyte

Tumour infiltrating lymphocyte therapy

The adoptive transfer of naturally occurring, patient-derived tumour-infiltrating T cells is known as TIL therapy. TIL therapy is largely dependent on the surgical removal of tumour samples and the identification of tumour-reactive T cells from the dissected tissue. Following an intensive ex vivo manufacturing and expansion process, a high dose of tumour-reactive T cells (up to 10^{11}) is reinfused into patients. The feasibility and efficacy of TIL therapy for the control of metastatic melanoma were first demonstrated in the 1980s [193]. Though objective tumour regression was observed, reinfused T cells were often short-lived and barely detectable several days post-reinfusion. Significant progress has been made in improving TIL therapy efficacy by incorporating lymphodepletion prior to TIL administration and administering high-dose IL-2 immediately following T cell reinfusion [194]. These strategies significantly enhanced tumour regression with improved TIL persistence and functionality and have now become standard practice for ACT.

To date, TILs have been successfully applied to a variety of solid tumours, including melanoma, non-small cell lung cancer (NSCLC), head and neck cancer, ovarian cancer, and breast cancer. Early-phase clinical trials have shown that TIL-based ACT can induce objective tumour regression in several of these cancers, highlighting its potential as a broadly applicable immunotherapeutic

strategy [195–199]. A landmark achievement occurred in 2024 when the FDA approved lifileucel for the treatment of uveal melanoma, marking the significant progress made in the field.

However, the widespread clinical application of TIL therapy is constrained by several significant limitations. As with ICB, a primary challenge is the reliance of TIL therapy on pre-existing tumour-reactive T cells within the dissected tissue, which are often functionally exhausted and may exhibit diminished anti-tumour activity [200]. Moreover, the autologous nature of TIL therapy requires labour-intensive manufacturing processes for each patient, which is time-consuming and prolongs the period of treatment [201]. In addition, TILs are a mixture of polyclonal T cells that include a large proportion of non-tumour-specific "bystander" T cells that may not contribute to tumour regression [202, 203]. This introduces massive variation between ACT products leading to differences in the therapeutic response of patients.

As TILs are normally exhausted, one promising approach under investigation is combining TIL therapy with ICB to enhance TIL activation and persistence within the TME [195, 204]. Other key focuses include identifying more potent TIL populations through improved selection and expansion strategies, and the enrichment of neoantigen-specific TILs to enhance tumour targeting and therapeutic efficacy [205, 206]. Moreover, genetically engineering TILs to lack inhibitory receptors or overexpress co-stimulatory receptors has shown promise in augmenting TIL anti-tumour activity [207].

Genetically modified T cell therapies

The recent advancement in genetic engineering tools, such as clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 and viral vector delivery systems, has greatly expanded the application of ACT, enabling the expression of artificially designed tumour antigen reactive CARs or TCRs on bystander T cells, redirecting these T cells towards the tumour [191]. Unlike TIL therapy, which relies on a limited number of largely exhausted tumour-reactive cells, genetic modification enables the use of a near-inexhaustible supply of healthy T cells for effective tumour control and introduces de novo tumour-reactive T cells into patients. Additionally, further genetic modifications can improve T cell persistence, functionality, and infiltration into the TME making genetically modified T cells a powerful and adaptable tool for cancer therapy.

The chimeric antigen receptor

CAR-T cells are genetically engineered T cells that express a CAR in place of, or in addition to, their endogenous TCR. The CAR consists of an extracellular antigen recognition domain fused to a transmembrane domain and intracellular signalling domains [208] and redirects T cells towards cells expressing the target antigen regardless of the T cells' endogenous antigen specificity. The antigen recognition domain is usually an scFv which directly recognises antigen on the surface of tumour cells, leading to MHC-independent T cell activation. In addition to introducing a desired antigen specificity, the MHC-independent recognition of tumour antigens prevents immune evasion via MHC downregulation, restoring effective T cell-mediated killing of MHC-deficient tumours. However, this mechanism of antigen recognition limits potential CAR targets to cell surface proteins.

