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REVIEW ARTICLE

Immunotherapy in cancer: Where we are and what the future brings?

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ABSTRACT

Chemotherapy, radiotherapy, and surgery are recognized as the main treatment modalities for cancer. These therapeutic strategies may be effective in the early stages of the disease but are usually ineffective in advanced stages or when the cancer recurs. Recently, great efforts have been made to understand the complex interaction between the immune system and its surveillance of cancer and to find effective immunotherapies for all stages of cancer. Several types of immunotherapies, including adoptive immunotherapy, cancer vaccines, and immune checkpoint blockades, are receiving considerable attention. The clinical relevance of T lymphocytes and NK cells in combating carcinomas is beyond doubt, but their mechanism of tumor surveillance is far from being fully understood. In this review, much attention has been paid to the complex interplay between T lymphocytes, NK cells, and cancer cells and their role in immunotherapy. Moreover, in this review, we summarized the current data on cancer immunotherapies, especially cancer vaccines, T- and NK cell-based immunotherapies. In addition, we highlighted the role of biomarkers as important indicators of response to immunotherapy, as well as potential problems and solutions related to immunotherapy. Insights into the future of immunotherapy are also presented in this review.

Keywords: biomarkers; cancer; immune checkpoint inhibitors; immunotherapy

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1. Introduction

Cancer is a complex disease characterized by abnormal and altered immune response and excessive proliferation of malignanT-cells. It can be caused by various factors known as carcinogens, which can be either genetic (like BRCA1 and BRCA2 genes) or environmental (like UV radiation, tobacco smoke, and some specific viruses and bacteria). About 19.3 million newly diagnosed cancer cases and about 10 million cancer-related deaths around the world were reported in 2020[1]. The leading cancer diagnosis in both women and men was lung cancer which was followed by prostate cancer in the male population and breast cancer in females. It is important to mention that according to statistics these three cancer diagnoses make up over one-third of all cancer diagnoses around the world. As one of the leading causes of mortality worldwide, emphasizes the need for early detection and monitoring as well as the most effective, long-term treatments[2].

Chemotherapy, radiotherapy, and surgery are three types of well-known cancer treatment approaches that have been created so far. They either target tumour cells directly or try to neutralize them. These therapies were shown to be effective in the treatment of early-stage cancers, but they are most often useless when it comes to advanced-stage or recurrent cancer. Tumours microenvironment has become the focus of the newest research due to its role in creating efficient options for further cancer treatment. The use of substances to restore and/or strengthen the immune system's capacity to prevent and treat illness is known as immunotherapy (**Figure 1**). Adoptive immunotherapy, anti-cancer vaccines and immune checkpoints blockades (ICBs) are some of the immunotherapy techniques that can be used alone or in combination with other cancer treatment options[3]. Immunotherapy made both overcoming the immune evasion mechanism and reactivating the body's immune system possible. One of the significant advancements is the introduction and application of immune checkpoints like programmed cell death PD-1/PD-L1 and anti-lymphocyte-associated antigen 4 (CTLA-4) antibodies in cancer therapy. Adoptive cell transfer and immune checkpoint inhibitors are two methods that have shown great efficacy in inducing the long-term remission of therapy-resistant malignancies. Additionally, new immunotherapy methods like chimeric antigen receptor CAR-T, CAR-M as well as combinations of immunotherapy with other cancer treatments like radiotherapy and chemotherapy have emerged ushering in a new age of cancer treatment[1].

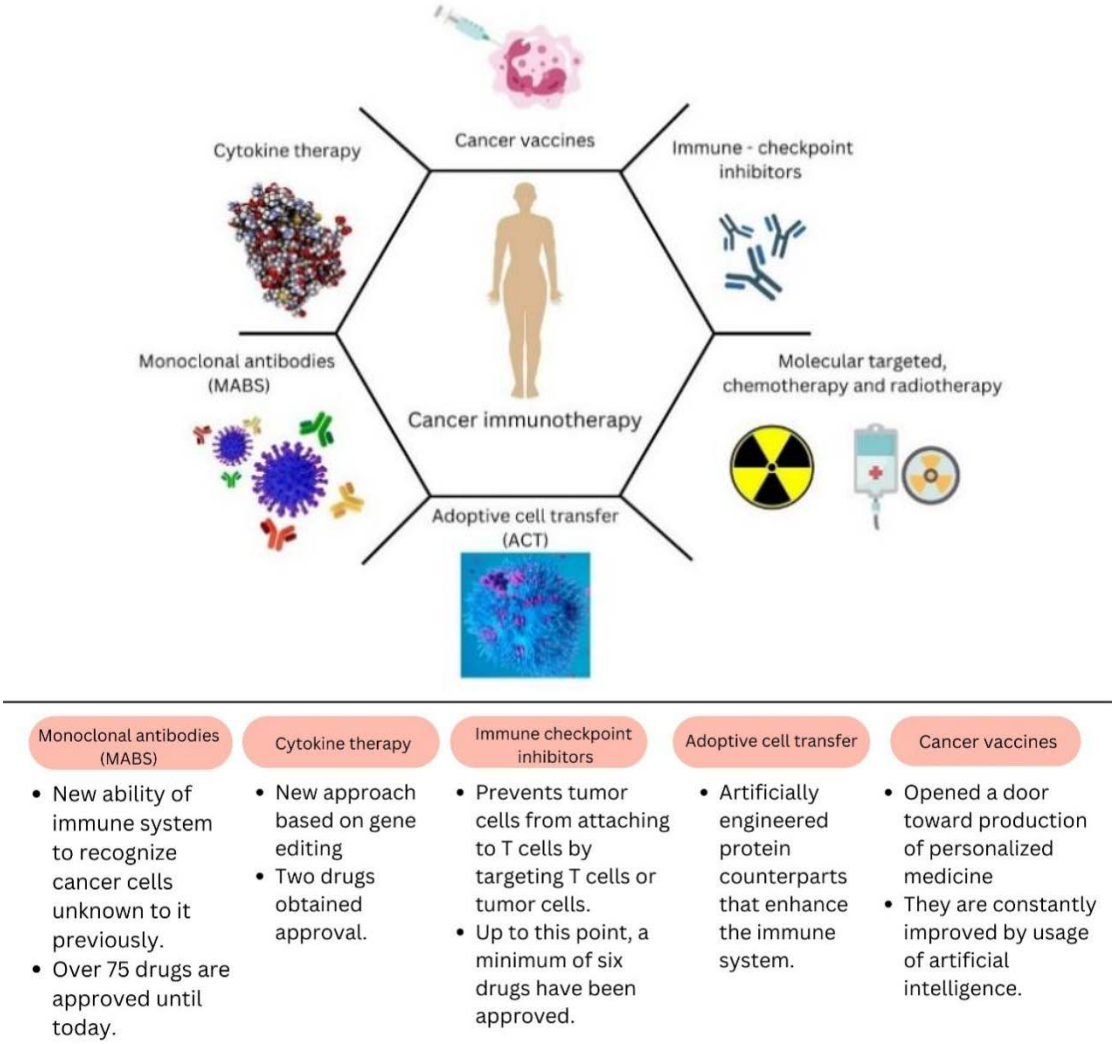

Figure 1. Types of immunotherapies.

2. History and background of cancer immunoediting and cancer immunotherapy

Understanding the relationship between the immune system and cancer cells is necessary to comprehend how immunotherapy has emerged as a key component of cancer treatment. While there are many distinct forms of immunotherapies, they all work by using the host immune system to fight against tumour cells[4]. The first grounds for immunotherapy were set in 1796, when Edward Jenner created the first effective vaccine against smallpox[5,6]. Future of immunotherapy was continued in 1891, when the "father of immunotherapy" Dr. William B. Coley, an orthopaedic surgeon at New York Memorial Hospital, started looking for an alternative method for surgery in the treatment of sarcoma. The whole hypothesis and research were based on findings indicating that people with infectious diseases had a low incidence of cancer, so he injected a mixture of live and inactivated *Streptococcus pyogenes* and *Serratia marcescens*[7]. Patients with a range of cancers like lymphoma, sarcoma, and testicular cancer went into lasting or/and full remission[8]. In 1974, a turning point moment in modern tumour immunotherapy was set by applying interleukin (IL)-2 in the cancer therapy process[9]. This method triggered numerous strategies associated with cytokine application in immune response stimulation in cancer patients in the 1980s[10]. In 1986, after the CD28 molecule was detected in active T-cells, it was shown to be essential for T-cell activation coupled with T-cell receptor (TCR)[11]. At about the same time, cytotoxic T CTLA-4 was discovered and recognized to have a role in T-cell activation. Later research disclosed a negative correlation between CTLA-4 and T-cell immune response[12]. That knowledge was particularly important because in 2011 was listed first immune checkpoint inhibitor drug for melanoma treatment, known as ipilimumab, a CTLA-4 targeting antibody[13]. Simultaneously, PD-1 was found to be associated with the immune-suppressive effect[14]. In 1999, scientific research revealed that PD-1 is a receptor for the PD-L1 molecule, formerly known as B7-H1, which is proven to be expressed on tumour tissue and serves as an apoptosis-promoting molecule of tumour-specific T-cells[15,16]. Targeting the PD-1/PD-L1 pathway became an adverse drug-developing process and led to substantial influence on cancer therapy. Observing graft-versus-leukaemia effects in bone marrow transplants led to the development of cellular immunotherapy[17]. In 1989, the first Chimeric antigen receptor (CAR) strategy emerged[18]. Second-generation CARs with costimulatory domains presented good responses against B-cell type malignancies[19]. The initial CAR-T therapy was authorized by FDA in 2017 and since then become applied in the treatment of leukaemia, myeloma and lymphoma[20–22]. (**Figure 2**). In 2022, there were over 1000 registered studies about CAR-T's influence on different cancer treatments.

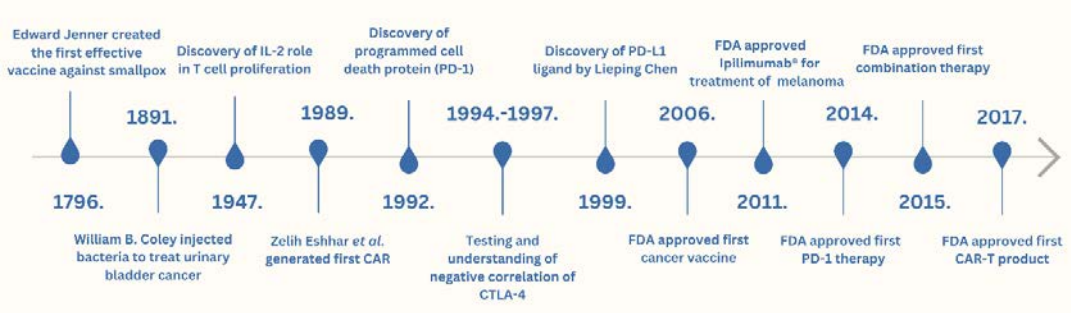

Figure 2. Immunotherapy breakthroughs through history.

Normal body cells' development, maturation and death are controlled by genes[23,24]. Each cell experiences about 20,000 DNA-damaging events, which are then mended by DNA repair mechanisms daily. In situations where cells are no longer needed, or unrepairable and present potential harm to the organism, programmed cell death—apoptosis occurs. Unchecked cell growth and proliferation that invades healthy tissue and spread throughout the body is a defining feature of cancer cells[25,26]. For decades, immune system destruction by

cancer has been studied[27]. The 1990s' were the onset of ideas and hypotheses of connections between cancer and the immune system, but lack of technology and physical evidence prolonged and delayed discoveries. In 1909, it was recognized that tumours could be controlled by the immune system[28,29]. Fifty years later, in 1957, a hypothesis of cancer immunosurveillance was set, which was showing lymphocytes as guards of the immune system that can mutate and differ from healthy cells. Once more, the research movement started in the middle of the 1970s with a focus on cancer immunosurveillance. The discovery of natural killer (NK) cells caused large enthusiasm until researchers were unable to precisely define and understand NK cells. Retrospectively, all further research brought science one more step closer to understanding cancer and its nature and "immunoediting" became more popular since it encompasses all stages of interactions outside immunosurveillance between the immune system and cancer[30].

3. Tools for immunotherapy development

The emergence of clustered regularly interspaced short palindromic repeat (CRISPR) genome editing, combined with advancements in computing and imaging technologies, has ushered in a new era where genetic diseases and individual susceptibility to diseases can be predicted and addressed[31].

