The Development and Future Prospects of Immunotherapy in Cancer Treatment

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Abstract

Immunotherapy has emerged as a novel, innovative, and promising approach to treating various advanced cancers. The advancement of cancer immunotherapy has revolutionised conventional cancer treatments by significantly reducing mortality rates and enhancing the quality of life for patients. This review highlights how the evolution of cancer immunotherapy history serves as groundwork for improvements integral to current standard medical practice. Furthermore, this review elaborates on the current drawbacks of different types of cancer immunotherapy and how further research in combination therapy, personalised tumour vaccines, cytokine involvement, tumour microenvironment, and glycosylation can be exploited to overcome these limitations.

Introduction

Immunotherapy has emerged as a promising approach for cancer intervention. It promotes a systemic and highly tolerable immune response with high tumour specificity and unrivalled tumour suppression efficacy compared to traditional treatment approaches.

In the 19th century, William B. Coley, an orthopaedic surgeon on bone sarcomas, observed erysipelas development leading to spontaneous regression in unresected tumours (McCarthy, 2006). In 1891, he developed “Coley’s toxin” derived from live, inactive *Streptococcus pyogenes* bacteria. The toxin was found to stimulate sepsis and to have a strong antitumor immune response. This led to the first established cancer immunotherapy achieving complete remissions in multiple malignancies. The mode of action of this toxin remains unelucidated until several decades after the findings of mediators involving cytokines: interleukins, interferons, and chemokines (Dinarello, 2007). High doses of interleukin 2 (IL-2) induce clinical remissions in metastatic renal cell carcinoma.

In the early 20th century, Paul Ehrlich proposed the immune system’s ability to distinguish between self and non-self antigens and protection against spontaneous cancer development (Ehrlich, 1909). Additionally, Burnet and Thomas elucidated the 'immune surveillance theory' on the involvement of T-cell immune checkpoints: CTLA-4 and PD-1. (Yuraszeck et al., 2017).

Generally, immunotherapies are limited by their immune-related adverse events (irAEs). Collectively, the above findings elevate the understanding of the fundamental antitumor immunity concept in currently practised immunotherapies. This review highlights the current approaches in cancer immunotherapies, their limitations, and future directions.

Types of Cancer Immunotherapy: Mechanism, Development, and Limitations

Currently, immunotherapy is categorised based on antigen specificities-dependent mechanisms that:

1) Modulate existing T-cell receptors using
    a) Immune checkpoint inhibitors (ICI), or
    b) Tumour vaccines,
2) Introduce new antigen specificities by using
    a) Chimeric antigen receptor (CAR)-T cells (stable), or
    b) Bispecific T-cell engaging (BiTE) antibody constructs (transient).

Immune Checkpoint Inhibitor (ICI)

Immune checkpoints, like CTLA-4 and PD-1 (on T cells) and PD-L1 (on tumour cells), are surface immune cell receptors regulating activation or inhibition of immune response elevating antitumor immunity. Blocking immune checkpoints induces tumour elimination (Figure. 1). Multiple ICIs have been developed and widely used in various cancer treatments as monoclonal antibodies (Table. 1).