The CAR's intracellular signalling domain is critical for effective CAR-T cell function and its structure has been progressively optimised over several generations. First-generation CARs were developed in the late 1990 s, included just CD3ζ, and only provided "signal 1", resulting in limited cytotoxicity and proliferation following CAR engagement. Second-generation CARs added a co-stimulatory domain, such as the intracellular domain of CD28 or 4-1BB, to provide "signal 2" [209, 210]. These were the first to show clinical efficacy and form the basis for all approved CAR-T cell therapies and most ongoing clinical trials. Advances in immunology and molecular engineering have since enabled the development of next-generation CAR-T cells with enhanced functionality, including additional costimulatory domains (third generation) or pro-inflammatory cytokine expression (fourth generation) [211, 212]. These innovations aim to overcome current limitations of CAR-T cell therapy discussed below.

CAR-T cells in haematological malignancies

Early clinical trials of second-generation CAR-T cells targeting CD19 achieved partial or complete remission in patients with advanced B cell malignancies [191, 213–217]. Like adoptive transfer of TILs, these trials established the importance of lymphodepletion prior to CAR-T cell infusion, which is thought reduce competition for space and growth factors, such as IL-15, enabling infused cells to expand up to 1000-fold [191, 215]. As of March 2025, there are five FDA approved second-generation autologous CAR-T cell therapies targeting CD19 for B cell malignancies, and two targeting BCMA for multiple myeloma.

A key advantage of CAR-T cell therapies is their ability to persist and provide long-term immunity without the need for constant re-infusion. In a longitudinal study following two patients for ten years post-infusion, $CD8^+$ CAR-T cells were observed to initially drive anti-tumour

immunity however, $CD4^+$ CAR T cells were observed to become progressively more dominant and eventually comprised over 95% of the CAR-T cell population [218]. Additionally, a study following 43 patients treated with anti-CD19 CAR-T cells found 51% of patients to be in complete remission three years post-therapy without additional intervention, highlighting the potential of CAR-T cell therapy as a durable and long-lasting treatment option [219].

However, a major limitation of CAR-T cell therapies is antigen escape due to immunoediting of the tumour. Loss of CD19 has been shown to occur in 30–70% of patients with recurrent disease treated with anti-CD19 CAR-T cells [220]. To address this, bi-specific CAR-T cells targeting multiple antigens, such as CD19/CD22 or BCMA/CD19, have shown promise in prolonging durable remission rates by increasing the likelihood of recognising and eliminating tumour cells even if one target is lost [221–224]. Alternatively, a universal CAR-T cell therapy targeting CD45 could revolutionise the treatment of haematologic malignancies by eliminating the need for individualised therapies based on specific lineage antigens [225].

CAR-T cells in solid tumours

CAR-T cells are also being extensively studied for the treatment of solid tumours, which account for > 90% of all malignancies; however, their clinical application remains challenging. Haematological malignancies often express lineage-specific antigens that, while not tumour-specific, can be safely targeted. In contrast, CAR-T cells targeting TAAs in solid tumours may exhibit on-target off-tumour activation leading to the fatal elimination of healthy tissues [226–229]. Additionally, TAAs may not be expressed by all malignant cells and antigen escape via immunoediting of heterogeneous tumours may occur [230].

While 22 TAAs are currently being investigated in clinical trials involving patients with solid tumours [231], the number of cell surface neoantigens that are structurally distinct from their wild-type counterparts, making them suitable CAR targets, is limited. One such neoantigen is epidermal growth factor variant III (EGFRvIII), which is found in ~ 30% of glioblastomas, and CAR-T cells targeting EGFRvIII have shown efficacy in mouse models [232]. However, targeting EGFRvIII would only eliminate a subset of tumour cells due to glioblastoma's high heterogeneity. This limitation was evident in a clinical trial of anti-EGFRvIII CAR-T cell therapy for recurrent glioblastoma, where none of the 10 patients achieved a partial or complete response (NCT02209376) [233]. CAR-T cells engineered with scFvs targeting neoepitope pMHC complexes may expand the potential antigenic space beyond cell surface proteins, limiting on-target off-tumour toxicity and tumour resistance [234].

Next-generation CAR-T cells

A meta-analysis of CAR-T therapy in solid tumours, including 22 clinical trials, reported an overall pooled response rate of only 9% (95% confidence interval: 4–16%), further highlighting the struggles of CAR-T cells in solid tumours [235]. Currently, several strategies are being explored to address limitations with TAA-targeting CAR-T cells. Purposefully reducing a CAR's antigen-binding affinity, as with Obe-cel, has been shown to increase specificity for tumours with high antigen density, reducing off-tumour toxicity [236]. Furthermore, targeting multiple TAAs simultaneously can enhance tumour recognition and reduce the acquisition of resistance. Strategies including pooling CAR-T cells targeting different antigens [237, 238], bi-specific and tandem CARs combining two scFvs for improved efficacy [239, 240], and synthetic Notch receptors that function as molecular logic gates and induce CAR expression only when another antigen is detected [241], have all been shown to reduce off-tumour toxicity. Finally, instead of targeting antigens in solid tumours that are also present in healthy tissue, tumour-restricted post-translational modifications could be targeted [242].

