UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

REVIEW OPEN ACCESS

Current Immunotherapy Techniques for Cancer Treatment: A Scoping Review

Liliane A. Kreuder, BSc Student [1]*

[1] Department of Cell and Systems Biology and Pharmacology, University of Toronto, Toronto, Ontario, Canada M5S 1A4

*Corresponding Author: liliane.kreuder@mail.utoronto.ca

Abstract

Introduction: Immunotherapy, or the utilization of the immune system in fighting cancer, has been of interest as of late. Many different immunotherapy strategies exist, such as modifying T cells, generating cancer vaccines, as well as using chemokines, to elicit a strong anti-tumor response. As a strong emerging field in cancer research, this paper aims to conduct a scoping review to investigate the current research in immunotherapy targeting cancer and to summarize popular methods versus under-researched topics in the field.

Methods: This scoping review follows PRISMA. Articles were found using MEDLINE, Scopus, and EMBASE, and were then screened using inclusion and exclusion criteria using the title and abstracts and then the full text. After the screening stage, papers chosen were categorized depending upon the authors' main method of adapting the immune system to target cancer.

Results: A total of 194 articles were included in this review. From the 194 articles, the method with the greatest amount of research in adapting the immune system to attack cancer are CAR-T cells, with 31 articles (16.0%). The second greatest category was cancer vaccines (28 articles; 14.4%), the third largest was other T cell-based immunotherapy strategies (25 articles; 12.9%) and the fourth largest was generating antibodies (24 articles; 12.4%). Other notable categories include cytokines and immune checkpoint inhibitors, while the smallest categories include bacteria, natural medicine, and nanoparticles.

Discussion: The main fields of CAR-T cells, cancer vaccines, and antibodies commonly target tumor antigens involved in either tumor proliferation and progression or cancer invasion and metastasis. Further research is needed to demonstrate the strengths or limitations of using one immunotherapy technique over the other when it comes to inhibiting both of these cancer hallmarks. Furthermore, the review identifies multiple promising future avenues of immunotherapy that are currently less extensively investigated, such as adapting other immune cells, coupling immunotherapy techniques with nanoparticles, or using bacteria proteins to elicit a stronger immune response.

Conclusion: This review aids in summarizing current focuses in the field of immunotherapy and provides future avenues and next steps for cancer research for new scientists pursuing a career in cancer research.

Keywords: cancer; immunotherapy; CAR-T cells; antibodies; T cells; cancer vaccines

Introduction

In a landmark paper published in 2000, Hanahan and Weinberg proposed the existence of six hallmarks of cancer that describe how tumors are able to grow and develop [1]. They argue that human tumor pathogenesis is a multistep process, where tumor cells acquire traits that ultimately lead them to become tumorigenic and ultimately malignant. These traits include the development of the tumor itself, such as self-sufficiency in growth signals, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, insensitivity to anti-growth signals, and evading apoptosis [1].

However, as the cancer field progressed and new research emerged, the original six characteristics were no longer sufficient to describe the many ways cancers develop, resulting in Hanahan and Weinberg adding two new hallmarks of cancer in 2011 [2]. The first new hallmark, deregulating cellular energetics, describes the ability of the tumor to modify cellular metabolism to enable its own proliferation. The second hallmark, avoiding immune destruction, describes how cancer cells evade immunological destruction by T cells and B cells, among other immune cells. Finally, the authors also included the existence of two enabling characteristics, genome instability and tumor-promoting inflammation [2] to provide a comprehensive

framework of our understanding of cancer and how tumors develop today.

More specifically, the ability for tumors to avoid immune destruction has garnered a significant amount of attention in the field and has resulted in the development of cancer immunotherapy. Unlike traditional treatments for cancer, such as radiotherapy or chemotherapy, immunotherapy attempts to modulate the immune system to attack cancer cells. Many different immunotherapy strategies exist, such as modifying T cells, generating cancer vaccines, as well as using chemokines, to elicit a strong anti-tumor response [3]. Due to the large amount of research in the field, the objective of this scoping review is to summarize the most recent developments in immunotherapy since 2000, and to identify which methods have been most extensively researched versus other areas that are under-studied in the field.

Methods

This review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) Statement [4]. The electronic search was conducted using online databases MEDLINE, Scopus, and Embase in September 2022 to search for papers with terms relating to immunotherapy and cancer. For inclusion in the scoping review, articles were required to have an approach that modifies the immune system either directly (modifying the immune cells themselves) or indirectly (utilizing drugs, antibodies, or antigens that will affect the immune system in some way, for example) as a treatment for cancer. Only peer-reviewed primary research articles that were published between 2000-2022 were included for the purposes of this review to focus the results on recent findings and focuses occurring in the field. All different immunotherapies were accepted, and articles were included regardless of model type, such as cell lines, animal models, or human clinical trials.

Articles were excluded if they were dissertations, review articles (systematic, meta-analysis, scoping), or protocol papers. Furthermore, papers were not included if they did not have a direct link for the treatment of cancer. Papers were excluded if they focused on the delivery of the immunotherapy, such as using a lipid nanoparticle, if the focus of the paper was on the delivery method itself and not the component that was modifying the immune system. This decision was made to focus the scope of the review, since delivery techniques is an entire field of research in itself. Other papers that were excluded did not adapt the immune system in any way, and simply identified potential molecular targets or biomarkers that could potentially be used as a treatment.

The screening process was conducted using Covidence, where the author screened all articles found from the online search using the title and abstracts. Articles that were included to the full-text review stage were screened twice by the reviewer to ensure that the screening stage was comprehensive. Articles that were accepted to the extraction stage were then extracted using a form on Microsoft Excel that included information regarding article type, immunotherapy method, cancer type, and results. In this article, "immunotherapy" is used as an encompassing term that includes all methods that either modify or enhance the immune system as a therapy to fight cancer. Additionally, "cancer" includes all cancer cell lines, cancer animal models, and cancer patients in clinical trials undergoing immunotherapy to include all stages of current research in the field. The review and extraction process was done iteratively over the span of a couple of weeks, and at the end of the extraction of information, the author categorized each paper depending on its primary immunotherapy technique. The different categories will be further explored in the results section, however, include groups such as T cells, antibodies, and vaccines.

Results

The initial search produced 8783 articles (Figure 1). During the initial round of screening, 4142 articles were removed as duplicates, and 3568 articles were removed after screening title and abstracts. Of the 574 articles remaining at the full-text stage, 380 were excluded with reasons. Thus, a total of 194 articles were included in this review.

From the 194 articles, the method with the greatest amount of research in adapting the immune system to attack cancer are Chimeric Antigen Receptor (CAR) T cells, with 31 articles (16.0%). The second greatest category was cancer vaccines (28 articles; 14.4%), the third largest was other T cell-based immunotherapy strategies (25 articles; 12.9%) and the fourth largest was generating antibodies (24 articles; 12.4%). Other notable categories include cytokines and immune checkpoint inhibitors, while the smallest categories, and thus least amount of research for the restraints within this paper include bacteria, natural medicine, and nanoparticles. A summary of all the categories and numbers can be found in Table 1 and in Figure 2.