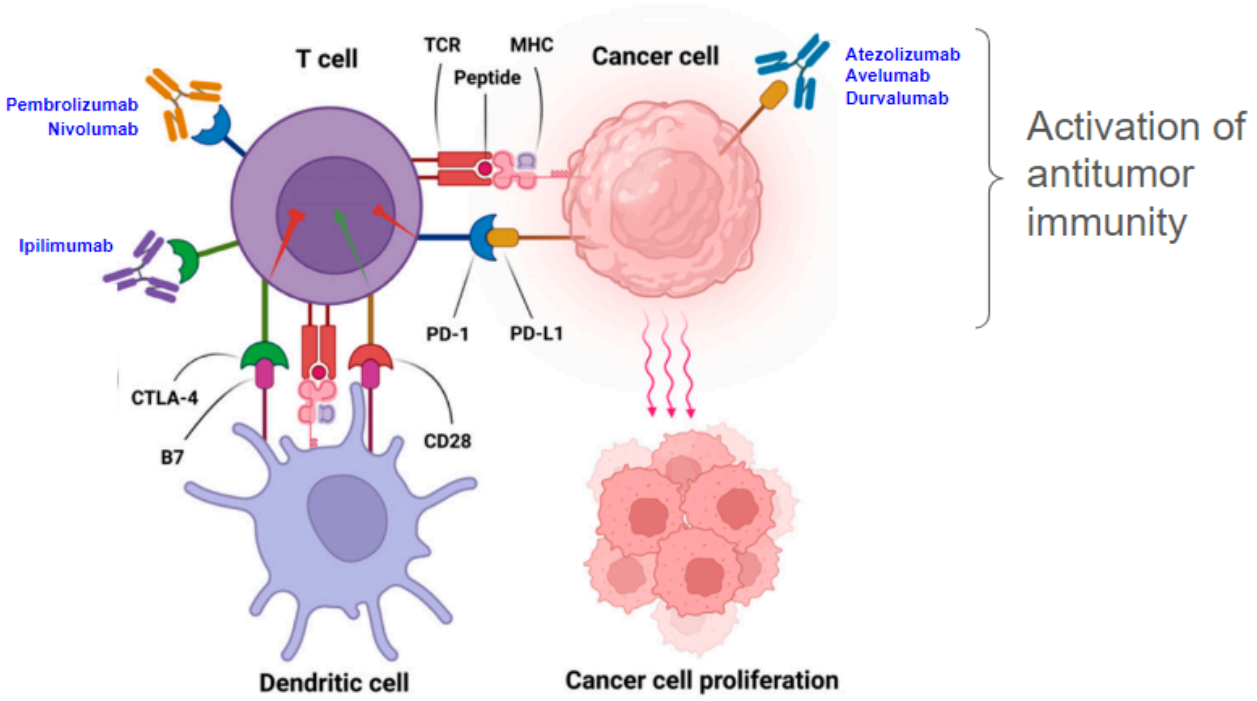

Figure 1. Mode of action of immune checkpoint inhibitors in antitumor immunity.
FDA-approved Immune checkpoint inhibitors (highlighted in blue texts). Pembrolizumab and Nivolumab (anti-PD-1 antibodies). Ipilimumab (anti-CTLA-4 antibody). Atezolizumab, Avelumab, and Durvalumab (anti-PD-L1 antibodies). The figure is adapted from Shiravand et al. (2022).

Table 1. Immune checkpoint inhibitors in Advanced-Stage Cancers treatment.

Inhibitors	Agents	Treatment of Advanced-Stage Cancers							
		NSCLC	Head and Neck	Urinary Tract	Melanoma	Hodgkin Lymphoma	Liver and Breast	RCC	MCC
CTLA-4	Ipilimumab	-	-	-	All lines	-	-	All lines	-
PD-1	Nivolumab	2nd line	2nd line	-	All lines	Post SC	-	2nd line	-
	Pembrolizumab	All lines	-	-	All lines	Post SC	-	-	-
Combination ICI therapy CTLA-4 + PD-1	Ipilimumab + Nivolumab	-	-	-	1st line	-	-	1st line	-
PD-L1	Atezolizumab	2nd line	-	2nd line	-	-	2nd line	-	-
	Avelumab	-	-	2nd line					2nd line
	Durvalumab	Post chemo-radio therapy stage III	-	-	-	-	-	-	-

NSCLC = non-small-cell lung cancer; Urinary Tract cancers involve renal pelvis, ureters, bladder, and urethra cancers; RCC = renal cell carcinoma; MCC = Merkel cell carcinoma; SC = autologous stem-cell transplantation; (-) no treatment. Obtained on 11 April 2024 from Cancer Research UK and Health Canada's Drug Product Database (https://www.cancerresearchuk.org/about-cancer/treatment/immunotherapy/types/checkpoint-inhibitors.html); (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html).

Another attempt to investigate the potential of various agonist and antagonist checkpoint inhibitors is currently being studied for their potency to induce tumour apoptosis (Table. 2). The drawback lies in their uneven clinical potential. For instance, with the same dose, the OX40 antibody gives promising results while the CD28 antibody leads to irAEs in healthy volunteers (Suntharalingam et al., 2006).

Cytokine modulation may act as a double-edged sword in ICI therapy by promoting tumour surveillance and acting as a mediator of autoimmunity. A study involving interleukin-17 antibody (secukinumab) treating psoriasis showed increased immunity but facilitated tumour escape (Esfahani and Miller, 2017). These opposing effects require further investigation and more clinical trials.

Further studies on ICI efficacy in tumour microenvironment (TME) showed that tumours exhibit the “Warburg effect” as part of its carcinogenesis hallmark, involving complex metabolic reprogramming and high glycolysis activity (Kareva and Hahnfeldt, 2013). Recent studies proposed the paradoxical effects of ICI in TME other than elevating antitumour immunity. CTLA-4 and PD-1 bindings inhibit glycolysis and reduce cytokine secretion in T cells, while PD-L1 binding increases glycolysis and lactate production to support tumour growth and metastasis in cancers (Patsoukis et al., 2015; Saunders et al., 2005; Wangpaichitr et al., 2017).