While CAR-T cells can be engineered to have desirable sensitivity and specificity, and incorporate costimulatory domains, reducing the need for exogenous support, CAR-T cell therapies do little to address the immunosuppressive nature of the TME which has been shown to hinder CAR-T cell expansion, persistence, and function [243]. Preventing exhaustion is a major focus in optimising CAR-T cell therapies for solid tumours [244]. One strategy involves combining CAR-T cells with immune checkpoint inhibitors like anti-PD-1/PD-L1 ICB, which has shown promise in early studies [245–247].

Additionally, engineering CAR-T cells to resist immunosuppressive signals, such as TGF-β, or to secrete pro-inflammatory cytokines, such as IL-12 and IL-15, may enhance their efficacy [248–250]. These fourth generation "armoured" CARs, or T cells redirected for universal cytokine-mediated killing (TRUCKs), aim to reshape the TME and increase T cell survival, proliferation, and anti-tumour activity [212].

Recent studies also highlight transcriptional and epigenetic modifications as key targets. Knocking out DNA methyltransferase 3 alpha (DNMT3A), inhibitor of DNA binding 3 (ID3), or SRY-box transcription factor 4 (SOX4) has been shown to delay exhaustion and improve CAR-T cell cytotoxicity under chronic antigen exposure [251–253]. Overexpressing Runt-related transcription

factor 3 (Runx3) has also been linked to increased CAR-T cell persistence in mouse melanoma models [254].

Finally, physical barriers limit migration and infiltration of CAR-T cells into solid tumours. One strategy to overcome this is to use localised delivery methods which enhance efficacy by directing CAR-T cells to the tumour site while minimising potential on-target off-tumour toxicity [255–257]. Another approach involves engineering CAR-T cells to express chemokine receptors, such as CXC chemokine receptor (CXCR) 1 or CXCR2, which has been shown to improve their trafficking to tumours [258–260]. To enhance tumour infiltration, CAR-T cells have been modified to express heparinase which degrades the extracellular matrix component heparan sulphate proteoglycan (HSPG), or to target fibroblast activation protein (FAP) to reduce tumour-associated fibroblasts in mouse models [261, 262].

TCR-transduced T cell therapy

Tumour reactivity can also be introduced by engineering T cells to express a tumour-reactive TCR to generate TCR-T cells. Compared to CARs, TCRs possess several advantages for application to solid tumours. TCRs recognise a broader range of antigens due to their capacity to recognise immunogenic peptides from intracellular and plasma membrane associated proteins [263]. Additionally, TCRs requires significantly lower antigen density than CARs due to an increased affinity for their target [264, 265], and a single pMHC complex can be sufficient to elicit T cell responses [266]. This makes TCR-T cells more effective for targeting tumours with low antigenicity and is especially beneficial when the target antigen is exclusively expressed by malignant cells.

TCR-T cells have already demonstrated the potential for a bright future in the clinic. TCR-T cells targeting the CTA New York esophageal squamous cell carcinoma 1 (NY-ESO-1) have shown remarkable efficacy in clinical trials for synovial sarcoma and multiple myeloma, with objective response rates of 50–60% [267, 268]. Similarly, TCR-T cells recognising the HPV E7 oncoprotein exhibited significant anti-tumour potential in previously untreatable or refractory HPV-associated metastatic epithelial cancers. Therapy was well-tolerated with manageable side effects and durable remission in some cases [269]. In a milestone development for TCR-T cell therapy, afamitresgene autoleucel, a melanoma antigen gene (MAGE) A4 targeting TCR-T cell therapy, was approved in 2024 for the treatment of synovial sarcoma [270].