The advancement of CRISPR/Cas9 technology has significantly advanced our knowledge of tumour genomics and played a crucial role in cancer immunotherapy. Therapeutic immune cells can be altered using this genome editing technology to improve their capacity to recognize cancers and lessen cell exhaustion[32,33]. In order to prove the safety of CRISPR editing in T-cells, the first clinical research utilizing these cells was launched in China in 2016. In further research, it was shown that non-small cell lung cancer (NSCLC) resistant to radiation and chemotherapy might be treated by using CRISPR to eliminate PD-1 in T-cells[34]. This breakthrough opened up possibilities for combining CRISPR technology with other T-cell modification approaches. Additionally, CRISPR-mediated deletion of TCRs and PD-1 in NY-ESO-1 TCR-T-cell therapy represents the first clinical application of tumour-specific T-cells with further genetic modifications[35]. The CRISPR gene editing system also enables the broader use of allogeneic T-cell therapy by depleting endogenous TCRs and HLA molecules, minimizing the risk of rejection and graft-versus-host disease. Moreover, CRISPR-mediated screening systems have been a tool in clinical studies to identify targets that enhance T-cell cytotoxicity against tumour cells. These screenings have also identified critical factors in therapeutic immune cells, such as CAR-T-cells, in order to improve cellular immunotherapy in future research[1].

4. Immune checkpoint therapy

4.1. Programmed cell death protein (PD-1)

Various immune cells like activated T-cells, NK cells, B-cells and myeloid lineage cells on their surface express a checkpoint receptor called PD-1. Its natural ligand PD-L1 may be expressed in a wide range of both immunological and non-immunological cells but it is also usually expressed in tumour cells, tumor-infiltrating cells and antigen-presenting cells (APC) causing various biological effects[27]. PD-1 is a known suppressor of T-cell proliferation, cytokine production and immune function by inhibition of CD28 mediated cellular metabolism, TCR signaling and induced T-cell co-stimulator signaling (ICOS). PD-1 is thought to inhibit T-cell immunological activities in a cross periphery during the later stage of immune reactions[36,37].

According to research, PD-1 and PD-L1 are potential biomarkers for cancer treatment, they are closely linked to the development of human cancer and are effective in predicting the sensitivity of PD-1/PD-L1 inhibitors[24]. Anti-PD-1/PD-L1 drugs are known as "immune normalizers" that lead to the normalization of T-cell immunity but can also result in consequential immune-related adverse events (irAEs)[25]. Recent research proved that major histocompatibility complex (MHC)-I and MHC-II were necessary for tumour antigen presentation and immunity surveillance. Studies also showed that MHC-II and PD-L1 interact to affect PD-

1/PD-L1 immune checkpoint inhibitor therapy in terms of its expression and effect. Additionally, it is considered that the interplay of PD-1 and PD-L1 is one of the main mechanisms of how tumours successfully avoid hosts' immune systems. The results of numerous clinical trials in recent years have shown that PD-1/PD-L1 antibodies have a promising role in the therapeutic approach of cancer treatment in many segments such as life expectancy, objective response rate (ORR), and medium of progression-free survival[38,39].

It's important to note that PD-1/PD-L1 immune checkpoint inhibitors have the role of immunomodulatory drugs and can stop some tumour facilitation and proliferation while leading to immune injuries of normal body tissue but some types of tumour cells facilitate the proliferation without involvement of adaptive immunity by expressing intrinsic PD-1 form[40]. Moreover, PD-1 checkpoint inhibitors can stop intrinsic PD-1 and PD-L1 binding, which is followed by recognition and restored killing effect of immune cells, which results in blockage of tumours' escape from the immune system and consequently tumour proliferation[41].

4.2. T-cell immunoreceptor with Ig and ITIM domains (TIGIT)

TIGIT (T-cell immunoreceptor with Ig and ITIM domains) has gained considerable attention in the field of cancer immunotherapy due to its emerging role as a potential target for immune modulation. Over the past three years, numerous studies have provided valuable insights into the functional significance of TIGIT in cancer and its therapeutic implications due to its central role in limiting anti-tumor responses, and its potential for safer and fewer immune-related adverse effects compared to other immune checkpoint inhibitors. TIGIT is an inhibitory receptor expressed on various immune cells, including T-cells, natural killer (NK) cells, and regulatory T-cells (Tregs). Its ligands, CD155 and CD112, are expressed on antigen-presenting cells and tumor cells. Engagement of TIGIT with its ligands leads to the suppression of immune responses, facilitating immune evasion by tumor cells. TIGIT interacts with three ligands, CD155, CD112, and CD113, which belong to the nectin and NECL family of molecules. CD155 serves as the primary ligand for TIGIT in both humans and mice, while CD112 and CD113 exhibit lower affinity binding. CD155 is expressed in various immune cells such as dendritic cells, T-cells, B-cells, and macrophages, as well as non-hematopoietic tissues including the kidney, nervous system, and intestines. CD112 has a wide expression in both hematopoietic and non-hematopoietic tissues, while CD113 is restricted to non-hematopoietic tissues. Notably, CD155 and CD112 are overexpressed in many human malignancies, often influenced by factors like oncogene expression or cytokine stimulation such as interferon-gamma[42].

DNAM-1 and CD96 also interact with CD155 but with different affinities. TIGIT exhibits the highest affinity binding to CD155, followed by CD96 and then DNAM-1. This relationship between the receptors mirrors the competition observed in the CTLA-4/CD28 pathway, where the inhibitory receptor with higher affinity competes with the activating receptor with lower affinity for the same ligands, thereby fine-tuning immune responses. However, the TIGIT/CD96/DNAM-1 pathway is even more intricate, as TIGIT and DNAM-1 also share CD112 as a ligand. Additionally, CD112R (PVRIG), a recently discovered immune checkpoint receptor expressed mainly in T-cells and NK cells, competes with DNAM-1 and TIGIT for the binding of CD112, further adding complexity to this pathway[43,44].

Researchers are exploring combination therapies, including dual immune checkpoint inhibitor (ICI) therapy, to enhance the anti-tumor immune response, expand the treatment response, and overcome resistance to PD-1/PD-L1 blockades[45,46]. Recent studies have highlighted the complex role of TIGIT in cancer immune regulation. TIGIT expression has been found to be upregulated in tumor-infiltrating lymphocytes (TILs) and associated with T-cell exhaustion and dysfunction. TIGIT-expressing TILs exhibit reduced effector functions and impaired cytotoxicity, promoting tumor immune escape[47]. Its association with T-cell exhaustion and immunosuppression throughout the cancer immunity cycle and the combined inhibition of TIGIT and PD-1/PD-L1 has been shown to enhance anti-tumor immune responses and improve treatment outcomes in

preclinical and clinical investigations[48–50]. Furthermore, TIGIT expression on NK cells and Tregs contributes to immune suppression and tumor progression. DNAM-1, TIGIT, and CD96 are present in both T-cells and NK cells, and they interact with CD155, which serves as a ligand for these receptors and is also known as poliovirus receptors (PVR) or NECL-5[51].

TIGIT is a member of the expanding family of PVR-like proteins. Its discovery in 2009 was the result of genome-wide analysis conducted by three independent research groups aiming to identify proteins with characteristic domain structures found in immunomodulatory receptors[49,50]. TIGIT is composed of an extracellular immunoglobulin variable domain, a type I transmembrane domain, and a short intracellular domain containing an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoglobulin tyrosine tail (ITT)-like motif. The immunoglobulin variable domain of TIGIT shares sequence similarity with other members of the PVR-like family, such as DNAM-1, CD96, CD155, CD111, CD112, CD113, and PVRL4[52]. Human TIGIT exhibits 58% sequence homology with its mouse counterpart, and the cytoplasmic tail of TIGIT containing the ITIM sequence is identical between mice and humans. While TIGIT expression is typically low in naive cells, it can be up-regulated upon activation in both T-cells and NK cells. As a result, TIGIT is most prominently expressed in Tregs, memory, and activated T-cells, as well as NK cells, in naive mice and healthy individuals[53].

4.2.1. TIGIT inhibition in T-cells and NK cells

NK cells and T-cells play crucial roles in anti-tumor immunity, with NK cells serving as key effectors of innate immunity and T-cells driving adaptive immune responses. Studies have shown that TIGIT is expressed on exhausted CD8+ T-cell subsets associated with T-cell exhaustion, characterized by high levels of TOX and TCF-1, in both mice and humans[54–56]. The transcription factor Eomes, important for CD8+ T-cell differentiation, can upregulate TIGIT expression by binding to its promoter[57]. Additionally, TIGIT with NK cells exhibit reduced anti-tumor cytotoxicity compared to TIGIT without NK cells[58].

TIGIT exerts its immunosuppressive effects through its intracellular signaling domains. Upon binding of TIGIT to its ligand CD155, the ITT-like motif within TIGIT is phosphorylated, leading to the recruitment of SH domain-containing inositol-5-phosphatase (SHIP1) and subsequent interference with multiple signaling pathways[59]. SHIP1, an inhibitor of the PI3K signaling pathway, hydrolyzes PI, and P3, thereby inhibiting kinases with pleckstrin homology (PH) domains like Akt, Btk, and phospholipase C-γ[60–62]. Moreover, early binding of TIGIT to CD155 hampers the phosphorylation of Erk and MEK kinases, which are involved in the MAPK signaling cascade. Blocking TIGIT signaling restores Erk phosphorylation and reverses TIGIT/CD155-mediated inhibition of NK cell cytotoxicity, and silencing SHIP1 also restores cytotoxic function[63]. The nuclear factor-κB (NF-κB) pathway plays a critical role in TIGIT/CD155-mediated immunosuppression, as inhibiting TIGIT results in increased phosphorylation levels of Erk, IκBα, and NF-κBP65, along with decreased SHIP1 expression in activated T-cell culture. Animal models further suggest that TIGIT, upon binding and activation by CD155, suppresses PI3K, MAPK, and NF-κB pathways by recruiting SHIP1, leading to the depletion of T and NK cells and reduced interferon-γ production[62]. Notably, phosphorylation of either the ITIM (Y227) or ITT-like motif (Y233) within TIGIT triggers inhibitory signaling in mice, while TIGIT/CD155 binding primarily initiates the inhibitory signal through the ITT-like motif in human cell lines. TIGIT exerts its immunosuppressive effects by competing with CD226, similar to the B7-CD28-CTLA-4 pathway, to regulate the functions of T and NK cells. TIGIT binds with higher affinity to CD155 and CD112, inhibiting CD226 activity when both molecules are present in the same cell[64]. Additionally, TIGIT directly interferes with the co-stimulatory function of CD226 by preventing its homodimerization[59]. CD226, also known as DNAX accessory molecule-1 (DNAM-1), enhances the cytotoxic function of T lymphocytes and NK cells by binding to its ligands CD155 and CD112, which are often overexpressed in tumors. Intracellularly, activated CD226 aggregates lymphocyte function-associated antigen 1 (LFA-1), leading to conformational

changes in intracellular adhesion molecule 1 (ICAM-1). This recruits Fyn and activates the Akt signaling pathway, promoting tumor cytotoxicity by NK/T-cells[65–67]. CD226 binding to CD155 triggers the phosphorylation of FOXO1, a transcription factor that negatively regulates NK cell homing and effector functions. Phosphorylated FOXO1 translocates from the nucleus to the cytoplasm for degradation, allowing the normal killing of targeT-cells by NK cells[68]. CD226-mediated inactivation of FOXO1 also promotes T-cell survival, homing, proliferation, and differentiation[69]. Under IL-12-induced FOXO1 inactivation, CD8+ T lymphocytes acquire effector functions and FOXO1 directly promotes the transcription and differentiation of CD8+ T lymphocytes into memory phenotypes[70]. Furthermore, CD226 plays a critical role in the trans-endothelial migration of effector memory cells, enabling their infiltration into inflammatory sites, including tumors[71]. CD226 also facilitates immune synapse formation between T-cells and antigen-presenting cells through interactions with CD155, supporting the activation of CD8+ T lymphocytes in peripheral tissues and augmenting NK cell cytotoxicity against tumor cells[67,72,73]. By competing with CD226, TIGIT inhibits the Akt signaling pathway, hampers FOXO1 phosphorylation, suppresses T and NK cell activation, and migration, reduces cell toxicity, and promotes T and NK cell exhaustion. Genome-wide microarray analysis revealed that TIGIT binding leads to the downregulation of molecules involved in T-cell receptor (TCR) and CD28 signaling, particularly components of the TCR complex, interfering with early signaling events. In contrast to other co-inhibitory molecules like PD-1, which act downstream, TIGIT affects upstream processes. Additionally, TIGIT can modulate T-cell metabolism by inhibiting glycolysis and, in collaboration with hypoxia-inducible factor 1-α (HIF1-α), promote tumor cell invasion, colony formation, and angiogenesis (**Figure 3**)[74,75].