Additionally, the efficacy of ICI on TME led to the proposed “Immune contexture” concept, where tumours are categorised based on PD-L1 expression directly proportional to good ICI response: hot (high PD-L1 expression), and cold (low PD-L1 expression) (Fridman et al., 2017; Gajewski et al., 2017; Hegde et al., 2016). Converting cold tumours to hot tumours is an active area of research aiming to increase the potency of ICIs.

Table 2. Agonist, antagonist, and other pathways immune checkpoint modulators under research and development.

Category	Agents	Target	Clinical Phase
Agonist antibodies (costimulatory)	APX005M	CD40	I/II
	CP870893		I
	BMS-986178	OX40 (CD134)	I/II
	GSK3174998		I
	MEDI0562/6469/6383		I
	PF-0451860		I/II
	CDX-1127 (varlilumab)	CD27	I/II
	ARGX-110 (cusatuzumab)	CD70	I/II
	INCAGN01876	GITR (CD357)	I/II
	BMS-986156		I/II
	MK-4166		I
	TRX 518-001		I/II
	JTX-2011	ICOS (CD278)	I/II
	GSK3359609		I/II
	INBRX-105	4-1BB (CD137)	I
	Utomilumab		I
	Urelumab		I/II

Category	Agents	Target	Clinical Phase
Antagonist antibodies (co-inhibitory)	MEDI9447 (oleclumab)	CD73	I
	TTI-621	CD47	I
	Galunisertib	Transforming growth factor β	II
	M7824		I/II
	Ciforadenant	A2aR	I
	AB154	TIGIT	I/II
	MTIG7192A		II/III
	BMS-986207		I/II
	Tislelizumab		I/II/III
	Epacadostat	IDO-1,2	II
	Indoximod		II
	Lirilumab	KIR (2DLI-3)	I/II
	LAG525	LAG-3 (CD223)	I/II
	IMP321 (eftilagimod alpha)		II
	BMS-986016 (relatlimab)		I/II
	MEDI9447 (oleclumab)	TIM-3	I
	Sym023		I
	MBG453		I/II
	TSR-022		I
	8H9	B7-H3 (CD276)	I
	MGD009		I
	Mogamulizumab	CCR4 (CD194)	I/II
	CA-170	VISTA (B7-H5)	I

Category	Agents	Target	Clinical Phase
Other Pathways	AM0010 (pegilodecakin)	Interleukin 10	I/II
	LTX-315	Oncolytic Peptides	II
	CB-1158	Arginase Inhibitors	I/II
	THOR-707	Interleukin 2 receptor	I/II
	RO6874281		I/II
	NKTR-214		I/II/III
	CMP-001	Toll-like receptors	II
	Rintatolimod		II
	DSP-0509		I/II
	SD-101		I/II
	MGN1703 (lefitolimod)		I
	Poly-ICIC		I