Overcoming tumour heterogeneity with TCR-T cells

As with CAR-T cell and T cell redirection therapies, tumour heterogeneity and potential antigen loss dampen the efficacy of TCR-T cell therapy. One possible solution is to target public neoantigens derived from oncogenic tumour-driving mutations. In addtion to being essential to tumour development and persistence, these neoantigens are often more immunogenic and can elicit stronger immune responses associated with higher-affinity TCRs [271, 272]. A recently published phase I clinical trial showed that patients with metastatic pancreatic cancer exhibited significant tumour regression following reinfusion of $KRAS^{G12D}$ targeting TCR-T cells, and experienced prolonged disease stabilisation with manageable side effects [273]. This study provides proof-of-concept of a personalized treatment for a disease with historically poor outcomes. Targeting multiple antigens simultaneously to minimise immune-evasion through antigen loss has also been attempted with a proof-of-concept study demonstrating the safety and feasibility of ACT with up to three TCR-T cell products [274].

Adoptive cell therapy toxicity

The use of TCR-T cells for ACT still faces challenges that must be addressed to ensure their efficacy and safety before wide-spread clinical application. TCR-T cell related toxicity can be mainly categorized into two distinct categories with unique mechanisms and implications. On-target off-tumour toxicity following TCR-T cell therapy has already been described where carcinoembryonic antigen (CEA) targeting TCR-T cells also attacked CEA^{+} normal gut tissues, resulting in a severe but transient inflammatory colitis [229]. Off-target toxicity is also important to consider, especially following affinity enhancement of TCRs. A well-documented example is the lethal cross-reactivity of an affinity enhanced MAGE-A3 targeting TCR with the striated muscle specific antigen titin [275]. Fatal neurotoxicity has also been observed following ACT with MAGE-A3 targeting TCR-T cells due to cross-reactivity with neuronal MAGE-A12 [276].

These cases underscore the importance of intensive safety screening to minimize potential risks at the preclinical stage. Using patient or healthy donor derived cell lines, induced pluripotent stem cells (iPSCs), and tissue-derived organoids could provide a broad overview of cross-reactivity to non-tumour and tissue-specific antigens [277–281]. The combination application of in silico "off-target" prediction tools and large-scale validation platforms, such as peptide-based positional scanning, allows for rigorous systematic evaluation of TCR specificity [282], and methods such as yeast or phage display enable high-throughput analysis of TCR interactions with a vast array of pMHC complexes [283, 284].

Despite their successes, CAR-T cell therapies have been limited by severe adverse events driven by excessive cytokine production, including cytokine release syndrome (CRS) and immune effector cell-associated

neurotoxicity syndrome (ICANS) [285, 286]. In some cases, these toxicities can be managed via IL-6 blockade with tocilizumab and IL-1 inhibition with anakinra [287]. Alternatively, the risk of severe CRS can be reduced by modifying the CAR. Obe-cel, a second generation CD19 CAR-T cell with an intermediate affinity binding domain, has shown durable responses in relapsed or refractory B-ALL with reduced high-grade immune-related toxicities compared to existing FDA-approved CAR-T cells bearing higher affinity binding domains, leading to its FDA approval in November 2024 [288]. Additionally, CD28-based CARs show higher efficacy but greater CRS risk than 4-1BB-based constructs [289].

As cellular therapies become more commonplace, concerns have been raised over potential long-term consequences of ACT, especially CAR-T and TCR-T therapy, due to the persistence of reinfused cells.

B cell aplasia leading to hypogammaglobulinemia and immunosuppression, caused by CAR-T cell activity post resolution of disease, is a recognised complication of anti-CD19 CAR-T cell therapy requiring immunoglobulin replacement therapy [290, 291]. This could be addressed by making CAR/TCR expression transient via mRNA delivery or controllable with small molecules, or by incorporating suicide genes like inducible caspase 9 (iCasp9) to selectively eliminate engineered cells should excessive toxicity arise [292–295].

Although rare, engineered T cell therapies have also been associated with secondary primary T cell malignancy. Current therapies utilising viral vectors to integrate the CAR or TCR of interest into the host cell genome carry the risk of insertional mutagenesis and transcriptional dysregulation [296]. Insertional mutagenesis may activate oncogenes, deactivate tumour suppressor genes, or introduce genomic stability to increase the risk of malignant transformation [296, 297]. A shift towards targeted engineering approaches, such as CRISPR/Cas9-mediated homologous-directed repair, may help alleviate this issue [298].

Additionally, lymphodepletion has been associated with drastic changes in patients' immune system post-reconstitution, including skewing of T cells towards effector and effector-memory-like phenotypes, increased immunosenescence, and limited clonal diversity [299, 300]. Clinically, this may result in compromised T cell immunity and an increased risk of autoimmunity and tumour-relapse [301–303].