CAR-T Cells

CAR-T cells have been an incredibly promising avenue of cancer research, where CARs are engineered receptors that redirect T cells to recognize a specific antigen, commonly expressed by the tumor, resulting in T cell activation and the promotion of an antitumor response. However, some limitations of this therapy include antigen escape, poor tumor infiltration, and limited efficacy against solid tumors. Many approaches attempt to solve these limitations by employing novel innovations in CAR-T cell engineering, such as by editing the antigen binding domain, hinge region, or transmembrane domain on the receptor [5].

Of the 31 CAR-T cell articles, the majority of papers were research articles utilizing either cell or animal models (26 articles), while the rest were data obtained from clinical

trials (5 articles). 17 research articles engineered CARs that would recognize a specific protein on the surface of the tumor. Common targets include targeting Human Epidermal Growth Factor 2 (HER2) or Epidermal Growth Factor Receptor (EGFR) [6–8], which are believed to have a role in the growth of the tumor. There was also a strong focus in targeting proteins that are highly expressed on the surface of tumors, such as Epithelial Cell Adhesion Molecule EpCAM [9,10], L1 Cell Adhesion Molecule (L1CAM) [11], or fibronectin [12]. Cell adhesion proteins have been proposed to be important targets for its role in cell-cell and cell-extracellular matrix adhesion that may play a role in cancer invasion and signaling [13]. Three research articles engineered CARs that would specifically activate T cells by targeting CD5 [14], CD4 and CD8 [15], and CD3 [16].

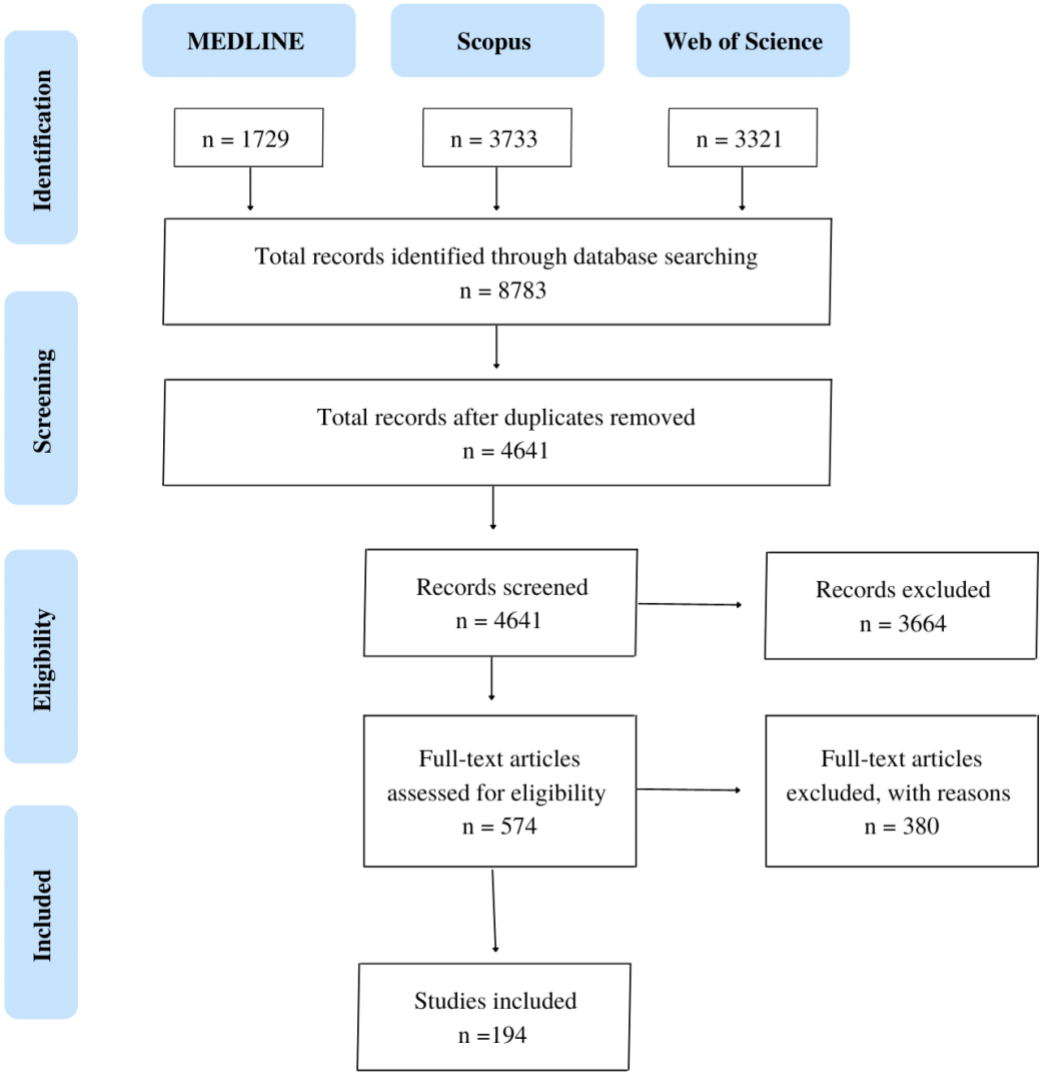

Figure 1. Scoping review selection process in identifying the included articles. Created using Canva.

Table 1. The different immunotherapy techniques identified by the review and the respective number of articles in each category, in descending order

Immunotherapy Technique	Number of Articles
CAR-T cell	31
Cancer vaccines	28
T cells	25
Antibodies	24
Other immune cells (dendritic cells, macrophages, natural killer cells, B cells)	23
Immune checkpoint inhibitors	17
Cytokines	14
Nanoparticles	8
Bacteria	7
Drugs	6
CpG oligodeoxynucleotides	4
Viruses	5
Natural medicine	2
Total articles	194

Less investigated topics include creating CAR-T cells that secrete anti Programmed Cell Death Protein (PD-1) antibodies that prevents the inhibitory effects of PD-1 signaling in T cells and prevents T cell exhaustion [17], and combining the usage of CAR-T cells and a reactive oxygen species (ROS) accelerator prodrug, PipFcB to increase the cytotoxicity of the tumor microenvironment [18]. Lastly, one paper focuses on engineering the hinge region of CAR-T cells by enhancing the cysteine residues in the hinge region to generate enhanced tumor lysis and larger CAR-T cell clusters [19].

In a phase I clinical trial, authors engineered a bispecific CAR-T cell that targets both CD19 and CD22 for patients with relapsed or refractory B cell acute lymphoblastic leukemia [20]. The paper found that the CAR-T cells successfully proliferated in vivo and mediated anti-leukemic activity in patients. In another phase I clinical trial, patients with relapsed refractory multiple myeloma were given bispecific CAR-T cells targeting CD38 and protein BM38 and found that after 9 months follow-up 87% of patients had a clinical response to the treatment [21].