Tumour vaccines

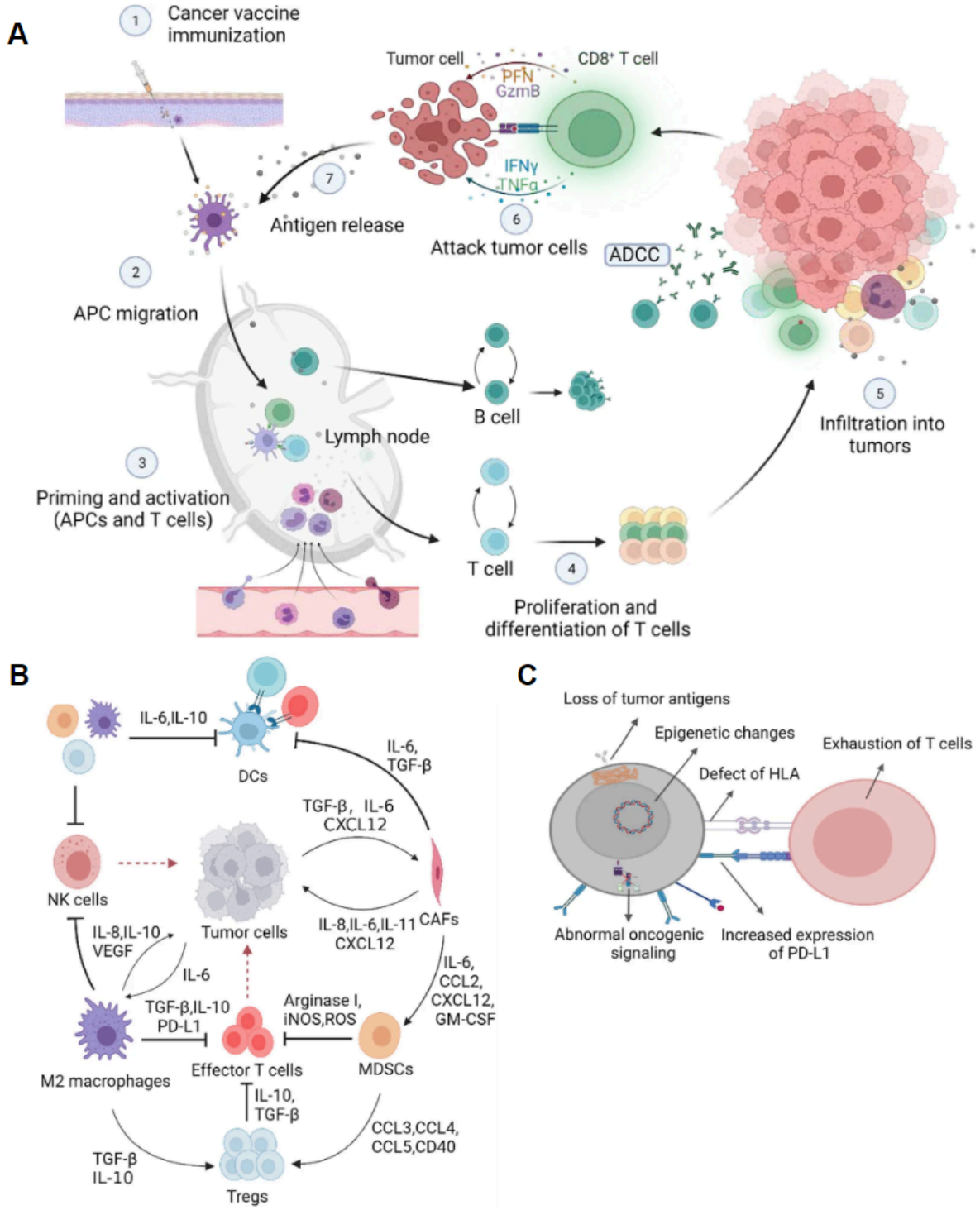

Figure 2. Tumour vaccines in immunotherapy

(A) Tumour-immune cycle during the mode of action of tumour vaccines involving tumour antigen recognition by DCs uptake and presentation to MHC II or MHC I. This leads to the formation of memory B cells and plasma cells promoting apoptosis via ADCC and differentiation into memory T cells and effector T cells respectively. Subsequently, effector T cells localised to TME by stimulating apoptosis or eliminating tumour cells directly. Further responses in the following cycles are enhanced by TAAs released from immunogenic dead tumour cells.

(B) Tumour external resistance. Effector T cells and DC-mediated T cells activation in the TME are inhibited by immunosuppressive cells: cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), T regulatory cells (Tregs), M2 macrophages, and immunosuppressive cytokines.

(C) Tumour intrinsic resistance involving different aspects was noted. The figure is adapted from Liu et al. (2022).

Tumour vaccine is another antigen-specific immunotherapy approach which uses tumour antigens to induce antitumour immunity: humoral and cellular, overcoming immunosuppression (Figure. 2A). Current therapeutic tumour vaccines are classified into cells (tumours and DCs), protein, peptide, DNA, mRNA, and viral vaccines based on their approaches and purposes, each with their advantages and disadvantages (Table. 3). Current approved vaccines and those in clinical trials are mentioned (Table. 3) (Liu et al., 2022).

The efficiency of tumour vaccines is limited by two resistance mechanisms leading to the tumour's immune escape (Figure. 2B and C). Extrinsic resistance, caused by upregulation of immunosuppressive cytokines and receptors, and inhibition of dendritic cell (DC) function leads to remodelled extracellular matrix (ECM) in TME, favoring pro-tumourigenesis M2 macrophage. Meanwhile, intrinsic resistance by mutations leads to TAA-downregulated expression and poor T-cell recognition. Currently, tumour vaccines focusing on overcoming resistance implications stated above are in development.

Table 3. List of different tumour vaccine approaches available in current immunotherapy.