In summary, T cell-based ACT represents a broad class of therapies, with each flavour displaying distinct context-specific advantages (Table 2), that has demonstrated the potential to revolutionise the treatment of cancers whose current therapeutic options are inadequate. To further improve treatment efficiency, combination strategies that integrate ACT with other immunotherapeutic approaches are proving effective in counteracting the immunosuppressive TME, leading to enhanced T cell persistence and anti-tumour reactivity [304, 305]. Moreover, researchers are developing "off-the-shelf" products using allogeneic or unconventional (e.g. γδ) T cells to improve scalability and manufacturing [9, 306], and expanding the number of characterised tumour-reactive TCRs and targetable tumour antigens. Despite the need for further optimisation and long-term safety evaluations, ACT holds immense promise to deliver highly personalized treatment for future cancer therapy [272].

Cancer vaccines

Vaccines are biological formulations designed to stimulate the adaptive immune system to recognize and eliminate specific antigens [307]. Vaccines have been

Table 2 Advantages and disadvantages of T cell-based therapies

	Advantages	Disadvantages
TIL Therapy	Polyclonal – lower risk of immunoediting and escape	Dependent on endogenous tumour-reactivity
	Improved tissue homing	Presence of bystander T cells
	No need to define tumour antigen(s)	MHC-dependent
	Opportunity to select/enrich desirable phenotypes	Requires tumour resection
CAR-T Cell Therapy	Removes need for co-stimulation from antigen-presenting cells	Single specificity—prone to immunoediting and escape
	Introduces de novo specificity	Targeting neoantigens is challenging
	CAR is modular and highly tuneable	On-target off-tumour toxicity
	Opportunity for additional editing	Limited tissue-homing
	MHC-independent T cell activation	
TCR-T Cell Therapy	Increased antigen sensitivity for tumours with low antigenicity	Single specificity—prone to immunoediting and escape
	Introduces de novo specificity	MHC-dependent
	Better at targeting neoantigens	Toxicity (esp. engineered receptors)
	Opportunity for additional editing	Limited tissue-homing

TIL: tumour infiltrating lymphocyte, CAR: chimeric antigen receptor, TCR: T cell receptor, MHC: major histocompatibility complex

extensively applied to infectious diseases with great success [307–310], and have garnered significant attention for their potential applications to the treatment and prevention of cancer.

Antigen selection for prophylactic vaccines

In virus-associated tumours, vaccines that prevent viral infection or promote the elimination of infected cells before oncogenesis can prevent the development of virus-induced malignancies [311, 312]. Currently approved HPV and HBV vaccines can prevent the development of cervical cancer and HCC, respectively [313–315].

For tumours that develop in the absence of a viral infection, selection of suitable antigens for vaccination is more challenging due to the unpredictable and heterogeneous antigen profiles of tumours. Studies that identify shared tumour antigens are therefore of particular importance [316]. A recent study suggests that the membrane of pluripotent stem cells could be used to generate prophylactic cancer vaccines as tumour cells frequently express stem cell associated proteins [317]. Likewise, due to their abnormal expression across multiple cancer types, TAAs including MUC-1 [318–321] and human epidermal growth factor receptor 2 (HER2) [322, 323] are being explored as prophylactic vaccine targets. However, the associated risk of on-target off-tumour toxicity is especially concerning when developing interventions for healthy individuals [311].

Identifying antigens that are exclusively expressed by tumours is crucial for minimizing these risks, and targeting "public" neoantigens presents a promising solution. A clinical trial in a subset of colorectal cancer patients demonstrated the immunogenicity of public neoantigens associated with Lynch syndrome, supporting their potential use in prophylactic vaccines for this high-risk population [324, 325].

Challenges with prophylactic vaccine trial design

Another challenge when developing prophylactic cancer vaccines is the design of clinical trials required to test their efficacy. These vaccines face long latency periods and low disease incidence, requiring especially large cohorts and extended follow-up, making trials expensive and logistically challenging. Therefore, initial testing of prophylactic formulations is normally done in patients who already have cancer as a proof-of-concept [323, 324, 326]. Once feasibility is proven, high-risk populations are selected to participate in the preventive trial to maximize the incidence of disease [315].