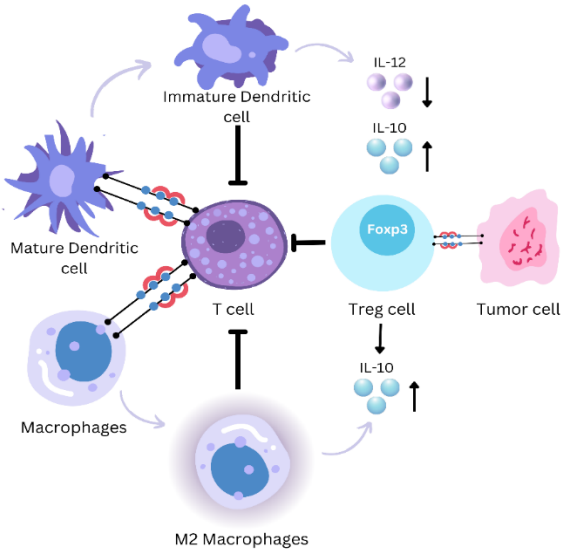

Figure 3. Indirect inhibitory effect of TIGIT.

4.2.2. TIGIT expression in TME

Dendritic cells (DCs) are important for immune responses as they capture antigens and activate T lymphocytes, but immature DCs can lead to immune tolerance. TIGIT activation can induce DCs to become immature and tolerogenic by triggering CD155, resulting in increased secretion of the immunosuppressive cytokine IL-10 and reduced production of IL-12, which suppresses T-cell proliferation and immune-stimulatory cytokine production. TIGIT is also constitutively expressed on regulatory T-cells (Tregs) and plays a crucial role in their function and maintenance. TIGIT promotes the differentiation of naïve T lymphocytes into Tregs, enhances Treg stability, and inhibits the development of pro-inflammatory T-cell phenotypes. In melanoma, Tregs with high TIGIT expression exhibit sustained immunosuppression. Inhibiting TIGIT in Tregs may have anti-tumor effects[76,77]. Additionally, TIGIT activation in macrophages promotes an anti-inflammatory M2 phenotype, while inhibiting TIGIT can reprogram M2 macrophages to the pro-inflammatory

M1 phenotype, which benefits patients with acute myeloid leukaemia (AML)[78]. Myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment also play a role in suppressing anti-tumor immune responses. MDSCs express high levels of CD155 and PD-L1, suggesting that the TIGIT/CD155 and PD-1/PD-L1 pathways may enhance their suppressive effects. Targeting TIGIT and PD-L1 may have implications for reversing immune suppression in MDSCs[79]. Moreover, increased expression of TIGIT has been observed in tumor-infiltrating lymphocytes (TILs) in both mice and humans across various malignancies, including melanoma, breast cancer, non-small-cell lung carcinoma (NSCLC), colon adenocarcinoma (COAD), gastric cancer, acute myeloid leukaemia (AML), and multiple myeloma (MM). Upregulated TIGIT expression has been reported on CD8+ T lymphocytes, tumor-infiltrating regulatory T-cells (Tregs), and natural killer (NK) cells. TIGIT expression on tumor-infiltrating CD8+ T lymphocytes often coincides with increased expression of other inhibitory receptors like PD-1, LAG-3, and TIM-3, and decreased expression of DNAM-1. Consequently, TIGIT marks dysfunctional CD8+ T-cells with reduced cytokine production and degranulation capacities. In gastric cancer patients, TIGIT expression on CD8+ T lymphocytes in peripheral blood has been associated with impaired cellular metabolism, leading to compromised proliferation, cytokine production, and migration. Additionally, TIGIT+ NK cells in subcutaneous tumors and endometrial cancers co-express other inhibitory receptors such as LAG-3 and TIM-3[42].

4.2.3. Clinical studies on TIGIT and PD-1/PD-L1 co-inhibition

Ongoing clinical trials are evaluating the safety and efficacy of TIGIT-targeted therapies in various cancer types. These trials aim to determine the optimal combination strategies, dosing regimens, and patient selection criteria to maximize the therapeutic benefits of TIGIT blockade.

A number of clinical trials are currently underway to evaluate the effectiveness of targeting TIGIT and PD-1/PD-L1 co-inhibition in various types of cancer. These trials involve different treatment approaches, including simultaneous administration of anti-TIGIT and anti-PD-1/PD-L1 agents, coformulation of these agents, and the use of bispecific antibodies targeting both TIGIT and PD-1/PD-L1. The trials cover a wide range of solid tumors and haematological malignancies, and they are conducted at different stages of treatment, such as neoadjuvant, adjuvant, and palliative settings. Some studies also explore combinations of anti-TIGIT and anti-PD-1/PD-L1 therapies with other treatments, including chemotherapy, radiation therapy, concurrent chemoradiotherapy, and targeted therapies[80].

Limited results from clinical trials evaluating the combination therapy of anti-TIGIT and anti-PD-1/PD-L1 treatments are currently available. In a phase I study, vibostolimab, an anti-TIGIT antibody, alone or in combination with pembrolizumab, was assessed for advanced solid tumors and NSCLC[81]. The treatment was generally well-tolerated, with no dose-limiting toxicities observed. Treatment-related adverse events were reported in a portion of patients, and the most common ones included pruritus, fatigue, rash, and hypoalbuminemia. The efficacy of the treatment varied, with objective response rates ranging from 0% to 7% in different groups. Another phase I trial investigated the safety and tolerability of etigilimab, an anti-TIGIT antibody, alone or in combination with nivolumab for advanced solid tumors[82]. The treatment was well-tolerated, and no maximum tolerated dose was reached. Treatment-related adverse events were reported, with rash and pruritus being the most frequent immune-related adverse events. In terms of efficacy, partial responses, and stable disease were observed in some patients receiving the combination therapy[83,84]. Other studies also showed acceptable safety profiles and preliminary antitumor activity with combination therapy. Overall, these results suggest that the combination therapy of anti-TIGIT and anti-PD-1/PD-L1 treatments has manageable toxicity and promising antitumor effects[85].

The CITYSCAPE trial, a phase II randomized controlled trial, Investigated the efficacy and safety of combining anti-TIGIT and anti-PD-1/PD-L1 agents. The trial included 135 patients with NSCLC who received tiragolumab or placebo plus atezolizumab[86]. The results showed a significant improvement in progression-

free survival in the tiragolumab plus atezolizumab arm compared to the placebo plus atezolizumab arm, particularly in patients with high PD-L1 expression. Overall survival was also extended in patients with high PD-L1 expression. Treatment-related adverse events occurred in a significant number of patients, but most were mild. The ARC-7 trial also demonstrated the superiority of the combination therapy over zimberelimab alone in terms of overall response rate and progression-free survival in a subset of patients[87]. However, the SKYSCRAPER-02 study showed that the combination therapy did not prolong progression-free survival or overall survival when combined with chemotherapy in patients with extensive-stage SCLC[88]. The current research mainly focuses on solid tumors, and there is limited data on the efficacy of anti-TIGIT and anti-PD-1/PD-L1 combination therapy in haematological malignancies. More prospective clinical studies are needed to further evaluate the effectiveness of this combination therapy.

4.2.4. TIGIT blockade therapeutic strategies prospectives

Recent studies indicate that combining TIGIT blockade with radiotherapy (RT) may have a synergistic effect on cancer treatment. RT can induce both an immunogenic antitumor response and immunosuppressive barriers depending on the fractionation protocols used. Different fractionation protocols have been found to induce specific immune responses, such as lymphoid or myeloid responses[89]. TIGIT expression by CD8+ T lymphocytes was found to be influenced by the fractionation protocols. Combining anti-TIGIT, anti-PD-L1, and specific fractionation protocols showed promising results in terms of treatment efficacy[90]. Additionally, the combination of radiotherapy and anti-TIGIT therapy has shown benefits in slowing primary tumor growth and improving survival outcomes. The combination treatment can stimulate CD8+ T-cell responses and modulate the tumor microenvironment[91]. Furthermore, nanoparticle-mediated combination therapy with radiation and TIGIT/PD-1 inhibitors has shown potential in eliminating primary and secondary tumors[92]. However, further research is needed to fully understand the synergistic relationship between TIGIT-targeted immunotherapy and radiotherapy. Despite being in the early stages, this approach represents a promising avenue for cancer treatment, and ongoing studies will provide more insights into its potential benefits.

In light of these findings, targeting TIGIT has emerged as a potential strategy for cancer immunotherapy based on its immunoregulatory functions and its association with tumor immune evasion. Scientific studies conducted in the past three years have significantly expanded our understanding of TIGIT's role in cancer and its therapeutic implications. Several monoclonal antibodies against TIGIT have been developed and tested in preclinical and early clinical trials. These antibodies have demonstrated the ability to restore T-cell and NK cell functions, resulting in enhanced anti-tumor immune responses. Combination therapies involving TIGIT blockade with other immune checkpoint inhibitors, such as anti-PD-1 or anti-CTLA-4 antibodies, have shown synergistic effects in promoting tumor regression and long-term responses. Continued research and clinical investigations will pave the way for the development of effective TIGIT-targeted immunotherapies to improve patient outcomes.

4.3. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)

The immune system plays a crucial role in defending the body against infections and cancer. Checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 have been successfully used in clinical practice[93]. However, there are ongoing discussions about whether these drugs truly inhibit checkpoints or correct dysregulated immune responses in cancer[94]. Recent research has shed light on the utilization of anti-CTLA-4 antibodies in cancer immunotherapy, offering new perspectives. Contrary to previous assumptions, it has been observed that tumor rejection can be achieved without triggering autoimmunity, challenging the notion that autoimmunity is an inherent outcome of CTLA-4 blockade[95]. Moreover, experiments conducted on mouse models have revealed that the toxicity associated with anti-CTLA-4 antibodies is not dependent on their ability to block CTLA-4's interaction with CD80/CD86. Antibodies that induce autoimmune side effects hinder CTLA-4

recycling, leading to lysosomal degradation, while antibodies that do not cause autoimmunity maintain CTLA-4 recycling. Notably, pH-sensitive antibodies that dissociate from CTLA-4 in the acidic environment of lysosomes have shown increased efficacy in tumor rejection and depletion of regulatory T-cells, while minimizing autoimmune side effects[96]. These findings propose a novel approach for safer and more potent cancer immunotherapy through the use of anti-CTLA-4 antibodies. Differences in the effectiveness and adverse effects of anti-CTLA-4 antibodies between human patients and preclinical models have raised inquiries regarding the underlying mechanisms[95]. The conventional hypothesis of checkpoint blockade suggests that blocking CTLA-4's interaction with CD80 and CD86 is crucial for the therapeutic impact of anti-CTLA-4 antibodies. However, recent studies have challenged this hypothesis. Evidence indicates that inhibiting CTLA-4's interaction with CD80 and CD86 is neither necessary nor sufficient for successful cancer immunotherapy. Instead, an alternative mechanism involving the interplay between the Fc fragments of anti-CTLA-4 antibodies and host Fcγ receptors (FcγR) has been proposed. Antibody-dependenT-cell-mediated cytotoxicity (ADCC) and antibody-dependenT-cell-mediated phagocytosis (ADCP) mediated by FcγR contribute to the targeted elimination of regulatory T-cells (Tregs) within the tumor microenvironment, ultimately resulting in tumor rejection[97]. This alternative mechanism underscores the crucial role of Fcγ receptors in the anti-CTLA-4 antibody-induced eradication of tumors. Clinical data and genetic studies provide support for the significance of Treg depletion in the therapeutic efficacy of anti-CTLA-4 antibodies. Notably, Treg depletion in melanoma samples has been associated with improved clinical outcomes in patients treated with Ipilimumab[98]. Ongoing research is exploring strategies to enhance ADCC activity, such as the development of afucosylated Fc variants of anti-CTLA-4 antibodies. However, it is important to address the potential heightened toxicity associated with enhancing ADCC function when considering such approaches for checkpoint inhibition. Several drugs have been identified that can modulate the expression of PD-L1, including metformin, PARP inhibitors, chemotherapy drugs, and various targeted inhibitors. These drugs have demonstrated efficacy in different types of cancer by either suppressing or enhancing PD-L1 expression[99,100]. Furthermore, certain PD-L1 inhibitors such as Pembrolizumab, Nivolumab, and Atezolizumab have received FDA approval for clinical use, while others are still undergoing investigation in clinical trials. In the case of CTLA-4, Ipilimumab and Tremelimumab have been approved as inhibitors and alternative approaches like synthetic peptides and HDAC inhibitors have been explored to target CTLA-4[101,102]. These findings underscore the potential of targeting PD-L1 and CTLA-4 in cancer immunotherapy. The development of anti-CTLA-4 antibodies for cancer immunotherapy has faced challenges in terms of efficacy and toxicity. In the phase III clinical trial, the initial anti-CTLA-4 antibody, Ipilimumab, demonstrated improved survival rates in melanoma patients[103]. However, it also exhibited increased toxicity, with a significant number of patients experiencing severe immunotherapy-related adverse events (irAE). In contrast, anti-PD therapy targeting the PD-1/PD-L1 pathway has been validated by multiple clinical products across different cancer types. In head-to-head comparisons, anti-PD-1 therapy has shown superior efficacy and lower toxicity compared to Ipilimumab in advanced melanoma patients[104–106]. Combining Ipilimumab with anti-PD-1 therapy has resulted in improved outcomes, although it has also been associated with higher rates of severe irAE. Despite these challenges, there is ongoing interest in targeting CTLA-4 as Ipilimumab has been shown to enhance the therapeutic response to anti-PD-1 therapy, especially in melanoma patients. However, the significant occurrence of severe irAE, resembling autoimmune diseases, underscores the importance of immune tolerance to self-antigens that can be disrupted by anti-CTLA-4 therapy[107–110]. However, further research and clinical trials are required to optimize their utilization and comprehend their mechanisms of action in diverse cancer types.