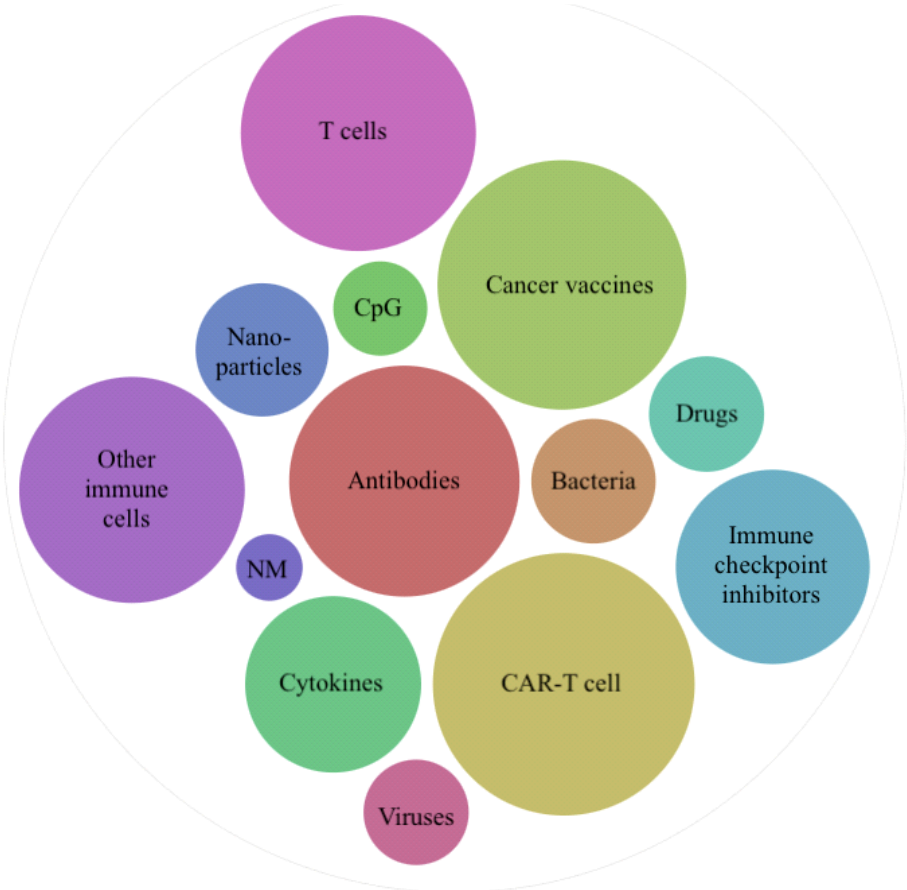

Figure 2. Circular packing chart visual representation of the number of articles found in each immunotherapy technique. Other immune cells include macrophages, dendritic cells, natural killer cells, and B cells. Abbreviations NM – Natural Medicine, and CpG – CpG oligodeoxynucleotides. Created using RAWgraphs.

The clinical trials show mixed efficacy of CAR-T cell therapy, where patient's CAR-T cells were able to proliferate and expand [20,22], but not in all studies [23]. Furthermore, the range of clinical response varies, where some trials had high success of over 80% of patients achieving a response from treatment [21,22,24], while another study only received a 27% response from treatment [23].

Vaccines

Cancer vaccines typically function by administering exogenous material, such as tumor antigens, that then activate an immune response. The goal of vaccines is to be able to induce an immune response against specific tumor antigens that will result in tumor regression [25]. Of the 28 total articles that utilized vaccines as a method to attack cancer, 26 were research articles, and two were clinical trials. 12 research papers used proteins or antigens in their vaccines to elicit an immune response, such as using the HER1 [26] or HER 2 protein [27] to inhibit proliferative responses from the tumor. Other proteins found on tumors that were used in vaccines include targets of other proliferative pathways such as EGFR [28], adhesion protein EpCAM [29,30], and other tumor surface proteins [31–33].

Some novel vaccination strategies include ectopically expressed a codon-optimized granulocyte macrophage-colony stimulating factor (GM-CSF) in cells, which were later injected into mice. GM-CSF is an immunomodulatory factor that facilitates humoral and cellular immunity. The authors found that the GM-CSF vaccination resulted in greater cytokine production and dendritic cell localization to lymph nodes compared to control, demonstrating a greater immune response [34]. Another study used a recombinant lentiviral vector expressing human telomerase reverse transcriptase (lv-hTERT) vaccination. The overexpression of telomerase has been cited as a hallmark of cancer, since telomerase activation circumvents telomerase-dependent cell apoptosis. The authors found lv-hTERT vaccination improved the strength of T-cell immune response against cancer tumor cells [35].

Another popular strategy was culturing dendritic cells in vitro, and then injecting them as a vaccine against tumors. Dendritic cells were commonly stimulated using a mixture of antigens and cytokines in vitro [36–38], which would allow them to then present the antigens to T cells in the lymph nodes to activate an immune response against tumors once injected. Other strategies include creating a dendritic cell and tumor cell fusion, resulting in the stable secretion of cytokine IL-12 and activation of T cells causing a reduction in tumor metastasis [39], as well as dendritic cells primed using cancer stem-like cell (CSC) associated antigens which resulted in a specific T-cell response against CSCs expressing tumor cells [40]. Overall, eight research articles investigated dendritic cell vaccination.

Two papers conducted clinical trials on the usage of cancer vaccines. The first paper primed dendritic cells using Human Papillomavirus (HPV) oncoproteins which were then delivered subcutaneously to patients with cervical cancer, which was found to increase the number of T cells against HPV oncoproteins [41]. In the second study, authors administered personalized peptide vaccines, a vaccine that utilizes the patient's cancer peptides, to create a personalized therapy. Patients that were administered the vaccine experienced a longer progression-free survival compared to controls [42].

T Cells

Aside from CAR-T cell research, there is also notable interest in other strategies to adapt T cells as a treatment for cancer. A total of 25 articles were found, with one paper being a clinical study. The most common strategy was to modify T cells either structurally or by their activity (13 articles). A team of researchers added a fucose group to T cell surface glycoproteins to improve homing to tumor tissue [43]. Comparatively, a different study engineered T cells to express an additional cysteine residue on each receptor chain to promote the formation of a second disulfide bond, which mediated higher cytokine secretion and tumor lysis than normal T cells [44]. T cell activity was modified in a variety of different ways. One study knocked out a RAS GTPase protein in T cells (RASA2) that becomes downregulated during T cell activation, which resulted in enhanced cytolytic activity in response to the cancer antigen and increased cytokine production [45]. Another study constructed a constitutively active cytokine signaling receptor CR7 in T cells that resulted in increased T cell-proliferation and antitumor activity [46]. Other studies modified the target of T cells by selectively inducing them to target a specific antigen, such as Melanoma-Associated Antigen 4 (MAGE-A4) in Hodgkin's lymphoma [47], human tumor antigen EphA2 [48], and human tumor antigen DEP domain containing 1 (DEPDC1) [49].