Among the most studied individuals in prophylactic clinical trials are those with inherited mutations that increase their susceptibility to cancer. Mutations in the *BRCA1* and *BRCA2* genes cause increased susceptibility to breast and ovarian cancer [327], while mutations in DNA mismatch repair (MMR) genes can cause Lynch syndrome [328]. Other groups that have been recruited for MUC-1-targeting prophylactic vaccine trials included smokers [321] and individuals with colorectal polyps [319, 320]. Unfortunately, only limited responses were observed [319, 321]. While earlier intervention in at-risk individuals could offer more promising outcomes, the challenge of waiting for tumours to develop remains a critical limitation of these studies.

Therapeutic vaccines

Beyond prevention, cancer vaccines are being developed for therapeutic use, with HPV vaccines showing early promise in recurrent cervical cancer [329]. As discussed above, most current immunotherapies rely on the presence of a pre-existing tumour-reactive immune response [330, 331] or are limited to a single specificity, often leading to tumour escape [230]. In contrast, therapeutic cancer vaccines prime naïve T cells, generating a novel tumour-specific immune response, while also expanding pre-existing tumour-reactive cells in the periphery [332–335]. Vaccination can therefore be beneficial to patients who lack a pre-existing anti-tumour immune response and those with an endogenous immune response that is failing to control the tumour.

Numerous therapeutic cancer vaccine formulations have been tested in clinical trials [336], yet they all share two fundamental components: the antigen and the adjuvant (Fig. 6). The antigen serves as the immune system target and is usually selected upon evaluation of the tumour to ensure tumour expression [337]. Antigens can also be non-specifically sourced from whole cancer cell products, such as tumour lysate or mRNA extracts, or from live cell fusion partners in DC-based vaccines [338–343]. The use of these products eliminates the need to evaluate suitable antigens, while also ensuring vaccination against a wide range of targets, reducing the risk of immune evasion. However, these approaches require surgical removal of the tumour and therefore cannot be applied to unresectable disease.

To enhance immune activation, vaccines incorporate adjuvants, which play a crucial role in promoting strong and durable T cell priming [344–346]. In addition to conventional adjuvants, immunogenic delivery methods, such as viral particles or DC-based strategies, can further improve antigen presentation and immune response efficiency, making them valuable tools in cancer vaccine development.

Despite extensive research and numerous formulations being tested in clinical trials, only a single therapeutic cancer vaccine, Sipuleucel-T, has been approved