4.4. Lymphocyte-activation gene 3 (LAG-3)

Lymphocyte-activation gene-3 (LAG-3) are relatively new checkpoint inhibitors. The evidence suggests

that tumour cells can evade the immune system through immune checkpoint receptor proteins, leading to the exploration of blocking these receptors as a new immunotherapy for cancer (**Figure 4**). The prognosis of human tumors is closely associated with the expression level of LAG-3. Elevated levels of LAG-3 in kidney renal clear cell carcinoma, non-small cell lung cancer (NSCLC), primary central nervous system lymphoma (PCNSL), hepatocellular carcinoma (HCC), and muscle-invasive bladder cancer (MIBC) are indicative of a poor prognosis. Conversely, in gastric carcinoma and melanoma, high levels of LAG-3 are associated with a better prognosis[111]. While immune checkpoint receptors like PD-1/PD-L1 and CTLA-4 have been extensively studied, there is a need to investigate new targets. LAG-3 is identified as a key member of the immunoglobulin superfamily and its expression level is linked to the prognosis of different types of tumours. It is expressed on effector T-cells and regulatory T-cells and plays a role in T lymphocytes and antigen-presenting cells signaling pathways. Persistent antigenic stimulation induces the expression of LAG-3 on activated immune cells. High levels of LAG-3 result in exhausted T-cells and immunosuppression. Blocking or inhibiting LAG-3 can restore T-cell cytotoxic activity and reduce immunosuppression, thereby enhancing tumor-killing effects[112]. Simultaneous blockage of LAG-3 and other immune checkpoint receptors has shown promising inhibitory effects on tumor cells. Studies were conducted to describe the properties and functional consequences of Lymphocyte activation gene-3 (LAG-3) engagement with stable peptide-MHC class II complexes (pMHCII) and fibrinogen-like protein 1 (FGL1). While LAG-3 is known to function as an inhibitory co-receptor, its specific ligand preferences and signaling mechanisms remain incompletely understood. The results indicate that LAG-3 selectively recognizes conformationally stable pMHCII complexes rather than universally binding to MHCII. The interaction of LAG-3 with stable pMHCII leads to T-cell suppression, while its engagement with FGL1 does not produce the same effect. Importantly, the absence of FGL1 binding does not impact the inhibitory function of LAG-3 induced by stable pMHCII[113]. These findings highlight that stable pMHCII acts as the functional ligand for LAG-3, triggering its immune-inhibitory role. This understanding has implications for the involvement of LAG-3 in conditions such as type 1 diabetes and anti-cancer immune responses[114–117]. LAG-3 exhibits co-localization with CD4, CD8, and CD3 within lipid rafts, although its structure differs from CD3 and CD8, it shares significant homology with CD4. LAG-3 consists of distinct regions including a transmembrane region, an extracellular region, and a cytoplasmic region. Metalloproteinases ADAM10/17 can modulate its function by causing LAG-3 to detach from the cell membrane. The extracellular domain of LAG-3 encompasses four IgSF domains, while the cytoplasmic region contains phosphorylation sites and conserved motifs crucial to its functionality. LAG-3 is primarily expressed on activated T lymphocytes, NK cells, B-cells, and DCs, where it exerts a negative regulatory role on T-cell function. Within tumor microenvironments, LAG-3 is highly expressed on tumor-infiltrating lymphocytes and facilitates tumor immune evasion[118]. Upon stimulation with antigens, the expression of LAG-3 is induced on both CD4+ and CD8+ T lymphocytes[119]. Prolonged exposure to chronic infections or tumor-associated antigens results in elevated levels of LAG-3 and other inhibitory co-receptors on T lymphocytes, leading to functional exhaustion. Blocking LAG-3 has shown promise in rejuvenating exhausted T-cells and enhancing immune responses against infections[120]. LAG-3 is also present on regulatory T (Treg) cells and type 1 T regulatory (Tr1) cells, which are subsets of CD4+ T lymphocytes with suppressive functions[121]. The precise role of LAG-3 in Treg and Tr1 cell activities is still under investigation[122]. Transcriptional regulators such as TOX, NFAT, NR4A, and EGR2 play a role in controlling LAG-3 expression in T-cells[123,124]. T-bet, another transcription factor, suppresses LAG-3 expression to sustain the antigen-specific response of CD8+ T lymphocytes during chronic infections[125]. LAG-3 is additionally expressed on various other cell populations, including CD3+ CD4− CD8− T-cells, intraepithelial lymphocytes, γδT-cells, NKT-cells, NK cells, plasmacytoid dendritic cells, activated B-cells, and neurons[126]. However, the functional roles of LAG-3 in these cell populations are not yet fully understood. LAG-3 interacts with several ligands, including galectin-3, major histocompatibility complex II (MHC II), fibrinogen-like protein 1 (FGL1), and hepatic sinusoid endothelial cell lectin (LSECtin). While MHC II serves

as the primary ligand, galectin-3, FGL1, and LSECtin also contribute to modulating T-cell responses and promoting tumor immune escape[118]. Blocking LAG-3 using an anti-LAG-3 antibody can restore the functionality of CD4+ T lymphocytes. LAG-3 exhibits selective binding to antigen peptide-MHC II (pMHC II), thereby inhibiting the response of CD4+ T lymphocytes to pMHC II. LAG-3 negatively regulates the mitochondrial activity in naïve CD4+ T-cells, limiting their normal metabolic processes and expansion, leading to T-cell exhaustion and impaired anti-tumor immune responses. Furthermore, LAG-3 is upregulated in CD8+ T-cells upon stimulation with tumor antigens, and inhibiting LAG-3 enhances the activity of CD8+ T lymphocytes. LAG-3 also enhances the function of regulatory T-cells (Treg cells), promoting their activation and immunosuppressive effects. LAG-3 may work in synergy with other inhibitory molecules such as PD-1 and CTLA-4 to augment the inhibitory activity of Treg cells, thereby contributing to immune tolerance. Additionally, LAG-3 has immunostimulatory roles and can induce the maturation and activation of dendritic cells (DC cells). LAG-3 is highly expressed on tumor-infiltrating lymphocytes (TILs) in various solid tumors and plays a crucial role in regulating T-cell activation, proliferation, and homeostasis in the tumor microenvironment[127]. Co-expression of LAG-3 and PD-1 on TILs leads to T-cell exhaustion through different signaling pathways. Preclinical studies have shown that blocking both LAG-3 and PD-1 has enhanced anti-tumor responses. LAG-3 expressed on regulatory T-cells (Treg cells) contributes to tumor immune escape by inducing the production of immunosuppressive cytokines. Inhibiting LAG-3 allows T-cells to regain cytotoxic activity and reduces the suppressive function of Treg cells, enhancing the killing effect on tumors. LAG-3 inhibitors, including monoclonal antibodies, double antibodies, and small molecule drugs, have entered clinical research and show promising results[128]. These inhibitors can directly bind to LAG-3 or its ligands, disrupting the inhibitory interaction and downregulating LAG-3's suppressive effect. Unlike PD-1 antibodies, LAG-3 inhibitors can also inhibit Treg cell activity[129]. Overall, LAG-3 represents a novel target for tumor immunotherapy beyond PD-1/PD-L1 and CTLA-4, with ongoing clinical trials evaluating LAG-3 inhibitors globally.

Researchers were investigating the binding and functional consequences of FGL1 (fibrinogen-like protein 1) on the inhibitory co-receptor LAG-3 (lymphocyte activation gene-3)[130]. The scientists engineered recombinant FGL1 proteins fused with the Fc portion of human IgG1 or the pentameric domain of cartilage oligomeric matrix protein (Comp-FGL1) and examined their binding affinity to LAG-3-expressing cells. It was observed that FGL1 specifically binds to LAG-3; however, the binding strength is low, and multimerization of FGL1 is necessary for detection. The study aims to determine whether FGL1 enhances the inhibitory effect of LAG-3 on T-cell activation and whether FGL1 independently inhibits T-cell activation. The results indicate that FGL1 binding does not enhance the inhibitory function of LAG-3 in the presence of stable peptide-MHC class II complexes (pMHCII), nor does it independently suppress the activation of CD4+ and CD8+ T lymphocytes[131]. These findings provide valuable insights into the interaction between LAG-3 and its potential ligands, as well as their impact on T-cell activation. Furthermore, several LAG3 modulators have been identified and are currently undergoing evaluation as potential anticancer drugs in clinical trials. Among these, eftilagimod alpha, a modulator that activates APCs by interacting with the canonical ligand MHC class II. It has demonstrated the ability to enhance Treg immunosuppression, promote dendritic cell proliferation, and improve antigen presentation to CD8+ T-cells. Multiple clinical trials for eftilagimod alpha have either been completed or are actively recruiting participants. Additionally, various monoclonal antibodies specifically targeting LAG3, as well as bispecific antibodies, are being investigated at different stages of clinical development for cancer treatment. Relatlimab, the first anti-LAG3 human IgG4 monoclonal antibody, is being examined in 46 clinical trials for cancer therapy[127]. It is often used in combination with other checkpoint inhibitors, such as CTLA-4 or PD-1 inhibitors, to enhance therapeutic efficacy. Relatlimab, commercially developed as the first anti-LAG-3 antibody, entered clinical trials in 2013[132]. Notably, the combination of relatlimab and the PD-1 inhibitor nivolumab has received FDA approval as the first monoclonal

antibody therapy for unresectable or metastatic melanoma[127]. These advancements underscore the growing interest and progress in the field of LAG3-targeted cancer immunotherapy[133,134].

Although further investigation is necessary to uncover additional ligands and explore the functions of LAG-3 beyond the immune system, LAG-3 may also play a role in activating NK cells, with the specific underlying mechanisms requiring elucidation.

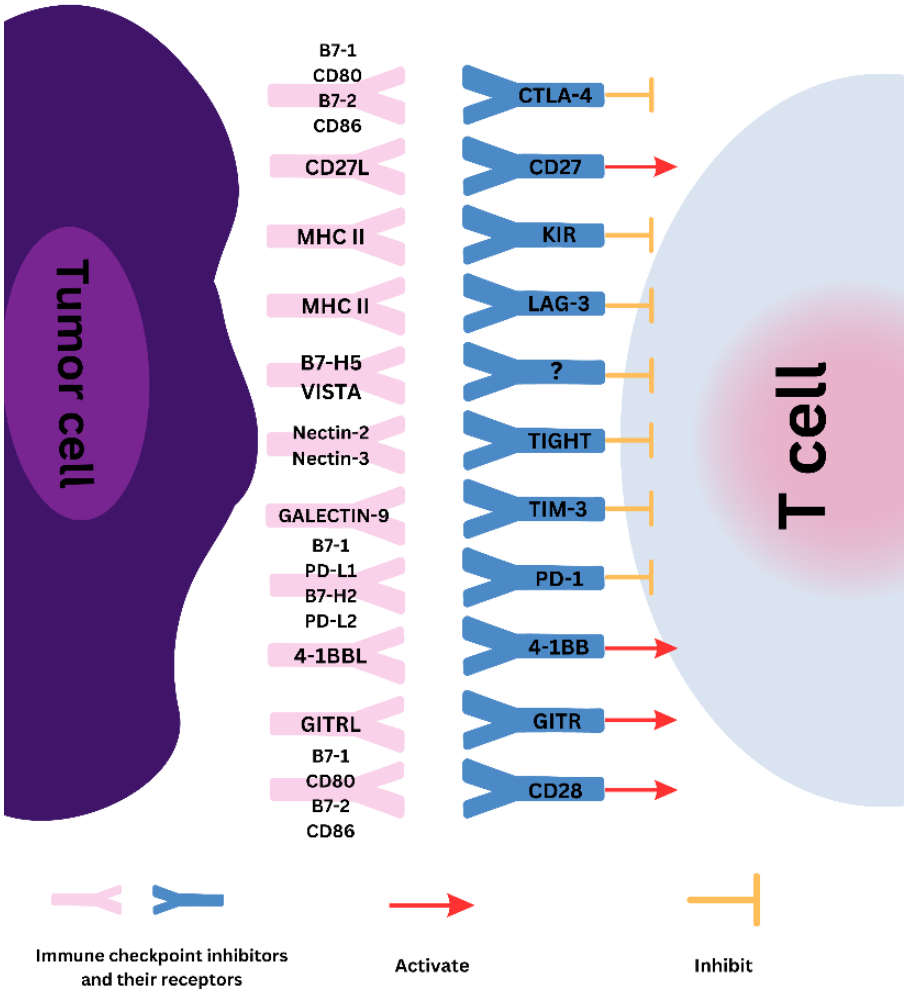

Figure 4. Immune checkpoint inhibitors and activating receptors.