Fewer studies investigated how to activate T cells, such as by administering lysosomes [50] or by using synthetic microbead based artificial antigen presenting cells [51] One study investigated preventing T-cell exhaustion by administering nicotinamide (water soluble form of vitamin B3), which was found to inhibit the expression of inhibitory receptors and reduce the release of ROS [52]. Lastly, a clinical trial investigated the feasibility of T-cell based immunotherapy by extracting T lymphocytes from patients diagnosed with advanced urothelial urinary bladder cancer, which were then enhanced and expanded in vitro, and then reintroduced back into the patients. The treatment was only a partial success, with re-infusion of the T cells being only feasible for half of the patients, while the other half experienced technical failures [53].

Antibodies

Antibodies are a potential therapeutic for cancer due to its role in manipulating tumor-related signaling and immunomodulatory properties by activating immune cells

[54]. Of the 24 papers that studied antibodies, all of them were research articles. One possible method to use antibodies in the treatment of cancer is to design the antibody to target an antigen present on the tumor, which can either direct immune cells such as T cells to destroy the tumor or destroy the tumor itself (8 articles). Two articles designed antibodies targeting growth factors such as Erbb2 (55) and HER2 [56], however had different mechanisms of action. The Errb2 antibody was able to bind to Errb2 positive tumors and inhibit growth [55] directly, whereas the HER2 antibodies exerts its function by activating and directing T cells to the tumor [56]. Other tumor antigens that were targeted using antibodies include a surface glycoprotein, carbonic anhydrase IX [57], a membrane-bound protein mucin 1 (MUC1) [58], and a cell surface fibroblast activating protein (FAP) [59].

Antibody immunotherapy was also used to target a type of cancer called lymphomas, which is characterized by lymphocytes proliferating out of control and causing swelling of the lymph nodes. Antibodies have been created to target ligands on these proliferating lymphocytes as a potential cancer treatment. To treat Hodgkin's lymphoma, a study created an antibody that targets the CD30 ligand found on resting B cells and activated T cells, which may have a potential function of apoptosis and cell cycle regulation. When injecting the anti-CD30 antibody into mice xenografted with Hodgkin's lymphoma, the authors found complete tumor regression [60]. Other authors targeted non-Hodgkin's lymphoma using bispecific anti-CD3 and anti-CD20 antibodies [61], or bispecific anti-CD3 and anti-CD3 antibodies [62].

Other

Smaller sections include cytokine immunotherapy (14 articles), where cytokines bind to receptors and induce differentiation and proliferation of immune cells to exert anti-tumor responses [63]. The majority of papers utilized IL-2 as a therapeutic (10 articles), due to its role in promoting the expansion of natural killer cells and T lymphocytes [63]. Some papers also fused IL-2 with other proteins, such as GM-CSF [64,65], to enhance IL-2 function in stimulating immune cell activity and phagocytosis. Other cytokines studied were IL-15 [66], which promotes anti-tumor activity of T cells [63], IL-8 [67], which recruits lymphocytes to the tumor [63], and lastly IL-7, which improves effector function of T cells by repressing negative regulatory signals [68].

17 articles investigated the use of immune checkpoint inhibitors, which commonly targets PD-1 expressed on T cells. When PD-1 is bound to the programmed cell death ligand 1 (PD-L1), T cell proliferation is reduced, and apoptosis is induced. Furthermore, it has been found that PD-L1 acts as a pro-tumorigenic factor in cancer cells and is implicated in tumor progression [69]. By inhibiting the PD-1/PD-L1 axis, it is possible to promote a greater immune cell response. Strategies include using siRNA to silence PD-1 expression [70], using peptides or antibodies to inhibit PD-1/PD-L1 binding [71,72], or knocking down PD-1 in T cells in vitro and then administering them back in vivo [73].

Smaller categories include targeting other immune cells such as B cells, dendritic cells, lymphocytes, macrophages, and natural killer cells (23 articles) as an immunotherapy by specific activation towards tumor cells. Some studies utilized bacteria proteins (7 articles) fused with tumor antigens to boost immune response. Furthermore, the use of CpG oligodeoxynucleotides, which are short single-stranded synthetic DNA molecules, as an immunostimulant (4 articles) was also explored. Similarly, 5 articles utilized viruses to promote an immune response against cancer, and another 6 articles investigated different drugs that target cancer. Two studies investigated the use of chinese natural medicine (Bojungikki-Tang and Gegen Qinlian decoction) in conjunction with PD-1 immune checkpoint inhibitors to elicit an antitumor response [74,75]. Lastly, 8 articles utilized nanoparticles to either stimulate and promote immune cell activation, or to directly target apoptosis in tumor cells.

Discussion

Cancer immunotherapy is a rapidly developing field with a variety of different approaches or techniques that can be pursued. CAR-T cells were identified as the current largest category, where T cell receptors are engineered to recognize a specific antigen and mount an immune response against tumors. The second largest category were cancer vaccines, which includes the administration of dendritic cells or other factors such as GM-CSF to induce anti-tumor effects. The third most researched category was T cells, which are modified either structurally or engineered to have a greater immune response. The last notable category are antibodies, which are used to either direct T cells to cancer tumors or destroy the tumor itself.

All categories targeted similar components of the tumor. Proteins that are involved in growth-factor signaling or proliferation are commonly overexpressed in cancers, so targeting proteins such as HER2 or EGFR allows for immune cells to specifically identify these tumors and generate an immune response. CAR-T cells were generated to specifically target HER2 or EGFR [6–8], and HER1/2 and EGFR proteins were also used in cancer vaccines [26–28]. Furthermore, antibodies were also used to target HER2 on cancer cells [56], as well as a different growth factor Erbb2 [55].

Another common target in immunotherapy includes cell adhesion molecules which play a role in tumor invasion and cancer signaling. CAR-T cells were engineered against EpCAM [9,10] and L1CAM [11], or fibronectin [12]. EpCAM was also a target in the development of a cancer vaccines [29,30], while antibodies targeted other surface proteins such as FAP [59], and MUC1 [58].

The common targets of tumor proliferation as well as tumor invasion demonstrate the connectivity of the hallmarks of cancer proposed by Hannahan and Weinberg [1,2], where the immune system is modified and adapted to recognize these tumorigenic factors and consequently destroy the tumor cells. Therefore, it is important to note that cancer research is interdisciplinary in nature, where research investigating how tumors proliferate or change their surroundings to benefit their own growth can potentially provide new targets for immunotherapy.