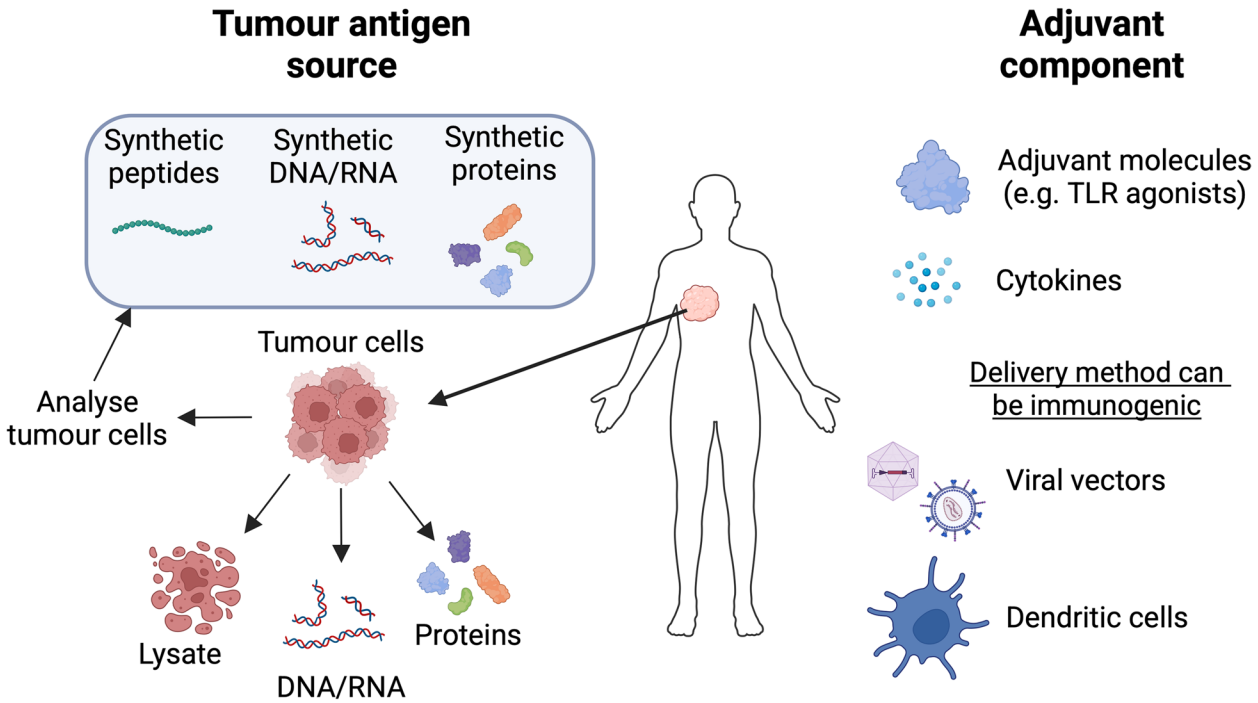


Fig. 6 Potential components of cancer vaccines. Cancer vaccines are composed of a tumour-specific antigen that may be defined or derived from tumour material, and an adjuvant to enhance immunogenicity

for clinical use by the FDA. This vaccine, targeting the prostatic acid phosphatase (PAP) antigen, confers a modest survival benefit to patients with metastatic castration resistant prostate cancer [347].

Predictive markers of therapeutic vaccine responses

The limited efficacy of cancer vaccines could be attributed to the profound immunosuppression present in cancer patients discussed above, especially the systemic dysfunction of APCs observed in cancer patients [348–350]. This prevents the proper priming and activation of tumour-reactive T cells, not only affecting existing anti-tumour immunity but also hindering the ability of vaccines to generate new, effective responses. Yet, numerous studies have demonstrated that a proportion of cancer patients show durable clinical responses to vaccination, with some achieving complete remission for years [351–355].

Understanding the factors that contribute to a successful immune response is key for extending these benefits to a wider patient population. Extended immune monitoring of patients vaccinated with telomerase peptides and neoantigens showed persistent presence of tumour-reactive T cells for more than 7 years [326, 356], indicating their possible role in long-term survivors. Other studies have also shown that clinical response correlated positively with the presence of tumour-reactive T cells post vaccination, demonstrating that the induction of tumour-reactive T cells is key for vaccine efficacy [357–359].

Recent advances in antigen-specific T cell profiling, particularly TCR sequencing, have enabled a more comprehensive assessment of vaccine-induced immunity. These studies show that not only the magnitude but also the diversity of T cell responses is critical to clinical outcomes [360, 361]. Developments in immune monitoring now also allow for the quantification of T cells targeting virtually all antigens within a tumour, allowing the evaluation of anti-tumour responses induced by vaccines that use whole tumour products [362, 363]. This technique has revealed that cytokines produced by tumour-reactive $CD4^+$ T cells can serve as indicators of response and recurrence to a DC-tumour cell hybrid vaccine [363].

Recently, a neoantigen vaccine has been shown to induce mainly $CD4^+$ neoantigen-specific T cells [364]. Mouse models have confirmed the preferential induction of functional $CD4^+$ neoantigen-specific T cells by neoantigen vaccines [365]. These findings show the crucial yet often overlooked role of $CD4^+$ T cells in anti-tumour immunity and highlight how immune monitoring can help uncover immunological predictors of response which may in turn guide the development of more effective and personalized cancer vaccines.

Significant breakthroughs have emerged in the field of neoantigen vaccines [366, 367]. These vaccines have elicited potent anti-tumour immune responses, even in low TMB tumours like breast cancer [199, 332, 335, 364]. Notably, when used in patients with fully resected tumours to prevent disease recurrence, they have shown very promising clinical results [364, 366]. Surgical resection likely reduces immunosuppression, enhancing vaccine efficacy.

The development of cancer vaccines has been driven by advances in our understanding of T cell biology, mechanisms of immune suppression, and the design of effective antigen-adjuvant combinations. Neoantigen-based strategies offer the potential for more effective and personalised treatments. As vaccine platforms continue to evolve, they are increasingly positioned to complement other immunotherapies, especially in tumours that are refractory to current approaches. This has been demonstrated in models of ICB resistant squamous cell carcinoma, where neoantigen vaccines, when combined with anti-PD-1 or anti-CTLA-4 therapy, successfully induced tumour regression [368].