5. Cancer vaccines

Based on current discoveries, cancer vaccines can be divided into three major categories defined by content and format: 1) cell vaccine [tumour or immune cells; dendritic cells vaccine (DC)], 2) protein/peptide vaccines, and 3) nucleic acid vaccines (DNA, RNA, viral vector vaccine) (**Figure 5**)[135–137].

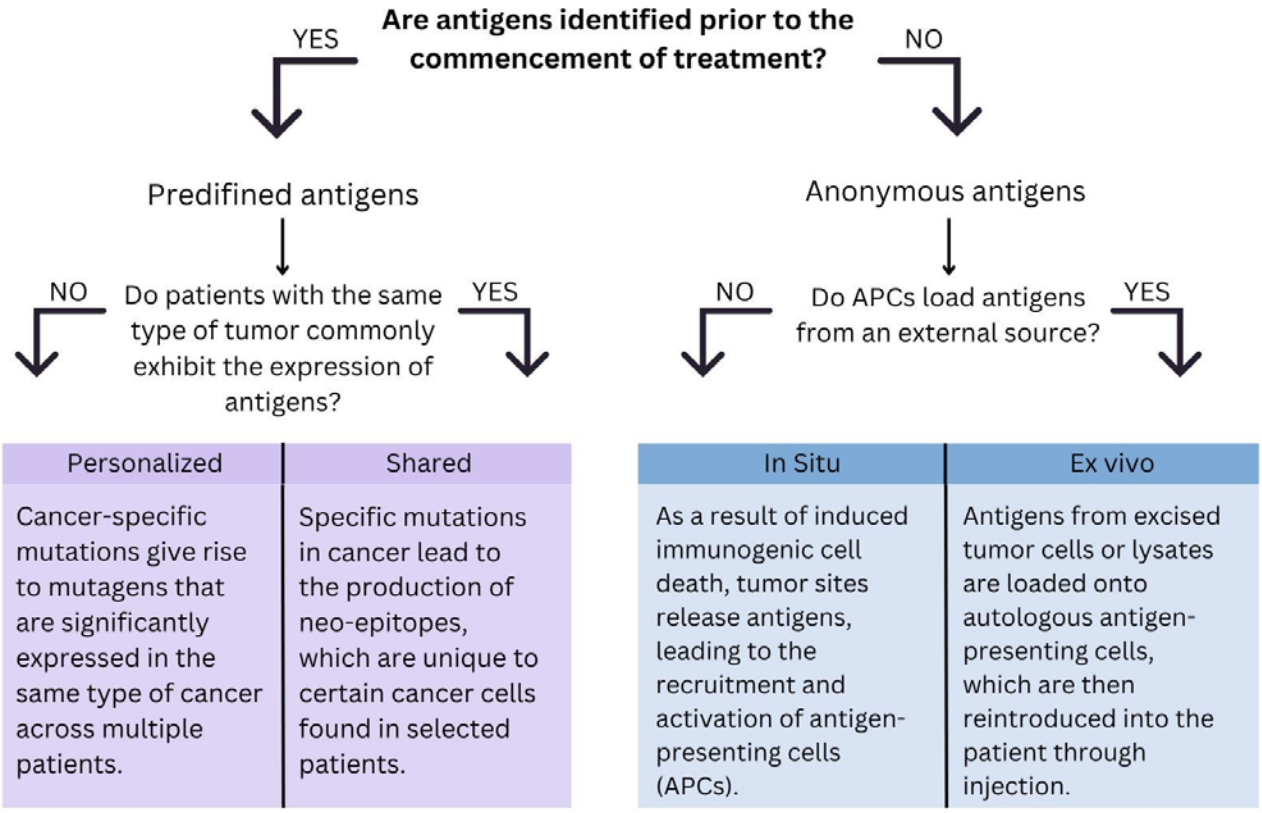

Figure 5. Scheme of four types of cancer vaccines.

5.1. Dendritic cell vaccines

One of the vaccination techniques being assessed is the usage of patients' own cancer cells to create an autologous tumour cell vaccine. In this method, eradicated tumour cells are combined with adjuvant and their goal is to stimulate T-cells, specific toward any antigen, exhibited by used cells. One of the limitations of this technique is the difficulty to obtain adequate cell numbers[138]. Since the development of this vaccine strategy started it was tested on different tumours like colorectal cancer, renal cell carcinoma, lung cancer, prostate cancer, melanoma, and ovarian cancer[139]. Tumour cells often undergo genetic modification that leads to the addition of their functions like co-stimulation of B7-1, synthesis of cytokines (e.g., IL-2), and granulocyte-macrophage colony-stimulating factor (GM-CSF). GVAX is one of the cancer vaccines that use cancer cells that have been genetically altered to release GM-CSF. It follows radiotherapy for the prevention of unregulated cancer cell growth. There are two GVAX vaccine strategies in which one uses allogenic cells, which are not patient-specific and the other uses autologous cells which are patient-specific. GVAX vaccination showed promising results in half clinical trials in non-small-cell lung carcinoma patients but no effects were seen in the third phase of clinical trials in prostate cancer patients. New studies also showed promising results in the maintenance of pancreatic ductal adenocarcinoma with GVAX therapy in combination with anti-PD-1[140]. An approach of combining allogenic GVAX against immune checkpoint inhibitors and metastatic castration-resistant prostate cancer (CRPC) has been evaluated despite homologous GVAX did not show results in the phase three clinical study against CRPC. Some limitations of personalizing autologous tumour vaccination may be overcome by the allogenic vaccine Canvaxin. Three types of vaccines were tested on breast, pancreatic, and prostate cancer. Basirat et al. reported allosteric plasma and serum therapy as possible alternative monotherapy or in combination with other therapies tested on mouse model colon cancer through allosteric serum intra-tumour injection[141].

5.2. Protein/peptide vaccines

Artificially synthesized protein/peptide vaccines aim to effect resistance against certain antigenic epitopes derived from vaccinated proteins/peptides expressed in cancer cells and preferably not in normal tissue. Antigen protein/peptide is exposed on the cell surface alongside HLA molecules. Tumour-specific immune responses are triggered when T-cell detects an antigen[138]. Additionally, increased interest attracted antigens generated by specific cancer gene mutations that are absent in healthy tissue and now are known as neoantigens[142]. Neoantigen vaccines' immunological mode of action is unclear. It is yet unknown how many antigen epitopes are necessary to produce the optimal anti-tumour activity, including the ideal ratio between CD4+ and CD8+ T-cell epitopes[143]. Further research is required to identify the key factors preventing neoantigen vaccines from being efficient against "cold immune" tumours. From the perspective of the immune system's microenvironment, the conversion of tumours to a "hot immune" state may be crucial for future progress in immunotherapy[142].

In recent years, a variety of analytical neoantigen identification processes have been put out to forecast peptides that may trigger tumour immune responses linked to T-cell activation (**Table 1**)[140–146]. Due to the binding ability between MHC and peptides, effective neoantigens were chosen against glioblastoma, melanoma, and colorectal cancer[147–149]. Neoscreen enables the selective development of tumour infiltrating lymphocytes (TILs) that specifically target neoantigens against colon cancer, ovarian, lung cancer, and melanoma. Neoscreen was also the first to apply computational techniques to identify new potential neoantigens which are subsequently pumped into modified B-cells for antigen display[150].

Quintana et al. findings suggest a negative connection between neoantigens and TILs in contrast to earlier research. They contend that neoantigens and cancer cells survive due to lymphocyte inability to enter the tumour. In contrast to TILs neoantigens can be considered as a negative prognostic biomarker according to the negative correlation between them. Data obtained can also be considered incomplete since they don't include patients with TIL percentages between 5% and 50% who may also be the main group that has to be taken into account, which may be the explanation why they arrive at different results than others[151].

Most peptide vaccinations created so far contain short-chain peptides (SPs) that are restricted to formulations of MHC class I. In contrast to long-chain peptides (LPs), SPs can attach to any cell without processing and if presented without a secondary costimulatory signal to CD8+ T-cell, may cause anergy. Immune tolerance occurs which favours a setting for cancer proliferation[138].

Table 1. Clinical trials of neoantigen-based cancer vaccines.

Vaccine	Year of discovery	Indications	Companies	Phases	Results	Reference
MAGE-A3 (protein vaccine)	2000	Melanoma	GlaxoSmithKline	III	Median DFS: vaccine group 11.0 months versus placebo group 11.2 months (P = 0.86)	Dreno B et al.[152]
MAGE-A3 (protein vaccine)	2003	NSCLC	GlaxoSmithKline	III	Median DFS: in the overall population, vaccine group 60.5 months versus placebo group 57.9 months (P = 0.74). Of the patients who did not receive chemotherapy, vaccine group 58.0 months versus placebo group 56.9 months (P = 0.76)	Vansteenkiste JF et al.[153]
L-BLP25 (a liposomal MUC1-targeted peptide vaccine with IL-2)	-	NSCLC	Oncothyreon	III	Median OS: vaccine group 25.6 months versus placebo group 22.3 months (P = 0.123)	Butts C et al.[154]

Table 1. (*Continued*).

Vaccine	Year of discovery	Indications	Companies	Phases	Results	Reference
RV001 (RhoC peptide vaccine)	2004	Prostate cancer	RhoVac	IIb	Results for RV001 (onilcamotide) failed to demonstrate the drug's superiority over the placebo in the Phase IIb BRaVac trial. [Data not disclosed]	[Data not disclosed]
algenpantucel-L (a whole-cell immunotherapy)	2002	Pancreatic cancer	NewLink Genetics	III	Median OS: vaccine + SOC group 27.3 months versus SOC group 30.4 months. 3-year survival rate: 42.1% versus 41.4%; 4-year survival rate: 32.7% versus 32.6%	Hewitt DB et al.[155]
IMA901 (a vaccine consisting of ten tumor-associated peptides)	2004	Renal cancer	Immatics	III	Median OS did not differ significantly between the groups (33.17 months in the sunitinib plus IMA901 group versus not reached in the sunitinib monotherapy group; $P = 0.087$)	Rini B et al.[156]
Rintega (EGFR vIII v3 peptides vaccine)	2003	Glioblastoma	Celldex	III	Median OS: Rintega + temozolomide group 20.4 months versus temozolomide group 21.1 months	Inman S[157]
PGV001 with atezolizumab; adjuvant Poly-ICLC	2020	Melanoma, NSCLC, SCCHN, RCC or urothelial carcinoma	-	I/II	Completed	Liu Z et al.[158]
GEN-009 alone or combined with nivolumab or pembrolizumab; adjuvant Poly-ICLC	2019	Melanoma, NSCLC, SCCHN, RCC or urothelial carcinoma	-	I/II	Completed	Liu Z et al.[158]
iNeo-Vac-P01; adjuvant GM-CSF	2020	Pancreatic cancer	-	I	Completed	Liu Z et al.[158]
IDH1-vac	Study concluded 2018; vaccine not approved yet	Grade 3 and 4 IDH1(R132H) + astrocytomas	-	I	Completed	Liu Z et al.[158]
NeoVax; adjuvant Poly-ICLC	Study concluded 2017; vaccine not approved yet	Stage IIIB/C or stage IVM1b high-risk melanoma	-	I	Completed	Liu Z et al.[158]
NEO-PV-01 plus anti-PD-1; adjuvant Poly-ICLC	Study concluded 2020; vaccine not approved yet	Advanced melanoma, NSCLC, or bladder cancer	-	Ib	Completed	Liu Z et al.[158]
iNeo-Vac-P01; adjuvant GM-CSF	Study concluded 2022; vaccine not approved yet	Advanced solid tumors	-	I	Active, not recruiting	Liu Z et al.[158]
Vaccine and retifanlimab; adjuvant Poly-ICLC	Study concluded 2023; vaccine not approved yet	Pancreatic cancer, colorectal cancer	-	I	Not yet recruiting	Liu Z et al.[158]

Table 1. (*Continued*).