While this scoping review identified some large categories, other less extensively researched methods were included as well. Although T cells or dendritic cells are a large current focus today, there is promising research regarding the utilization of B cells [76], or natural killer cell activation and expansion [77,78] in promoting the immune system response against cancers. Further research is needed in other immune cells to determine its efficacy in cancer therapy versus typical T cell therapeutics. Furthermore, a notable emerging field in immunotherapy is the use of nanoparticles. Although not a notable category in this scoping review due to the stringent inclusion and exclusion criteria that required papers to adapt the immune system and not focus on delivery techniques such as nanoparticles or liposomes, there is strong potential in coupling the immunotherapy methods identified in this review with delivery techniques to be administered into the body. Lastly, other potential avenues in research include inhibiting the PD1-PDL1 axis to promote T cell activity and proliferation. Inhibition of this pathway has been investigated in a variety of different ways, such as through the use of antibodies [79,80], peptides [71], or siRNA [70]. Further research is needed to investigate the strengths and limitations of each approach.

Conclusions

This scoping review identified a total of 194 articles that adapt the immune system to attack cancer. The most extensively researched categories include CAR-T cells, cancer vaccines, T cells, and antibodies. Less extensively researched categories include immune checkpoint inhibitors, nanoparticles, viruses, CpG oligonucleotides, and other immune cells. The review demonstrated the importance of cross-subject research in the field, where research investigating tumorigenic factors provides potential targets for the field of immunotherapy. Finally, this review provides insight into the latest development in cancer immunotherapy since 2000 and summarizes potential areas of future research for emerging scientists interested in pursuing research in a promising field.

List of Abbreviations Used

CAR- T cells: chimeric antigen receptor T cells
CpG: CpG oligodeoxynucleotides
NM: natural medicine
HER-2: human epidermal growth factor 2
EGFR: epidermal growth factor receptor
EpCAM: epithelial cell adhesion molecule
L1CAM: L1 cell adhesion molecule
PD-1: programmed cell death protein 1
ROS: reactive oxygen species
CSC: cancer stem-like cell
HPV: human papillomavirus
RASA2: RAS GTPase protein
MAGE-A4: melanoma-associated antigen 4
DEPDC1: DEP domain containing 1
MUC1: mucin 1
FAP: fibroblast activating protein
PD-L1: programmed cell death ligand 1

Conflicts of Interest

The author declares no conflicts of interest.

Ethics Approval and/or Participant Consent

The study did not require any ethics approval and/or participant consent because this was a scoping review.

Acknowledgements

I would like to thank my mentor, Alisha, for her support throughout the study.

Funding

This paper was not funded.

References

[1] Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000 Jan 7;100(1):57–70. https://doi.org/10.1016/S0092-8674(00)81683-9
[2] Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011 Mar 4;144(5):646–74. https://doi.org/10.1016/j.cell.2011.02.013
[3] Tan S, Li D, Zhu X. Cancer immunotherapy: pros, cons and beyond. Biomedicine & Pharmacotherapy. 2020;124:109821. https://doi.org/10.1016/j.biopha.2020.109821
[4] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009 Jul 21;339:b2700. https://doi.org/10.1136/bmj.b2700
[5] Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer J. 2021; 11(4):69. https://doi.org/10.1038/s41408-021-00459-7
[6] Ahmed N, Salsman VS, Yvon E, Louis CU, Perlaky L, Wels WS, et al. Immunotherapy for osteosarcoma: genetic modification of T cells overcomes low levels of tumor antigen expression. Molecular Therapy. 2009;17(10 PG-1779–1787):1779–87. https://doi.org/10.1038/mt.2009.133

[7] Ahn S, Li J, Sun C, Gao K, Hirabayashi K, Li H, et al. Cancer immunotherapy with T cells carrying bispecific receptors that mimic antibodies. Cancer Immunol Res. 2019;7(5):773–783. https://doi.org/10.1158/2326-6066.CIR-18-0636

[8] Wing A, Fajardo CA, Posey ADJ, Shaw C, Da T, Young RM, et al. Improving CART-cell therapy of solid tumors with oncolytic virus-driven production of a bispecific T-cell engager. Cancer Immunol Res. 2018;6(5):605–616. https://doi.org/10.1158/2326-6066.CIR-17-0314

[9] Li X, Zhang W, Lin J, Wu H, Yao Y, Zhang J, et al. T cell membrane cloaking tumor microenvironment-responsive nanoparticles with a smart "membrane escape mechanism" for enhanced immune-chemotherapy of melanoma. Biomater Sci. 2021;9(9): 3453–3464. https://doi.org/10.1039/d1bm00331c

[10] Shirasu N, Yamada H, Shibaguchi H, Kuroki M, Kuroki M. Molecular characterization of a fully human chimeric T-cell antigen receptor for tumor-associated antigen EpCAM. J Biomed Biotechnol. 2012;2012(101135740): 853879. https://doi.org/10.1155/2012/853879

[11] Textor A, Grunewald L, Anders K, Klaus A, Schwiebert S, Winkler A, et al. Cd28 co-stimulus achieves superior car t cell effector function against solid tumors than 4-1bb co-stimulus. Cancers (Basel). 2021;13(5):1–17. https://doi.org/10.3390/cancers13051050

[12] Wagner J, Wickman E, Shaw TI, Anido AA, Langfitt D, Zhang J, et al. Antitumor effects of CAR T cells redirected to the edb splice variant of fibronectin. Cancer Immunol Res. 2021;9(3):279–290. https://doi.org/10.1158/2326-6066.CIR-20-0280

[13] Okegawa T, Pong RC, Li Y, Hsieh JT. The role of cell adhesion molecule in cancer progression and its application in cancer therapy. Acta Biochim Pol. 2004;51(2):445–57.

[14] Dai Z, Mu W, Zhao Y, Jia X, Liu J, Wei Q, et al. The rational development of CD5-targeting biepitopic CARs with fully human heavy-chain-only antigen recognition domains. Molecular Therapy. 2021;29(9):2707–2722. https://doi.org/10.1016/j.ymthe.2021.07.001

[15] Jamali A, Kapitza L, Schaser T, Johnston ICD, Buchholz CJ, Hartmann J. Highly efficient and selective CAR-gene transfer using CD4- and CD8-targeted lentiviral vectors. Mol Ther Methods Clin Dev. 2019;13:371–379. https://doi.org/10.1016/j.omtm.2019.03.003

[16] Munisvaradass R, Kumar S, Govindasamy C, Alnumair KS, Mok PL. Human CD3+ T-cells with the anti-ERBB2 chimeric antigen receptor exhibit efficient targeting and induce apoptosis in ERBB2 overexpressing breast cancer. Cells. Int J Mol Sci. 2017;18. https://doi.org/10.3390/ijms18091797

[17] Li S, Siriwon N, Zhang X, Yang S, Jin T, He F, et al. Enhanced cancer immunotherapy by chimeric antigen receptor–modified T cells engineered to secrete checkpoint inhibitors. Clinical Cancer Research. 2017;23(22):6982–2992. https://doi.org/10.1158/1078-0432.CCR-17-0867