Vaccine approach	Aims	Advantages	Disadvantages	Vaccine products
Cellular (tumour cells and dendritic cells)	Tumour vaccines utilises inactivated cancer cells and mixed with an immunostimulant adjuvants. Meanwhile, dendritic vaccines presents TAAs to dendritic cells, then treated with immunostimulatory adjuvants.	Presents a wide range of TAAs, highly immunogenic, stimulates unique antitumour immunity.	Efficacy requires bulk tumours, time and resource intensive.	**GVAX** (prostate cancer)
Peptide	Introduce proteins/peptides to patients triggers an immune response against TAAs, which are distinctive or abundantly expressed on tumour cells.	Stimulates peptide-specific antitumour immunity response, safe, inexpensive.	Specific to small HLA types, only several clas II epitopes known.	****DSP-7888** (acute leukemia); **SurVaxM** (glioblastoma).
Protein		Appropriate for all HLA types, has both class I and II epitopes.	Requires adjuvant to have good sufficient immunogenicity, difficulty in obtaining pure protein.	**CIMAVAX EGF** (non-small cell lung cancer)
DNA	Deliver genetic materials to stimulate the production of TAAs through translation.	Inexpensive, safe, unlimited to size of cDNA	Low vaccine uptake efficiency.	*****VGX-3100** (HPV); ****GX-188E** (cervix cancer)
mRNA		Able to be produced in a large scale		****TriMix** (melanoma)
Viral	Induces virus-specific MHCs on host cells	Efficient gene transfer		**Talimogene laherparepvec (T-VEC**: melanoma)

Vaccines currently in clinical trial phase II (**), phase III (***).

(CAR)-T cells antibody

CARs are T-cell-engineered receptor proteins derived from monoclonal antibodies enabling diverse, high-specificity, and cytolytic T-cell efficacy on tumour antigens. However, overcoming tumour-induced MHC expression downregulation leads to tumour escape (June et al., 2018). Over the years, CAR-T cells have been through several optimisation designs (Figure. 3).

First-generation CAR-T cells were designed to imitate TCR function. However, studies revealed paradoxical effects: *in vitro* antigen-specific cytotoxic stimulation but weak cytokine secretion with minimal clinical benefits and persistence (Gong et al., 1999; Jensen et al., 2010).

Second-generation CAR-T cells integrated costimulatory domains like CD137/CD28 to increase T-cell persistence. Studies revealed elevated efficiency in antitumour immunity *in vitro* and cytokine secretion and persistence with significant clinical benefits *in vivo*. However, different costimulatory domains were reported to have contrasting impacts on T-cell function leading to irAEs (Davila et al., 2013; Maude et al., 2014).

Third-generation CAR-T cells utilised synergistic effects of two costimulatory domains in one CAR (CD137/CD28 and 4-1BB): T-cell function and signalling capacity. Studies revealed enhanced *in vivo* CAR-T cell antitumour function and persistence with increased clinical cytokine secretion (Zhao et al., 2015);(George et al., 2020), although patient responses in solid tumours were unconvincing.

Eventually, Armoured and Next-generation CAR-T cells were constructed for cytokine-mediated tumour killing to surpass immunosuppressive TME (Hawkins et al., 2021). However convincing, current clinical trials are limited to a small testing size.