Vaccine	Year of discovery	Indications	Companies	Phases	Results	Reference
Vaccine; adjuvant Poly-ICLC	Study is still active	Pancreas cancer	-	I	Not yet recruiting	Liu Z et al.[158]
Vaccine combined with targeted drug	Study concluded 2022; vaccine not approved yet	NSCLC	-	I	Recruiting	Liu Z et al.[158]
Vaccine alone	Study concluded 2022; vaccine not approved yet	Pancreatic cancer	-	I	Active, not recruiting	Liu Z et al.[158]
Vaccine alone or combined with durvalumab	Study is still active	TNBC	-	I	Active, not recruiting	Liu Z et al.[158]
Vaccine in combination with nivolumab/ipilimumab and PROSTVAC	Study concluded 2022; vaccine not approved yet	Metastatic hormone-sensitive prostate cancer	-	I	Active, not recruiting	Liu Z et al.[158]
Vaccine alone	Study is still active	Pediatric recurrent brain tumor	-	I	Not yet recruiting	Liu Z et al.[158]
Vaccine alone	Study is still active	Glioblastoma	-	I	Recruiting	Liu Z et al.[158]
Vaccine in combination with durvalumab	Study is still active	Extensive-stage small cell lung cancer	-	II	Recruiting	Liu Z et al.[158]
mRNA-4650	Study concluded 2019; vaccine not approved yet	Metastatic gastrointestinal cancer	-	I/II	Terminated, has results	Liu Z et al.[158]
mRNA vaccine alone or combined with PD-1 blockade	Study concluded 2019; vaccine not approved yet	Stage III-IV melanoma	-	I	Completed	Liu Z et al.[158]
RO7198457 alone or combined with atezolizumab	Study is still active	NSCLC, colorectal cancer, melanoma, and breast cancer	-	Ib	Active, not recruiting	Liu Z et al.[158]
SW1115C3	Study is still active	Solid tumor	-	I	Not yet recruiting	Liu Z et al.[158]
Vaccine alone	Study concluded 2016; vaccine not approved yet	Stage III melanoma	-	I	Completed	Liu Z et al.[158]
Vaccine alone or combined with PD-1 inhibitor	Study concluded 2020; vaccine not approved yet	Advanced lung cancer	-	I	Unknown	Liu Z et al.[158]
Vaccine alone	Study concluded 2020; vaccine not approved yet	Solid tumors	-	I	Unknown	Liu Z et al.[158]
Vaccine alone	Study concluded 2020; vaccine not approved yet	Lung cancer	-	I	Unknown	Liu Z et al.[158]
Vaccine and nivolumab	Study is still active	HCC	-	II	Recruiting	Liu Z et al.[158]

6. Adaptive cell therapy

6.1. Tumour-infiltrating lymphocytes (TIL) therapy

A potential method of cancer treatment known as TIL therapy is an autologous technique that's performed by collecting patients' tumour T-cells, their activation by IL-2, known for its T-cell stimulating effect and then putting them back in the patient. The quality and quantity of extracted lymphocytes are crucial for the therapy's success. In the last decade the scientific world has been intrigued by publications on TIL therapy in melanoma patients[159]. The most recent approach involves a combination of TILs and IL-2 for increased clinical effects. The same group tested the TILs effect on cervical cancer and showed some promising results. Newer studies were focused on a comparison of ipilimumab and TIL therapy. Rohaan et al. tested 168 patients with advanced melanoma. Median overall survival in TIL test group was 25.8 months and 18.9 months with ipilimumab. TIL group also showed longer progression-free survival for 4.1 months. It is important to notice that all patients taking TIL therapy had grade 3 or higher side effects mostly related to chemotherapy myelosuppression while adverse events in the ipilimumab group of patients occurred in 57% of patients[160].

6.2. Chimeric antigen receptor T-cell (CAR-T) therapy

Chimeric antigen receptor T-cell (CAR-T) cells are genetically modified T-cells that express a hybrid receptor combining the intracellular domain of a T-cell receptor with the antigen-binding domain of a B-cell receptor. These engineered T-cells are infused back into the patient and are capable of identifying and attacking tumour cells that express the particular antigen targeted by the receptor. Currently, CAR-T-cell therapy is primarily used in the treatment of hematologic malignancies, targeting CD19, a pan-B-cell antigen. Two CD19-specific CAR-T-cell products, tisagenlecleucel and axicabtagene ciloleucel, have been approved for the treatment of refractory B-cell precursor acute lymphoblastic leukaemia and relapsed diffuse large B-cell lymphoma. Clinical research has shown that some patient subsets have the potential for long-lasting full remissions[161]. Due to the unipilique toxicity profile and the potential for severe treatment-related adverse events, CAR-T-based therapies are limited to specialized canters with certification through a risk evaluation and mitigation strategy[162].

CAR-T-cell therapy is an innovative approach to cancer treatment that involves genetically modifying a patient's own T-cells to enhance their ability to target and destroy cancer cells. It utilizes CARs which are designed to recognize specific tumour-associated antigens (TAAs) on the surface of cancer cells[163]. Unlike traditional TCRs, CARs do not rely on the MHC for antigen presentation, enabling MHC-independent tumour recognition. The first step in CAR-T-cell therapy begins by collecting the patient's T-cells through a blood sample. These T-cells are then genetically engineered to express the CARs, which consist of an extracellular antigen-binding domain derived from antibodies, a transmembrane domain, and an intracellular signalling domain. The extracellular domain enables CAR-T-cells to specifically bind to tumour-associated antigens (TAAs), whereas the intracellular signalling domain, often including the CD3-zeta domain and one or more costimulatory domains, facilitates T-cell activation upon antigen recognition[164]. After the CARs are integrated into the T-cells, they undergo ex vivo expansion and cultivation to generate a large population of CAR-T-cells[165,166]. This step allows for the production of a sufficient number of tumour-targeting T-cells that can bypass the immunosuppressive environment created by the tumour. Once the CAR-T-cells have been expanded, they are reinfused back into the patient's body. These engineered immune cells are now primed to recognize and attack cancer cells expressing the specific TAAs targeted by the CAR. Upon encountering cancer cells, CAR-T-cells initiate a robust immune response, leading to the destruction of tumour cells. CAR-T-cell therapy has shown remarkable success in the treatment of certain haematological malignancies, particularly B-cell leukaemia's and lymphomas. Several CAR-T-cell therapies targeting the CD19 antigen have been approved by regulatory agencies and have demonstrated significant clinical values. Ongoing research and clinical trials

are exploring the application of CAR-T-cell therapy in other types of cancer, including solid tumours. Despite its remarkable efficacy, CAR-T-cell therapy is associated with unique challenges and potential side effects. The activation of CAR-T-cells can lead to cytokine release syndrome (CRS) and neurotoxicity, which can be managed with appropriate medical interventions[167]. Researchers are continuously refining CAR designs, incorporating additional immune-stimulatory factors or cytokines in "armoured" CAR-T-cells to enhance their potency and improve therapeutic outcomes. Overall, CAR-T-cell therapy represents a promising and rapidly evolving field in cancer immunotherapy, offering a personalized and targeted treatment approach that holds great potential for improving outcomes in patients with various cancer types (**Figure 6**)[1].

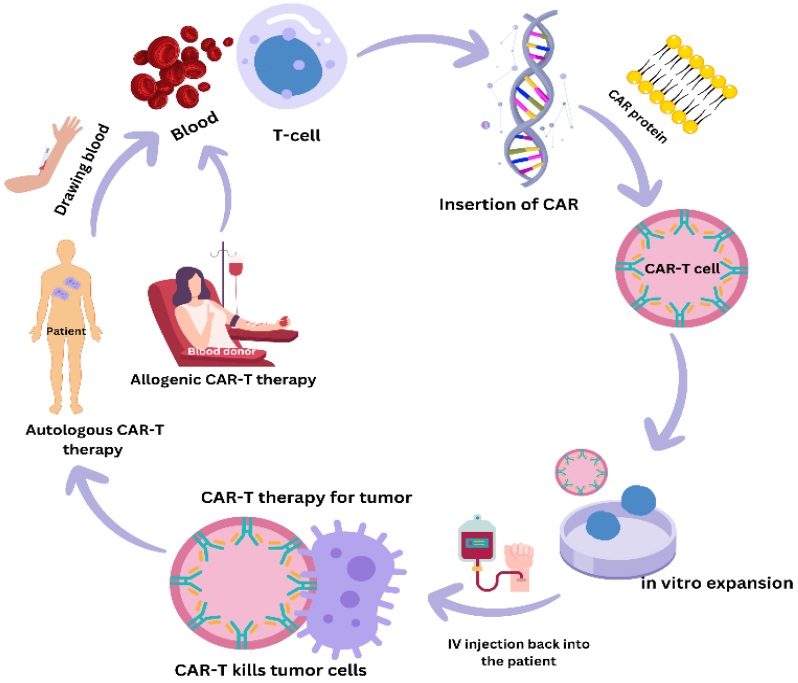

Figure 6. CAR-T-cell mechanism of action.

6.2.1. CAR-T-cell therapy challenges

Although CAR-T-cell therapy has demonstrated clinical effectiveness in treating certain tumours, it still has limitations that prevent it from being used more widely[168]. One major concern is the possibility of severe side effects and toxicities brought on by CAR-T-cells, such as immune effector cell-associated neurotoxicity syndrome (ICANS) and CRS[169,170]. CRS is characterized by a systemic inflammatory response that can lead to life-threatening complications. ICANS, on the other hand, is presented as nervous system toxicity and can be associated with behavioural abnormalities and neurological symptoms[171]. Another challenge is the risk of on-target, off-tumour toxicity, where CAR-T-cells may damage normal cells expressing the targeted antigen. This type of toxicity is normally presented in B-cell malignancies after CAR-T-cell therapy[172].

The time-consuming manufacturing procedure for CAR-T-cell products can be harmful to individuals whose malignancies are advancing quickly at that time. Additionally, the long-term efficacy of CAR-T therapy in blood cancers requires further observation, and its application in solid tumours needs more research due to challenges such as limited target options, tumour heterogeneity, and difficulties in T-cell infiltration[173]. Despite these challenges, continuous advancements in T-cell engineering aim to address these issues and improve the field of CAR-T-cell therapy. Further research and development are necessary to enhance tumour specificity, minimize toxicities, and improve long-term therapeutic outcomes[174].

6.2.2. CAR-T-cell enhancement strategies

The long-term effectiveness of CAR-T-cell therapy in treating tumours has been hindered by tumour recurrence after treatment. Designing bispecific CAR-T-cells that can target several TAAs is one way to deal with this problem. These CAR-T-cells are known as “OR-gated” because the expression of either TAA on tumour cells can activate them. This design is particularly relevant for B-cell acute lymphoblastic leukaemia (B-ALL) treated with CD19 CAR-T-cells, as recurrent malignanT-cells may downregulate CD19 while still expressing CD22. By targeting both CD19 and CD22, “OR-gated” CARs have the potential to reduce antigen escape. Nevertheless, the application of “OR-gated” CAR-T-cell therapy in solid tumours faces significant challenges[175]. Solid tumour TAAs often lack the stringent specificity required for effective targeting, increasing the risk of off-target effects if CAR-T-cells rely on either of the two TAAs for activation[176]. An alternate strategy is to create an “AND-gated” CAR construct that needs both TAAs to be present in order to activate T-cells. By using this method, the possibility of on-target, off-tumour effects can be decreased. The feasibility and applicability of these CAR-T-cell designs depend heavily on the characteristics of the targeted tumours and the specific clinical requirements[177].

Improving CAR-T-cell fitness and activity is essential for enhancing long-term antitumor effects. Strategies focus on preventing CAR-T-cell dysfunction through modifications in manufacturing, enrichment of memory T-cell subsets, engineering CAR constructs, and combining small molecules to inhibit activation signals[178]. Although these methods have produced encouraging results in preclinical animals, clinical trials are still needed to confirm their efficacy and safety.

The use of autologous T-cells throughout the existing manufacturing process for CAR-T-cell treatments leads in high production costs. Priced at $475,000 and $373,000, respectively, the authorized CAR-T medicines from Novartis and Kite have a smaller market potential. The high cost has impacted revenue expectations for these therapies. Furthermore, there are concerns regarding the quality and stability of autologous CAR-T-cell therapy, especially in patients who have undergone extensive pre-treatment with radiation and chemotherapy[179]. To address these challenges, the development of allogeneic “universal” CAR-T products is underway. These products aim to provide over-the-counter drugs with standardized properties, mass production capabilities, and lower costs.

To address the toxicity and side effects associated with CAR-T-cell therapy, control programs are being developed to regulate the activity of CARs. Incorporating suicide switches that may be activated by tiny chemicals or antibodies to quickly eliminate infused cells is one of several techniques used to increase the safety of CAR-T-cells. Common suicide switches include thymidine kinase (HSV-TK), inducible caspase-9 (iCasp9), and suicide epitopes. However, these switches clear all therapeutic CAR-T-cells, which compromises the antitumor response. Noncytotoxic reversible technologies are being developed to get around this restriction. Without entirely eradicating CAR-T-cells, these approaches have the ability to maintain the equilibrium between retaining cytotoxicity and regulating harmful reactions. This strategy attempts to maintain the therapeutic effectiveness of CAR-T-cell therapy while enhancing its safety profile[170].