[18] Yoo HJ, Liu Y, Wang L, Schubert ML, Hoffmann JM, Wang S, et al. Tumor-specific reactive oxygen species accelerators improve chimeric antigen receptor T cell therapy in B cell malignancies. Int J Mol Sci. 2019;20(10). https://doi.org/10.3390/ijms20102469

[19] Wang Y, Gao Y, Niu C, Wang B, Zhao S, Roex G, et al. Chimeric antigen receptor clustering via cysteines enhances T-cell efficacy against tumor. Cancer Immunol Immunother. 2022;(cn3, 8605732). https://doi.org/10.1007/s00262-022-03195-4

[20] Dai H, Wu Z, Jia H, Tong C, Guo Y, Ti D, et al. Bispecific CAR-T cells targeting both CD19 and CD22 for therapy of adults with relapsed or refractory B cell acute lymphoblastic leukemia. J Hematol Oncol. 2020;13. https://doi.org/10.1186/s13045-020-00856-8

[21] Mei H, Li C, Jiang H, Zhao X, Huang Z, Jin D, et al. A bispecific CAR-T cell therapy targeting BCMA and CD38 in relapsed or refractory multiple myeloma. J Hematol Oncol. 2021;14(1). https://doi.org/10.1186/s13045-021-01170-7

[22] Shah NN, Johnson BD, Schneider D, Zhu F, Szabo A, Keever-Taylor CA, et al. Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial. Nat Med. 2020;26(10):1569–1575. https://doi.org/10.1038/s41591-020-1081-3

[23] Ramos CA, Rouce R, Robertson CS, Reyna A, Narala N, Vyas G, et al. In vivo fate and activity of second- versus third-generation CD19-specific CAR-T cells in B cell non-Hodgkin's Lymphomas. Molecular Therapy. 2018;26(12):2727–2737. https://doi.org/10.1016/j.ymthe.2018.09.009

[24] Wei G, Zhang Y, Zhao H, Wang Y, Liu Y, Liang B, et al. CD19/CD22 dual-targeted car t-cell therapy for relapsed/refractory aggressive b-cell lymphoma: A safety and efficacy study. Cancer Immunol Res. 2021;9(9):1061–1070. https://doi.org/10.1158/2326-6066.CIR-20-0675

[25] Saxena M, van der Burg SH, Melief CJM, Bhardwaj N. Therapeutic cancer vaccines. Nat Rev Cancer. 2021;21(6):360–78. https://doi.org/10.1038/s41568-021-00346-0

[26] Aguiar Alpízar Y, Sánchez Ramírez B, Fernández DRH, Capote AR, Hidalgo GG, Rodríguez RP, et al. HER1-ECD vaccination dispenses with emulsification to elicit HER1-specific anti-proliferative effects. Hum Vaccin. 2009;5(3):158–165. https://doi.org/10.4161/hv.5.3.7129

[27] Chen Y, Xie Y, Chan T, Sami A, Ahmed S, Liu Q, et al. Adjuvant effect of HER-2/neu-specific adenoviral vector stimulating CD8+ T and natural killer cell responses on anti-HER-2/neu antibody therapy for well-established breast tumors in HER-2/neu transgenic mice. Cancer Gene Ther. 2011;18(7):489–499. https://doi.org/10.1038/cgt.2011.18

[28] Asadi-Ghalehni M, Ghaemmaghami M, Klimka A, Javanmardi M, Navari M, Rasaee MJ. Cancer immunotherapy by a recombinant phage vaccine displaying EGFR mimotope: an in vivo study. Immunopharmacol Immunotoxicol. 2015;37(3):274–279. https://doi.org/10.3109/08923973.2015.1027917

[29] Elia L, Mennuni C, Storto M, Podda S, Calvaruso F, Salucci V, et al. Genetic vaccines against Ep-CAM break tolerance to self in a limited subset of subjects: initial identification of predictive biomarkers. Eur J Immunol. 2006;36(5):1337–1349. https://doi.org/10.1002/eji.200535514

[30] Neighbors M, Apt D, Chang JCC, Brinkman A, Sipos-Solman I, Ong R, et al. EpCAM-specific vaccine response by modified antigen and chimeric costimulatory molecule in cynomolgus monkeys. Journal of Immunotherapy. 2008;31(7):644–655. https://doi.org/10.1097/CJI.0b013e3181826d89

[31] Blanchet JS, Valmori D, Dufau I, Ayyoub M, Nguyen C, Guillaume P, et al. A new generation of Melan-A/MART-1 peptides that fulfill both increased immunogenicity and high resistance to biodegradation: implication for molecular anti-melanoma immunotherapy. J Immunol. 2001;167(10):5852–5861. https://doi.org/10.4049/jimmunol.167.10.5852

[32] Chablani L, Tawde SA, Akalkotkar A, D'Souza MJ. Evaluation of a particulate breast cancer vaccine delivered via skin. AAPS J. 2019;21(2):12. https://doi.org/10.1208/s12248-018-0285-7

[33] Zheng Y, Zhang Y, Ma Y, Wan J, Shi C, Huang L. Enhancement of immunotherapeutic effects of HPV16E7 on cervical cancer by fusion with CTLA4 extracellular region. J Microbiol. 2008;46(6):728–736. https://doi.org/10.1007/s12275-008-0087-1

[34] Lin CC, Tsai CC, Lee JM, Fang CH, Chang KS, Wong KK, et al. The efficacy of a novel vaccine approach using tumor cells that ectopically express a codon-optimized murine GM-CSF in a murine tumor model. Vaccine. 2016;34(1):134–141. https://doi.org/10.1016/j.vaccine.2015.10.106

[35] Rusakiewicz S, Dosset M, Mollier K, Souque P, Charneau P, Wain-Hobson S, et al. Immunogenicity of a recombinant lentiviral vector carrying human telomerase tumor antigen in HLA-B*0702 transgenic mice. Vaccine. 2010;28(38):6374–6381. https://doi.org/10.1016/j.vaccine.2010.06.071

[36] Chang XH, Cheng HY, Cheng YX, Ye X, Guo HF, Fu TY, et al. Specific immune cell therapy against ovarian cancer in vivo and in vitro. Ai Zheng. 2008;27(12):1244–1250. https://pubmed.ncbi.nlm.nih.gov/19079987/

[37] Cho HI, Jung SH, Sohn HJ, Celis E, Kim TG. An optimized peptide vaccine strategy capable of inducing multivalent CD8+ T cell responses with potent antitumor effects. Oncoimmunology. 2015;4(11). https://doi.org/10.1080/2162402X.2015.1043504

[38] Lee JA, Shin JM, Song SH, Kim CH, Son S, Shin S, et al. Recruitment of dendritic cells using "find-me" signaling microparticles for personalized cancer immunotherapy. Biomaterials. 2022;282(a4p):121412. https://doi.org/10.1016/j.biomaterials.2022.121412