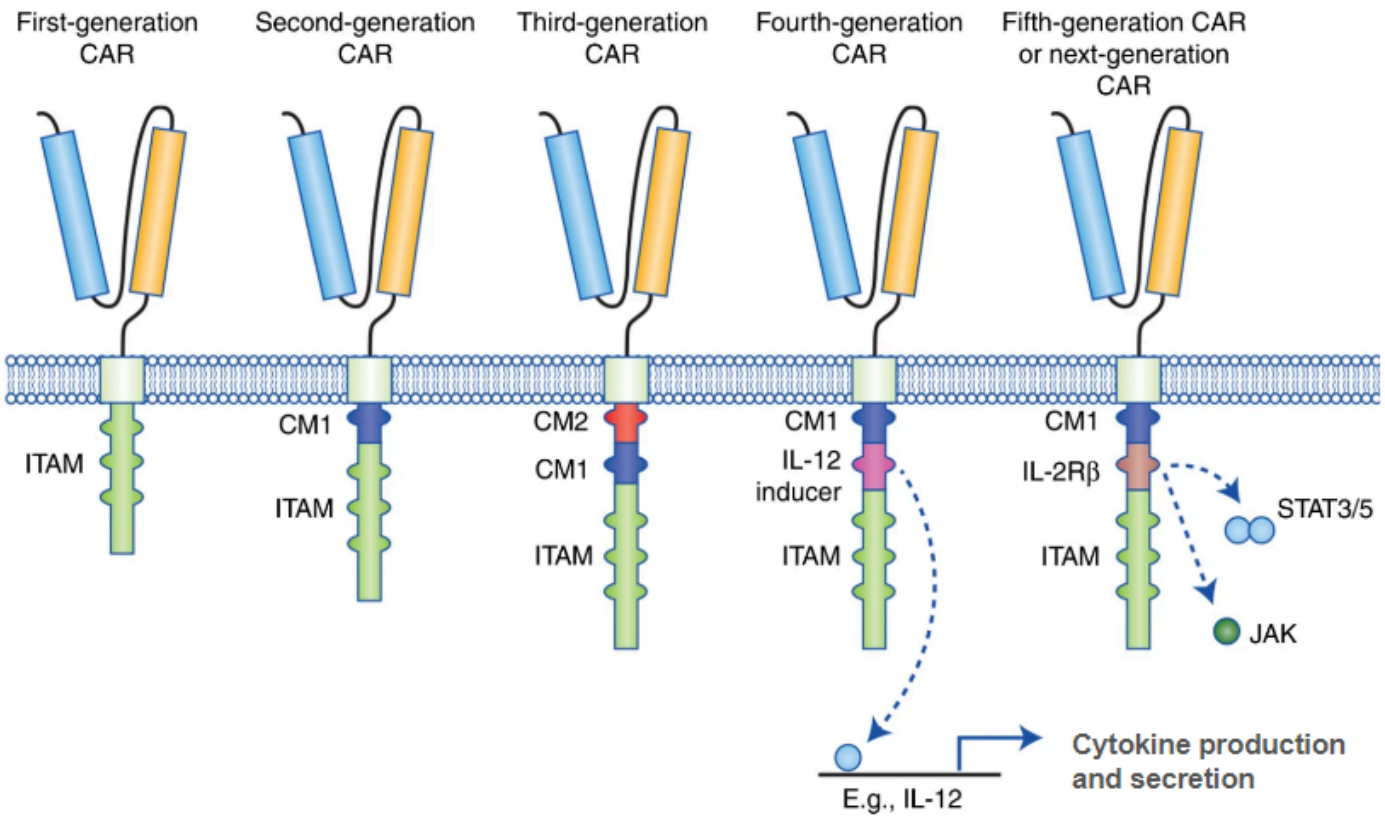

Figure 3. The evolution of CAR-T cells antibody.
Immunoreceptor tyrosine-based activation motif (ITAM). Co-stimulatory domain such as CD137/CD28 (CM1), Co-stimulatory domain 4-1BB (CM2). Interleukin-12 (IL-12). Interleukin-2Rβ (IL-2Rβ).

Like other immunotherapies, CAR-T cells have several limitations: toxicity and solid tumour efficacy. Post-CAR-T cell therapy may lead to high cytokine secretion described as cytokine release syndrome (CRS) stimulated by tumour burden, antigen-binding domain affinity, and antigen density (Minagawa and Di Stasi, 2016). Strategies for CRS severity reduction were proposed: (i) gradually increasing multiple CAR-T cell reinfusion and doses; (ii) using immunosuppressive drugs. However, immunosuppressive drugs decrease the efficiency of CAR-T cells, forcing alternatives like IL-1B and TNF-a inhibitors to reduce toxicity (Lee et al., 2014; Giavridis et al., 2018; Mahadeo et al., 2019). In addition to CRS, neurotoxicity was observed but its mechanism remains unknown. Clinical symptoms are reversible and self-improvable. However, in severe cases, IL-6 inhibitors can be utilised (Acharya et al., 2019).

Specific to solid tumours, its major problem lies in tumour-specific antigens (TSAs) recognition. A close breakthrough in anti-EGFRvIII CAR-T cell glioblastoma treatment reported no off-tumour toxicity or CRS, highlighting the success of CAR-T cell solid tumour treatment (Ruella and Levine, 2016). However, it was ruled an inappropriate approach as most TSAs are located intracellularly and have HLA-dependent immunogenicity, while CAR-T cells are surface recognition-engineered and HLA-independent (Wei et al., 2019).

Another approach focused on TME-derived antigens, predominantly cancer-associated fibroblasts (CAF) critical to immunosuppressive TME, cancer hallmarks, and cytokine secretion like VEGF. A xenograft tumour study revealed that CAR-T cells targeting VEGFR-1 exhibit reduced tumour growth and metastasis suppression (Lanitis et al., 2015). Moreover, complications in the trafficking and penetration of CAR-T cells through solid tumour extracellular matrix (ECM) remain unsolved (Zhang et al., 2018). Target site navigation is tumour- or stromal-secreted-chemokines-dependent. CAR-T cells are engineered with chemokine receptors to increase their sensitivity. Yet, drawbacks to CAR-T cell reduced efficiency can occur from: (i) chemokine loss-induced immune escape, and (ii) chemokine gradient production from inflammation in other organs. Hence, novel solutions counteracting heterogeneity are crucial.