6.3. NK cells immunotherapy

NK cells, a type of immune cell, play a crucial role in the immune response against cancer. They influence the immune system by secreting cytokines and chemokines that stimulate other immune cells[180]. They can have direct cytotoxic effects by releasing chemicals like perforin and granzyme or activating death receptors. Alongside strategies targeting immune checkpoints on NK cells, adoptive cell therapy (ACT) using NK cells is rapidly advancing[181]. Despite the intrinsic disparities between the innate and adaptive immune systems, NK cell-based ACT is comparable to T-cell-based approaches. Similar to CAR-T-cells, NK cells can be modified to express CARs. CAR-NK cell development has followed the same route as CAR-T-cell treatment, frequently

using CAR designs created originally for T-cells. In 2020, the first clinical study using CD19-targeted CAR-NK cells demonstrated safety and evidence of efficacy against B-cell malignancies[182]. Since then, many preclinical studies have also demonstrated the potential of CAR-NK cells to target different kinds of malignancies and elicit anticancer activity.

Benefits and challenges of NK cell therapy

One significant advantage of NK cell therapy stems from the innate immune nature of NK cells. Comparatively speaking, allogeneic NK cells are less likely to cause graft-versus-host disease (GvHD) than allogeneic T-cell products. Due to technological developments, it is now possible to produce "off-the-shelf" goods with more affordable costs by employing feeder cells to expand NK cells on a large scale[183]. NK cells exhibit cytotoxicity through "missing-self" recognition, making them effective in targeting tumour cells with downregulated MHC. They also possess the ability to kill virus-infected cells, making them suitable for treating tumours associated with viruses like human papilloma virus (HPV) or Epstein-Barr virus (EBV). Recent research has shown that NK cells can prevent the growth of blood vessels connected to tumours. Additionally, NK cells can be used in conjunction with specific antibody therapy and are important in antibody-dependenT-cell-mediated cytotoxicity (ADCC). Comparing NK cell treatment to CAR-T-cell therapy, clinical findings revealed a considerably lower frequency of CRS and immune effector cell-associated neurotoxicity syndrome (ICANS). This suggests the possibility of NK cell therapy being used more widely, with less limitations based on age and previous treatments, and benefiting a larger group of patients. Allogeneic NK cells' viability and cytotoxicity can be decreased by freeze-thaw cycles, and they do not have the same in vivo multiplication capacity as CAR-T-cells, which could result in an early tumour recurrence. Insertional mutagenesis is sensitive to CAR-NK cell infusions, and the position of CAR-binding epitopes can influence cytotoxicity. Alternative methods like the Sleeping Beauty transposon system and mRNA transfection are being explored for CAR-NK cell production[182].

6.4. TCR-T therapy

TCRs are specific receptors found on the surface of T-cells that recognize and bind to antigens presented by MHC[184]. The MHC presents antigens, which TCRs on the surface of T-cells identify and bind to. TCR-T treatment enlarges patient-derived T-cells and provides them new TCRs capable of recognizing specific tumour antigens. Some widely expressed antigens like NY-ESO-1 can be targeted with TCRs to treat various types of tumours[185]. As an alternative, patient-specific tumour cell mutations can direct the creation of TCRs that successfully target these alterations. The T-cells that have these TCRs are identified, cloned, and expressed before being grown in vitro and reinfused into the patient. This personalization method increases the specificity of the therapy[186].

7. Nanoparticles in cancer immunotherapy

Tumor immune responses involve both tumor-specific and non-specific immune responses. Tumor-specific immune responses rely on antigen-presenting cells (APCs) capturing tumor antigens and presenting them to T-cells[187]. However, the antigenicity of most human tumors is weak, limiting the effectiveness of specific immune responses. On the other hand, non-specific immune responses, mainly mediated by macrophages and NK cells, provide an additional defence against tumours[188]. In recent years, there has been significant interest in engineering immunostimulatory nanoparticles. These nanoparticles can be taken up efficiently by APCs, particularly dendritic cells (DCs), allowing selective delivery of cancer antigens and adjuvants to initiate antigen-specific immune responses. Furthermore, they can directly activate T-cells, macrophages, and NK cells[189–193]. The formation of a protein corona on the nanoparticle surface in the presence of serum proteins contributes to the desired immunostimulatory effect[194]. Surface-engineered nanoparticles also protect cargo molecules, preserving their biological activity during circulation and

minimizing off-target side effects[195]. Nanoparticle delivery platforms offer a promising strategy to address the limitations of current treatments in cancer therapy[196]. These nanoparticles provide advantages such as improved drug delivery, prolonged circulation time, enhanced accumulation in tumors, and controlled release[197]. However, existing nanoparticles lack specificity and struggle to target specific cell types, overcome physiological barriers, or block multidrug resistance. To overcome these challenges, surface engineering of nanoparticles has emerged as an attractive approach[198]. By attaching small molecules or large biomolecules to the nanoparticle surface, important properties like surface charge, hydrophobicity, and stability can be modified to regulate cellular absorption. Surface engineering enables improved immune cell targeting, overcoming biological barriers, and enhancing biodistribution in vivo[199,200]. Recent advances in surface-engineered nanoparticles show promise in cancer immunotherapy, and several clinical trials have been conducted in this area[201]. These engineered nanoparticles are designed to specifically target tumor-infiltrating immune cells, inducing tumor immune responses and improving immunotherapy. This innovative approach represents a powerful tool in the fight against cancer.

Advancing cancer immunotherapy with engineered nanoparticles

Surface-engineered nanoparticles offer promising strategies for enhancing tumor killing by stimulating tumor-specific immune responses and non-specific immune responses in the body. Targeting DCs is a key strategy for nanoparticle-based immunotherapy. Lipovaxin-MM, a surface-engineered nanoparticle designed to specifically target DCs by binding to CLR receptors, demonstrated promising results in phase I clinical trials. The nanoparticle induced T-cell responses and showed partial disease remission in some melanoma patients, indicating successful DC targeting in vivo (NCT01052142)[202]. There are also clinical trials exploring surface-engineered nano formulations that target T-cells. Tecemotide (L-BLP25), a vaccine consisting of a lipopeptide combined with liposomes, has shown efficacy in inducing T-cell immune responses in NSCLC patients without severe adverse effects (NCT00409188)[203,204]. Clinical trials for L-BLP25 have also been conducted in other cancers, including rectal cancer (NCT01507103), colon carcinoma (NCT01462513), and prostate cancer (NCT01496131). Recent research presented a Phase 0 trial evaluating the safety, pharmacokinetics, intratumourally accumulation, and gene-suppressive activity of NU-0129, a surface-engineered nanoparticle composed of gold nanoparticles conjugated with small interfering RNA (siBcl2L12), for glioblastoma multiforme (GBM) treatment (NCT03020017). The study demonstrated the rapid elimination of siRNA, accumulation of the nanoparticle in macrophages, and its potential as a brain-penetrating precision medicine approach for GBM immunotherapy[205].

Although clinical trials investigating the efficacy and safety of surface-engineered nanoparticles targeting different immune cells have been conducted, the number of trials is still limited. Further research is necessary to explore the variations in efficacy among different nanoparticles and surface modifications (**Figure 7**). Additionally, there is a need to investigate the efficacy and safety of surface-engineered nanoparticles targeting NK cells in tumour immunotherapy.

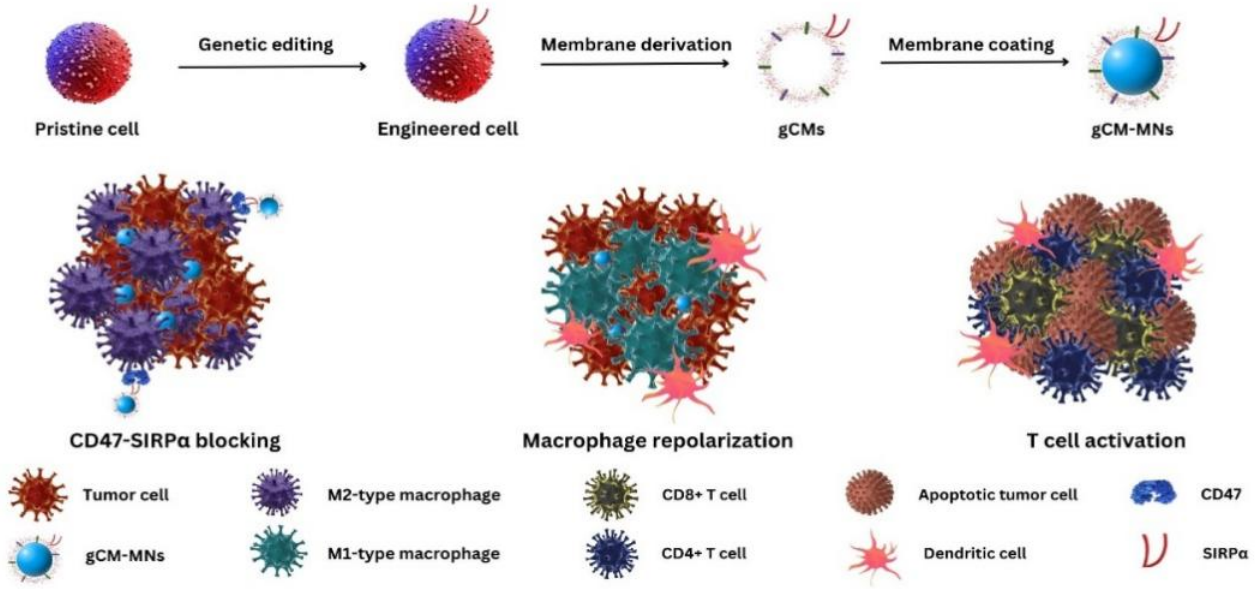

Figure 7. Genetically edited cell membrane-coated magnetic nanoparticles inducing a strong immune response from macrophages for cancer immunotherapy.

8. Biomarkers

Biomarkers are considered one of the most powerful tools in early detection of various tumours. Being non-invasive, economically acceptable, and easily accessible, their value is inestimable in cancer diagnosis. Therefore, many efforts are being invested in finding new biomarkers that will become standard biochemical cancer-evaluation strategies.

8.1. Lung cancer biomarkers

Although the lung immune prognostic index (LIPI) was recognized as a valuable biomarker, its predictive value is yet unknown. The research investigated the unsearched relationship between oncologic therapy for NSCLC and COVID-19 infection, but it also studied the therapeutic value of HPI in patients with NSCLC and PD-L1 mutations sustainable to the combination of immunotherapy and chemotherapy. Results proved LIPI's high prognostic value and clinical applicability as a biomarker in advanced NSCLC. Unexpected results were obtained that patients infected but that can also be justified by constant medical care in infected patients. LIPI can be used as a valuable non-invasive, affordable, and easily accessible biomarker for NSCLC[206]. Targeted therapies have shown remarkable efficacy against specific oncogene-driven tumours, such as EGFR, ALK, ROS1, BRAF, TRK, RET, and MET[207]. Through the protein-based molecular compartmentalization strategy, a study identified CD66b as a potential biomarker associated with resistance to immune checkpoint inhibitor (ICI) therapy (NSCLC). The analysis assessed 284 protein variables and identified CD66b in the CD45 + CD68 molecular compartment as significantly predicting shorter overall survival in relation to ICI resistance. Further validation confirmed the association between CD66b expression and resistance to ICI therapy, specifically in NSCLC patients. CD66b, which identifies neutrophils, warrants further investigation to better understand the role of neutrophils in ICI resistance[208].

8.2. Gastrointestinal cancer biomarkers

In 2020, Bhardwaj et al. presented 275 plasma proteins as possible biomarkers for the early identification of colorectal cancer. Markers were identified from plasma samples using the proximity extension assay (PEA). For early-stage, late-stage, and all-stage colorectal cancer, three signatures made up of 12, 11, and 9 protein markers were found, respectively. The external evaluation confirmed a moderate level of accuracy of 0.76–

0.80. Even though this finding needs further investigation they are promising blood-based CRC detection tests[209]. Besides preventive and early detection biomarkers in CRC, research for treatment outcomes was also conducted. CALGB 80405 study focused on identifying biomarkers in bevacizumab or cetuximab with coupled chemotherapy approach in advanced CRC. Results pointed to VEGF-D in combination with chemotherapy in the treatment of advanced CRC lower survival rate and overall survival[210].