[39] Tan C, Dannull J, Nair SK, Ding E, Tyler DS, Pruitt SK, et al. Local secretion of IL-12 augments the therapeutic impact of dendritic cell-tumor cell fusion vaccination. Journal of Surgical Research. 2013;185(2):904–911. https://doi.org/10.1016/j.jss.2013.06.045

[40] Xu Q, Liu G, Yuan X, Xu M, Wang H, Ji J, et al. Antigen-specific T-cell response from dendritic cell vaccination using cancer stem-like cell-associated antigens. Stem Cells. 2009;27(8):1734–1740. https://doi.org/10.1002/stem.102

[41] Santin AD, Bellone S, Palmieri M, Ravaggi A, Romani C, Tassi R, et al. HPV16/18 E7-pulsed dendritic cell vaccination in cervical cancer patients with recurrent disease refractory to standard treatment modalities. Gynecol Oncol. 2006;100(3):469–478. https://doi.org/10.1016/j.ygyno.2005.09.040

[42] Yoshimura K, Minami T, Nozawa M, Kimura T, Egawa S, Fujimoto H, et al. A phase 2 randomized controlled trial of personalized peptide vaccine immunotherapy with low-dose Dexamethasone versus Dexamethasone alone in chemotherapy-I castration-resistant prostate cancer. Eur Urol. 2016;70(1):35–41. https://doi.org/10.1016/j.eururo.2015.12.050

[43] Alatrash G, Qiao N, Zhang M, Zope M, Perakis AA, Sukhumalchandra P, et al. Fucosylation enhances the efficacy of adoptively transferred antigen-specific cytotoxic T lymphocytes. Clinical Cancer Research. 2019;25(8):2610–2620. https://doi.org/10.1158/1078-0432.CCR-18-1527

[44] Cohen CJ, Li YF, El-Gamil M, Robbins PF, Rosenberg SA, Morgan RA. Enhanced antitumor activity of T cells engineered to express T-cell receptors with a second disulfide bond. Cancer Res. 2007;67(8):3898–3903. https://doi.org/10.1158/0008-5472.CAN-06-3986

[45] Carnevale J, Shifrut E, Kale N, Nyberg WA, Blaeschke F, Chen YY, et al. RASA2 ablation in T cells boosts antigen sensitivity and long-term function. Nature. 2022;609(7925):174–182. https://doi.org/10.1038/s41586-022-05126-w

[46] Shum T, Omer B, Tashiro H, Kruse RL, Wagner DL, Parikh K, et al. Constitutive signaling from an engineered IL7 receptor promotes durable tumor elimination by tumor-redirected T cells. Cancer Discov. 2017;7(11):1238–1247. https://doi.org/10.1158/2159-8290.CD-17-0538

[47] Cruz CR, Gerdemann U, Leen AM, Shafer JA, Ku S, Tzou B, et al. Improving T-cell therapy for relapsed EBV-negative Hodgkin lymphoma by targeting upregulated MAGE-A4. Clinical Cancer Research. 2011;17(22):7058–7066. https://doi.org/10.1158/1078-0432.CCR-11-1873

[48] Iwahori K, Kakarla S, Velasquez MP, Yu F, Yi Z, Gerken C, et al. Engager T cells: A new class of antigen-specific T cells that redirect bystander T cells. Molecular Therapy. 2014;22:S297. https://doi.org/10.1038/mt.2014.156

[49] Tosi A, Dalla Santa S, Cappuzzello E, Marotta C, Walerych D, del Sal G, et al. Identification of a HLA-A*0201-restricted immunogenic epitope from the universal tumor antigen DEPDC1. Oncoimmunology. 2017;6(8):e1313371. https://doi.org/10.1080/2162402X.2017.1412885

[50] Alhallak K, Sun J, Wasden K, Guenthner N, O'Neal J, Muz B, et al. Nanoparticle T-cell engagers as a modular platform for cancer immunotherapy. Leukemia. 2021;35(8):2346–2357. https://doi.org/10.1038/s41375-021-01127-2

[51] Caserta S, Alessi P, Guarnerio J, Basso V, Mondino A. Synthetic CD4+ T cell-targeted antigen-presenting cells elicit protective antitumor responses. Cancer Res. 2008;68(8):3010–3018. https://doi.org/10.1158/0008-5472.CAN-07-5796

[52] Alavi S, Emran AA, Tseng HY, Tiffen JC, McGuire HM, Hersey P. Nicotinamide inhibits T cell exhaustion and increases differentiation of CD8 effector T cells. Cancers (Basel). 2022;14(2). https://doi.org/10.3390/cancers14020323

[53] Sherif A, Hasan MN, Marits P, Karlsson M, Winqvist O, Thorn M. Feasibility of T-cell-based adoptive immunotherapy in the first 12 patients with advanced urothelial urinary bladder cancer. Preliminary data on a new immunologic treatment based on the sentinel node concept. Eur Urol. 2010;58(1):105–111. https://doi.org/10.1016/j.eururo.2009.09.026

[54] Weiner LM, Surana R, Wang S. Monoclonal antibodies: versatile platforms for cancer immunotherapy. Nat Rev Immunol. 2010;10(5):317–27. https://doi.org/10.1038/nri2744

[55] Arafat W, Gomez-Navarro J, Buchsbaum D, Xiang J, Casado E, Barker S, et al. Effective single chain antibody (scFv) concentrations in vivo via adenoviral vector mediated expression of secretory scFv. Gene Ther. 2002;9(4):256–262. https://doi.org/10.1038/sj.gt.3301639

[56] Grabert RC, Cousens LP, Smith JA, Olson S, Gall J, Young WB, et al. Human T cells armed with Her2/neu bispecific antibodies divide, are cytotoxic, and secrete cytokines with repeated stimulation. Clin Cancer Res. 2006;12(2):569–576. https://doi.org/10.1158/1078-0432.CCR-05-2005

[57] Chang DK, Moniz RJ, Xu Z, Sun J, Signoretti S, Zhu Q, et al. Human anti-CAIX antibodies mediate immune cell inhibition of renal cell carcinoma in vitro and in a humanized mouse model in vivo. Mol Cancer. 2015;14(1). https://doi.org/10.1186/s12943-015-0384-3

[58] Heuser C, Ganser M, Hombach A, Brand H, Denton G, Hanisch FG, et al. An anti-MUC1-antibody – Interleukin-2 fusion protein that activates resting NK cells to lysis of MUC1-positive tumour cells. Br J Cancer. 2003;89(6):1130–1139. https://doi.org/10.1038/sj.bjc.6601267

[59] Sum E, Rapp M, Frobel P, le Clech M, Durr H, Giusti AM, et al. Fibroblast activation protein a-targeted CD40 agonism abrogates systemic toxicity and enables administration of high doses to induce effective antitumor immunity. Clinical Cancer Research. 2021;27(14):4036–4053. https://doi.org/10.1158/1078-0432.CCR-20-4001