BiTE® antibody

BiTE® antibodies are small, flexible 50-60 kDa fusion proteins, linking two single-chain antibodies between CD3ε T-cell receptors and antigens on target cells to induce T-cell activation and target cell lysis (Figure. 4). This mechanism bypasses the need for cancer-specific MHC I peptide complex recognition (Offner et al., 2006). This suggests a reduction in tumour-induced immune evasion. Further BiTE® investigation leads to engineered cell lines, expressing pro-tumour immune evasion proteins: PD-L1, Bcl-2, and IL-10 (Deisting et al., 2015). Results showed positive tumour lysis without tumour resistance, elevating the potential of BiTE® antibodies in cancer treatment.

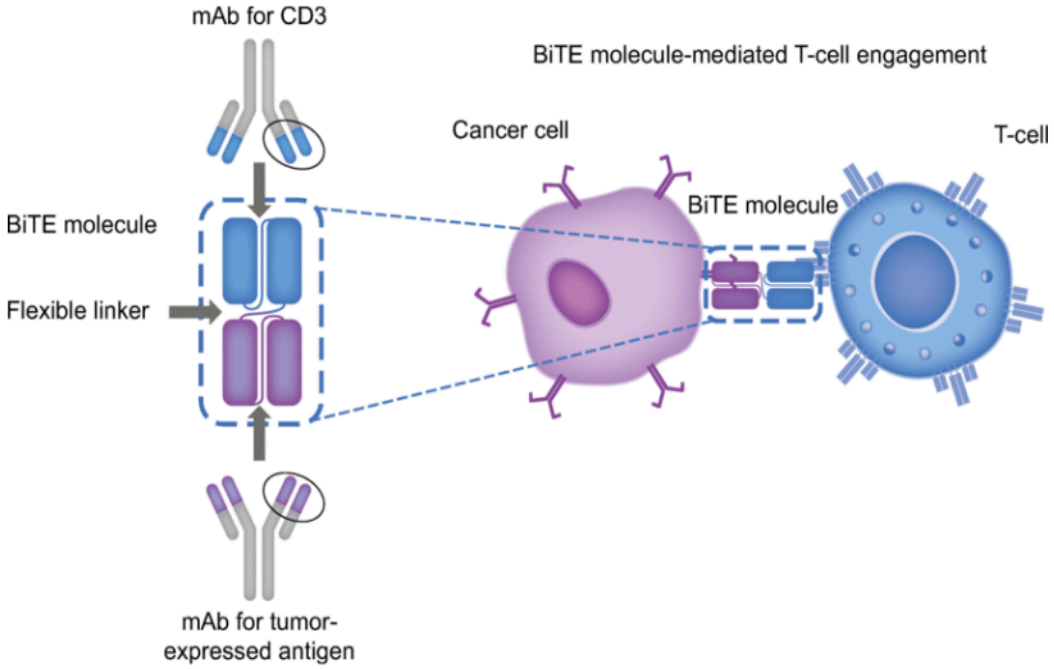

Figure 4. The mechanism of the BiTE® antibody.
Illustration of transient genetic modification. Monoclonal antibody (mAb). Adapted from Viardot et al. (2020).

In 2014, Blinatumomab (55 kDa), the first BiTE® antibody was FDA-approved after successful Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia (R/R ALL) treatment (Przepiorka et al., 2015). Blinatumomab is a high-potency drug with a response rate of 42.9% in R/R ALL patients. Clinical trial results showed its ability to transiently elevate cytokine levels and link T-cells-target cells to stimulate T-cell activation and proliferation. However, the efficacy of Blinatumomab is inversely proportional to leukaemia levels. Its low sensitivity in bulk tumours indicates its limitation in an effector-to-target ratio.

To this day, the relationship between leukaemia levels and T-cell effector function alongside the resistance mechanism of Blinatumomab remains a hot pursuit. BiTE® antibodies sharing similar characteristics to Blinatumomab are currently tested in clinical trials (Table. 4).

Table 4. Several Bispecific T cell-engaging antibody currently in clinical development as anticancer agents.