Future directions

While immunotherapy has significantly improved the clinical outcomes of many cancers, current therapies fail to induce durable immune responses in most patients. Here we have discussed the role of T cells in anti-tumour immunity, how T cell function breaks down in chronic malignancy, and how current therapies address these issues. However, immune failure is multi-faceted, and no monotherapy addresses all shortcomings (Table 3). While major strides have been made in developing novel therapies, we anticipate a shift towards combining cellular, antibody-based, and vaccine-based strategies to maximise efficacy, an approach already showing promise.

A key limitation remains the restrictive number of characterised tumour antigen-receptor pairs available for therapeutic use. Further research will help expand the library of antigen-receptor pairs to increase the applicability of antigen-specific therapies across cancers, enhance the feasibility of multi-antigen strategies, and reduce immune evasion. Notably, advances in computational antigen prediction [369, 370] and large-scale TCR-pMHC screening [371] have markedly improved discovery rates. Alternatively, better phenotypic characterisation of circulating tumour-reactive T cells may enable antigen-agnostic ACT using peripheral-blood derived cells without tumour resection [372].

Whole-genome CRISPR screening [179] and longitudinal sampling of patients undergoing therapy [373] are also enhancing our understanding of T cells interactions with the tumour, TME, and therapy. These efforts are uncovering novel inhibitory receptors and mediators of therapeutic response, enabling better biomarker discovery, patient stratification, and clinical outcomes.

Although not the focus of this review, we acknowledge that cost, lengthy vein-to-vein/surgery-to-vein times [374], ACT's reliance on autologous cells [375], toxicity [376, 377], and the limited availability of prognostic biomarkers

Table 3 Comparison of T cell immunotherapy approaches

	Advantages	Disadvantages	Ideal Scenario(s)
ICB	Off-the-shelf product	Requires endogenous tumour-reactive clones	Immunologically hot tumours
	Directly combats exhaustion	Cannot rescue terminally exhausted cells	High TMB Tumours
	Efficacious in solid tumours	Lacks comprehensive prognostic markers	
		Continuous treatment	
ACT (TIL/CAR-T/TCR-T)	Introduces antigen specificity	On-target off-tumour and off-target toxicity	Haematological malignancies
	MHC-independent T cell activity (CAR-T)	Limited capacity to infiltrate solid tumours	Tumours with a specific antigen
	Long-term immunity	Onset of exhaustion	Tumours without a suppressive TME
	Opportunity for additional engineering	Not off the shelf – costly and time consuming	Virus-driven tumours (CAR-T + TCR-T)
		Higher risk of antigen escape (CAR-T + TCR-T)	
Vaccination (Prophylactic/Therapeutic)	Prevents onset of cancer (prophylactic)	Predicting relevant future antigens is challenging	Preventing infection-associated cancers
	Can induce broad tumour-reactivity	Historically low efficacy	In conjunction with ICB (therapeutic)
	Negligible toxicity and side effects	Therapeutic vaccines are highly personal	Adjuvant treatment post-surgery
	Long-term immunity		

ICB: immune checkpoint blockade, TMB: tumour mutational burden, ACT: adoptive cell therapy, TIL: tumour infiltrating lymphocyte, CAR-T: chimeric antigen receptor T cells, TCR-T: T cell receptor transduced T cells

[378–380] remain major barriers to accessibility and efficacy. Each area is under active investigation, and addressing these, alongside the mechanistic challenges discussed above, will be essential to improve patient outcomes.

Translation of therapies from pre-clinical to clinical settings has often disappointed, in part due to models failing to reflect the time course, multicellularity, heterogeneity, and antigenicity of human cancer [381]. A shift towards multicellular human organoids [382], primary cancer cells, and immunocompetent models with de novo oncogenesis [383] is critical for improving translational success and accelerating drug development.

Trial design challenges have also led to the abandonment of promising agents due to poor therapeutic context or inappropriate endpoints. Despite insights into anti-PD-1 ICB highlighting the value of early intervention [137], trials often test new agents in late-stage, refractory patients. Here, the therapeutic window may have closed, and potential advantages in early-stage disease are missed.

Finally, clinical trials often lack a mechanistic framework for understanding therapeutic outcomes. The absence of longitudinal sampling limits our ability to determine why clinical endpoints are missed and identify biologically relevant, though clinically insufficient, responses. To fully realise T cell-based immunotherapy's potential, trials should include such analyses to rationally guide therapeutic combinations and disease contexts, and salvage insights from unsuccessful studies.

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