When it comes to colon cancer, high microsatellite instability (MSI-H) in combination with an immune checkpoint inhibitor, pembrolizumab, shows promising outcomes of therapy[211]. Factors like tumour mutation burden (TMB), gut microbiota, circulating immune cells, PD-L1 expression and TILs are the focus of further research for their possible role as immunotherapy response predictors. New techniques like multiplex immunohistochemistry (mIHC) and single-cell RNA sequencing both offer promising avenues for identifying precise biomarkers[212]. Constant improvement of technology also resulted in the development of tumour gene signature of TME has been proposed as a possible predictive biomarker in colon cancer immunotherapy. TILs and tumour-stroma ratio, among other TME-related gene signatures, have shown potential as prognostic biomarkers for colon cancer immunotherapy[213]. Two metabolic features of TME ferroptosis and hypoxia also have an impact on immunotherapy success and the patient's prognosis. To be clinically implanted, TME-related gene structures need further clinical studies[214,215]. The tumour stroma's major component cancer-associated fibroblasts (CAFs), which also play a crucial role in immune evasion and immunosuppression, will have an effect on the overall response of immunotherapy[216]. Immunotherapy responses can be predicted by CAF-derived gene signatures. Poorer patient outcomes and reduced immunotherapy efficacy are associated with high CAF levels. Within Consus molecule subtypes (CMS), CMS4 is characterized by CAF infiltration and shows very limited response to immunotherapy[217].

8.3. Biosensors biomarkers

Although serum tumour markers are progressing and showing promising clinical value, science went a step further. Biosensors have emerged as convenient and affordable tools for tumour-detecting biomarkers. These sensors utilize a variety of principles such as optics, electrochemistry, piezoelectricity, aptamers and photo electrochemistry as identification elements. They offer a range of advantages like speed, sensitivity, simplicity of use, and selectivity. Recent developments were focused on nanomaterials with enhanced ultrasensitive biosensors with a goal of early cancer detection[2].

In the medical community, early detection of cancer has long been a priority since late detection and poor prognosis are two factors contributing to low survival rates. Early detection increases the likelihood of successful therapy, increase the chances of full recovery and enhances patient quality and duration of life[218]. Currently, over 50% of cancers are found at advanced stages and lead to serious health problems and death. Achieving early detection is a complex process that involves cancer screening procedures, public education and reporting of potential cancer symptoms to healthcare providers[219].

9. Immunotherapy combined with other therapy forms

Studies like the phase two trial by Royal et al. published in 2010 and a phase one study from 2012 showed that monotherapy with ipilimumab and the anti PD-L1 therapeutic agent had no response or in the case of PD-L1, patients were presented with disease progression[220]. Promising results were seen in the Keynote-158 phase two study which selectively included 22 patients with advanced MSI-H/dMMR pancreatic adenocarcinoma. The overall response rate was 18.2% with a median duration of response of 13.4 months[221].

A major area of interest today is tumour immune microenvironment (TIM) in MSS pancreatic ductal adenocarcinoma (PDAC) to understand the mechanism of resistance. Many types of research showed that clinical benefit from ICI is correlated with increased levels of CD8+ TILs. PDACs' MIE is characterized by a

higher density of T-cells in the stromal compartment compared to the epithelial compartment of the tumour. Moreover, sites of juxta-tumour are shown to contain more macrophages and regulatory T-cells (T-reg) that will contribute to immunotherapy ineffectiveness and immune evasion. PDAC leads to the inhibition of T-cell activation and differentiation of T-reg through transforming growth factor beta (TGF-β) cytokines and IL-10 together with chemokine receptor 5. Mechanisms leading to the facilitation of tumour growth and metastases like tumour-associated macrophage (TAM) signaling, increased number of myeloid-derived suppressor cells (MDSC), and immunosuppressive cytokines signaling are shown to be present in PDAC. Research indicates variance in tumour microenvironment between primary tumour and metastasis. For instance, TMB frequency varies in different tumour types and densities levels of CD8+ and increased CD4+/CD8+ ratios in pre-treatment secondary PDAC specimens than in primary tumour tissue samples. PDAC has a tendency of decreased number of somatic mutations which may be an explanation of their low immunogenicity and ICI responses[222]. About 81% out of over 4000 PDAC tumour samples showed KRAS mutation, and they also showed increased infiltration of cancer-associated fibroblasts and M1 macrophages, decreased ratio of CD4+/CD8+, and MSI-H status. All of these results indicate a need of creating a strategy for combining ICI and other drugs to overcome barriers to tumour protective mechanisms and enhance immunogenicity[223].

First-choice chemotherapy is the current SOC for patients with advanced PDAC. FOLFIRINOX and the combination of gemcitabine and nab-paclitaxel yield ORRs of 31.6% and 23%, respectively, whereas the ORRs of single-agent gemcitabine or fluoropyrimidines vary from 5%–10%[224]. First-choice combination and single drug therapy show mOS of 8–11 months and six to seven months respectively. An mOS of 6.2 months is obtained with recent second-line chemotherapy procedures like 5-FU with liposomal irinotecan. Preclinical studies indicate that tumours' immunogenicity may be increased through T-cell reactivity, T-cell tumour infiltration, and amplified antigen presentation by chemotherapy-induced apoptosis[225].

All of these findings favour the combination of chemotherapy and ICI in PDAC. Furthermore, two phase-one studies assessed gemcitabine in combination with CTLA-4 inhibitors in untreated PDAC patients in the advanced stage[226]. Aglietta et al. reported ORR of 7.1% with a 4-month mOS[227]. Kalyan et al. evaluated the combination of gemcitabine and ipilimumab and reported ORR of 12.5% of which two out of 16 patients had only PR, PR + SD results were seen in 43% and a 2.5-month median progression-free survival and mOS of 8.5 months[228].

10. Immunotherapy toxicity

The basis for the development of immunotherapy developed with a gradual understanding of tumour escape mechanisms by the influence of the human immune system due to the manipulation of an antitumor immune response. Some of the first techniques in immunotherapy were targeting cytokines like interferon (IFN) α-2b and IL-2. Afterward, new approaches like adoptive cell therapy, neoantigens, cancer vaccines, immune checkpoint inhibitors (ICI), and oncolytic viruses started to be investigated. Adoptive cell therapy, which modifies a patient's T-cells ex vivo is another approach used in immunotherapy[229]. To address the toxicity and side effects associated with CAR-T-cell therapy, control programs are being developed to regulate the activity of CARs. Incorporating suicide switches that may be activated by tiny chemicals or antibodies to quickly eliminate infused cells is one of several techniques used to increase the safety of CAR-T-cells. Common suicide switches include thymidine kinase (HSV-TK), inducible caspase-9 (iCasp9), and suicide epitopes. However, these switches clear all therapeutic CAR-T-cells, which compromises the antitumor response. Noncytotoxic reversible technologies are being developed to get around this restriction. Without entirely eradicating CAR-T-cells, these approaches have the ability to maintain the equilibrium between retaining cytotoxicity and regulating harmful reactions. This strategy attempts to maintain the therapeutic effectiveness of CAR-T-cell therapy while enhancing its safety profile[230]. For these reasons, immunotherapy

toxicity requires strict monitoring and application of immunotherapy toxicity management agents like immune-modulating agents and steroids[231].

Various malignancies are now treatable with immunotherapy techniques but that comes with specific toxicity consequences that vary based on the immunotherapy type and are linked to its particular mode of action. Interaction of cytokines like IL-2 with NK cells and T-cells leads to sepsis-like syndrome and capillary leakage. In extreme cases, even multiorgan failure can occur which led to reduced therapeutic application of cytokine therapy[232].

According to research patients with NSCLC had an overall incidence of irAEs of any grade of 30% and 6% in severe grade[233]. The precise mechanism of actions of irAEs still needs to be clarified. Understanding of irAEs and toxicity prevalence requires special monitoring and regular screening processes of those prone to irAEs in order to minimize the harmful and toxic effects of immunotherapy. The most often reported negative side effect was diarrhoea which was most common among other gastrointestinal toxicity sides effects like nausea, vomiting, and liver damage[234,235]. In addition, skin reactions were also often observed; for example, skin rash was noticed in 17%–41% of patients. It Is important to note that checkpoint inhibitor pneumonitis (CIP) was rarely reported in patients receiving anti-CTLA-4 therapy[236]. In comparison to anti-PD-1 drugs, anti-CTLA-4 drugs in the treatment of NSCLC showed a greater prevalence of adrenal insufficiency. Ipilimumab was shown to frequently cause diarrhoea, nausea, and dermatitis, whereas tremelimumab was more often reported to cause gastrointestinal and skin toxicity. The most frequent side effect of anti-PD-1/PD-L1 is GIT toxicity. GIT side effects are followed by neurological, pulmonary, musculoskeletal, and endocrine toxicities. Retrospectively, the most common irAEs of nivolumab in NSLCL treatment were rash, diarrhoea, myalgia, and arthralgia while pembrolizumab is more likely to cause pneumonia, hyperthyroidism, rash, nausea, and vomiting. Atezolizumab was associated with hepatic dysfunction, hypothyroidism, diarrhea, arthralgia, rash, and myalgia while avelumab had rare adverse effects[237].

11. What does the future bring?

Although immunotherapy has contributed significantly to survival and quality of life in cancer patients, there are still many questions to be answered and much room for improvement. The future of immunotherapy as a treatment modality that uses the body's own immune system to fight diseases such as cancer, autoimmune diseases, and infectious diseases is certainly promising, especially in oncology, but also in other areas of medicine. In this context, future perspectives should focus on achieving the following goals: 1) Improving efficacy: scientific efforts are underway, and researchers are actively working to improve the efficacy of immunotherapy. This includes the development of new techniques and treatment strategies to activate and enhance the immune response against specific targets such as cancer antigens or signaling molecules. Combination therapies, in which multiple immunotherapeutic agents are used together or in conjunction with other treatments such as chemotherapy or radiation, are being explored to achieve better outcomes and improve patient's quality of life[238]. An emerging discipline with promising outcomes is targeting the cancer microenvironment[239]. 2) Targeted treatments: The future of immunotherapy lies in the development of more precise and targeted treatments. The scientific focus is on identifying specific biomarkers, genetic mutations, or individual patient characteristics. Combining epigenetic knowledge with immune checkpoint inhibitors in cancer immunotherapy shows promising results as well. Adjuvant and neoadjuvant settings are also being intensively investigated. This knowledge will enable personalized immunotherapies that can be tailored to individual patients, improving treatment efficacy and reducing side effects[240,241]. 3) Expanding indications: Immunotherapy is primarily associated with cancer treatment, but it shows great potential for expansion into other areas. Its use in autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and type 1 diabetes is under intense investigation[242]. In addition, the use of immunotherapy in infectious diseases such as HIV,

malaria and tuberculosis is currently being explored[243,244]. 4) Overcoming resistance: resistance to immunotherapy is a major problem in immuno-oncology. Scientific efforts are being made to understand the mechanisms of resistance and to develop strategies to overcome it. This may include combining immunotherapies with other modalities or developing new drugs to combat resistant tumours[245]. 5) Reducing side effects: due to its impact on the immune system, immunotherapy may cause more or less severe side effects. Future advances aim to minimize side effects through improved treatment strategies and a better understanding of the complex interactions of the immune system. 6) Collaboration and data sharing: collaboration between researchers, healthcare providers, and pharmaceutical companies will indeed play a critical role in advancing immunotherapy. Sharing data, clinical trials, and knowledge across institutions and countries will accelerate progress and facilitate the development of new therapies[246]. 7) Development of new therapeutic approaches: new innovative immunotherapy techniques are constantly being developed. These include the use of genetically engineered immune cells (e.g., CAR-T-cells) to target and destroy cancer cells, the development of therapeutic vaccines to stimulate an immune response, and the use of immune checkpoint inhibitors that prevent cancer cells from evading immune recognition[247,248]. Based on current knowledge and opportunities, the future of immunotherapy will most likely bring further breakthroughs and discoveries that could reshape our understanding of disease and revolutionize treatment options.

12. Conclusion

Links between the human immune system and cancer are better understood thanks to science and continued research. With the expansion of this understanding, there has been tremendous progress in the creation of clinically applicable and effective cancer immunotherapies. The effectiveness of CAR-T-cell therapy and immune checkpoint blockade has shown that it is possible to rewire the immune system to target cancer cells. However, difficulties still exist, such as low response rates and toxicity control. Important research issues include developing biomarkers to predict response and methods to increase response rates. Combination therapies involving immunotherapy and other treatment options, such as chemotherapy or radiation, show promise in enhancing efficacy and expanding the patient population that can benefit from immunotherapy. Biomarkers play a crucial role in predicting response to immunotherapy, but current biomarkers have their limitations. Future research should focus on improving biomarkers and comprehending the tumour microenvironment. Treatment options for tumours that are resistant to conventional medicines include neoantigen discovery, TCR-T-cell therapy, and other breakthrough techniques. The development of cancer immunotherapy will be influenced by improving our knowledge of tumour immunology and making use of new AI technology. It is crucial to integrate clinical and basic research programs to address clinical needs and guide research directions in cancer immunotherapy. Continued collaboration between scientists and informatics experts will lead to progress in this field and improve outcomes for cancer patients.

Conflict of interest

The authors declare no conflicts of interest.

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