Agents	Linking Targets	Clinical Phase	Target Cancers
MEDI-565/MT 111	CEA X CD3	I	Gastrointestinal adenocarcinoma
AMG 330	CD33 X CD3	I	AML
AMG 211/MT 211	CEA X CD3	I	Gastrointestinal cancer
AMG-212/BAY-2010112/MT-112	PSMA (FOLH1)/CD3	I	Prostate Cancer
AMG 420	BCMA X CD3	I	Multiple myeloma
AMG 110/MT 110	EPCAM X CD3	Unknown	Solid Tumors

Altogether, all of the mentioned current immunotherapy approaches exhibit particular benefits and drawbacks to intervening in cancer progression, as summarised in Table 5.

Table 5. Summary of immunotherapy approaches, their benefits and limitations.

Immunotherapy approaches	Advantages	Disadvantages
Immune Checkpoint Inhibitors (ICIs)	Specific; sensitive; has high potential in combination therapy.	Low response rates; likely to generate systemic toxicity.
Tumour Vaccines	Specific; has the potential to be personalised.	Potential of rejection by host due to administration of foreign antigens.
CAR-T cells	Overcomes tumor MHC downregulation; able to recognise various TSAs; able to produce large tumor-specific cells in short period of time.	Targets only surface antigens; lethal toxicity due to CRS.
BITE® antibodies	MHC independent; readily metabolised *in vivo*.	Efficacy is inversely proportional to tumor levels.

Future Directions

Despite convincing clinical results, the effects of currently approved FDA ICIs need to be further investigated to overcome irAEs and resistance, stressing cytokines and TME involvement. In the future, cancer immunotherapy can rely on ICI and personalised cancer vaccine combination therapies or targeted therapies on TME and glycosylation. This will lead to a more durable and potent therapy specifically paired with the host.

A better strategy for developing CAR-T cell pharmacokinetics improving its trafficking, overcoming immunosuppressive TME, improving efficacy, and recognising true tumour-specific targets needs further investigation. Promising targets for CAR-T cell therapy lie in receptors involved in T-cell adhesion, vascular adhesion, and T lymphocyte extravasation into tissues such as VCAM (Adusumilli et al., 2019), L-selectin (Yoon et al., 2018) and ICAM (D'Aloia et al., 2018).

Engineering ECM modifying enzymes on CAR-T cells may aid T-cell infiltration, as fibrotic ECM may pose physical barriers. A study on heparinase positively reflects heparan sulfate proteoglycans degradation favoring CAR-T cell infiltration (Caruana et al., 2015). An alternative approach using nanobodies-based CAR-T cells reported the ability to penetrate solid tumours and the blood-brain barrier and recognise markers inaccessible by large antibodies (Xie et al., 2019). Using nanobodies might expand the future scale of CAR-T cell immunotherapy, elevating its efficacy further.

Specific to the BiTE® antibody, it's crucial to delve into the mechanism underlying the lack of response in 57.1% of R/R ALL patients treated with Blinatumomab (Przepiorka et al., 2015). There is great interest in observing whether BiTE® antibody constructs can increase the delivery of functional T cells to solid tumours.

Combination Therapy

To increase potency and efficacy, combination ICI therapy (CTLA-4 and PD-1 inhibitor) was meta-analysed in advanced tumours, showing an increase in patient survival but also an increase in irAEs (Hodi et al., 2018; Wang et al., 2018). However, the challenge remains in developing optimised ICI combined therapy to stimulate antitumour immunity with low irAEs.

Multiple ongoing trials are conducted on ICI-vaccination strategy to sensitise tumours before ICI treatment with promising outcomes. However, anti-PD1 antibodies administration before vaccination reported adverse T-cell functionality effects (Verma et al., 2019). Further studies are required to determine the optimal ICI-vaccination stage, highlighting the importance of order and timing of treatment.

Bi-cistronic genes engineered against different antigens, containing CAR and BiTE® transferred to T cells, enable CAR expression and BiTE® secretion, providing the multi-targeting ability useful in targeting heterogeneous solid tumours to overcome immune escape. CAR-T:BiTEs® were developed for glioblastoma treatment (Sakemura et al., 2016). This success sparks a potential interest in CAR-T:BiTEs® as a future approach to intervene in cancer progression.

Concluding Remarks

Immunotherapy has dramatically elevated cancer treatment and patient survival rates. Despite rapid advances, the frontier of immunotherapy in cancer treatment remains delicate with multiple hurdles to overcome: subjective treatments with few responses, clinical toxicity, and challenging-to-optimise combination therapies. Therefore, more predictors and new strategies need to be employed to improve existing approaches limiting irAEs and resistance. The future of immunotherapy lies in better TAA recognition, more efficient trafficking, and overcoming TME immunosuppression.

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