[60] Borchmann P, Treml JF, Hansen H, Gottstein C, Schnell R, Staak O, et al. The human anti-CD30 antibody 5F11 shows in vitro and in vivo activity against malignant lymphoma. Blood. 2003;102(10):3737–3742. https://doi.org/10.1182/blood-2003-02-0515

[61] Gall JM, Davol PA, Grabert RC, Deaver M, Lum LG. T cells armed with anti-CD3 x anti-CD20 bispecific antibody enhance killing of CD20+ malignant B cells and bypass complement-mediated rituximab resistance in vitro. Exp Hematol. 2005;33(4):452–459. https://doi.org/10.1016/j.exphem.2005.01.007

[62] Malik-Chaudhry HK, Prabhakar K, Ugamraj HS, Boudreau AA, Buelow B, Dang K, et al. TNB-486 induces potent tumor cell cytotoxicity coupled with low cytokine release in preclinical models of B-NHL. Mabs. 2021;13(1). https://doi.org/10.1080/19420862.2021.1890411

[63] Berraondo P, Sanmamed MF, Ochoa MC, Etxeberria I, Aznar MA, Pérez-Gracia JL, et al. Cytokines in clinical cancer immunotherapy. Br J Cancer. 2019;120(1):6–15. https://doi.org/10.1038/s41416-018-0328-y

[64] Stagg J, Wu JH, Bouganim N, Galipeau J. Granulocyte-macrophage colony-stimulating factor and interleukin-2 fusion cDNA for cancer gene immunotherapy. Cancer Res. 2004;64(24):8795–8999. https://doi.org/10.1158/0008-5472.CAN-04-1776

[65] Wen Q, Xiong W, He J, Zhang S, Du X, Liu S, et al. Fusion cytokine IL-2-GMCSF enhances anticancer immune responses through promoting cell-cell interactions. J Transl Med. 2016;14(1). https://doi.org/10.1186/s12967-016-0799-7

[66] Hasan AN, Selvakumar A, Shabrova E, Liu XR, Afridi F, Heller G, et al. Soluble and membrane-bound interleukin (IL)-15 Rα/IL-15 complexes mediate proliferation of high-avidity central memory CD8+ T cells for adoptive immunotherapy of cancer and infections. Clin Exp Immunol. 2016;186(2):249–65. https://doi.org/10.1111/cei.12816

[67] Alagkiozidis I, Facciabene A, Tsiatas M, Carpenito C, Benencia F, Adams S, et al. Time-dependent cytotoxic drugs selectively cooperate with IL-18 for cancer chemo-immunotherapy. J Transl Med. 2011;9. https://doi.org/10.1186/1479-5876-9-77

[68] Kudling T v, Clubb JHA, Quixabeira DCA, Santos JM, Havunen R, Kononov A, et al. Local delivery of interleukin 7 with an oncolytic adenovirus activates tumor-infiltrating lymphocytes and causes tumor regression. Oncoimmunology. 2022;11(1):2096572. https://doi.org/10.1080/2162402X.2022.2096572

[69] Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. Am J Cancer Res. 2020;10(3):727–42.

[70] Barati M, Mirzavi F, Nikpoor AR, Sankian M, Namdar Ahmadabad H, Soleimani A, et al. Enhanced antitumor immune response in melanoma tumor model by anti-PD-1 small interference RNA encapsulated in nanoliposomes. Cancer Gene Ther. 2022;29(6):814–824. https://doi.org/10.1038/s41417-021-00367-9

[71] Bojko M, Wegrzyn K, Sikorska E, Kocikowski M, Parys M, Battin C, et al. Design, synthesis, and biological evaluation of PD-1 derived peptides as inhibitors of PD-1/PD-L1 complex formation for cancer therapy. Bioorg Chem. 2022;128(1303703): 106047. https://doi.org/10.1016/j.bioorg.2022.106047

[72] Lichtenegger FS, Rothe M, Schnorfeil FM, Deiser K, Krupka C, Augsberger C, et al. Targeting LAG-3 and PD-1 to enhance T cell activation by antigen-presenting cells. Front Immunol. 2018;9. https://doi.org/10.3389/fimmu.2018.00385

[73] Otano I, Escors D, Schurich A, Singh H, Robertson F, Davidson BR, et al. Molecular recalibration of PD-1+ antigen-specific T cells from blood and liver. Molecular Therapy. 2018;26(11):2553–2566. https://doi.org/10.1016/j.ymthe.2018.08.013

[74] Chun J, Park SM, Yi JM, Ha IJ, Kang HN, Jeong MK. Bojungikki-Tang improves response to PD-L1 immunotherapy by regulating the tumor microenvironment in MC38 tumor-bearing mice. Front Pharmacol. 2022;13. https://doi.org/10.3389/fphar.2022.901563

[75] Lv J, Jia Y, Li J, Kuai W, Li Y, Guo F, et al. Gegen Qinlian decoction enhances the effect of PD-1 blockade in colorectal cancer with microsatellite stability by remodelling the gut microbiota and the tumour microenvironment. Cell Death Dis. 2019;10(6). https://doi.org/10.1038/s41419-019-1638-6

[76] Zhang TY, Ren HY, Pan N, Dong HX, Zhao SM, Wen ZF, et al. Tumor cell-derived autophagosomes (DRibbles)-activated B cells induce specific naive CD8+ T cell response and exhibit antitumor effect. Cancer Immunol Immunother. 2021;70(2):463–474. https://doi.org/10.1007/s00262-020-02695-5

[77] Uppendahl LD, Felices M, Bendzick L, Ryan C, Kodal B, Hinderlie P, et al. Cytokine-induced memory-like natural killer cells have enhanced function, proliferation, and in vivo expansion against ovarian cancer cells. Gynecol Oncol. 2019;153(1):149–57. https://doi.org/10.1016/j.ygyno.2019.01.006

[78] Poznanski SM, Nham T, Chew M v, Lee AJ, Hammill JA, Fan IY, et al. Expanded CD56superbrightCD16+ NK cells from ovarian cancer patients are cytotoxic against autologous tumor in a patient-derived xenograft murine model. Cancer Immunol Res. 2018;6(10):1174–1185. https://doi.org/10.1158/2326-6066.CIR-18-0144

[79] Muik A, Altintas I, Gieseke F, Schoedel KB, Burm SM, Toker A, et al. An Fc-inert PD-L1×4-1BB bispecific antibody mediates potent anti-tumor immunity in mice by combining checkpoint inhibition and conditional 4-1BB co-stimulation. Oncoimmunology. 2022;11(1). https://doi.org/10.1080/2162402X.2022.2030135

[80] Qiao Y, Qiu Y, Ding J, Luo N, Wang H, Ling X, et al. Cancer immune therapy with PD-1-dependent CD137 co-stimulation provides localized tumour killing without systemic toxicity. Nat Commun. 2021;12(1):6360. https://doi.org/10.1038/s41467-021-26645-6

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Alisha Anand, Joseph Lee
Article Dates: Received Dec 01 22; Accepted Jan 29 23; Published Mar 10 23

Citation
Please cite this article as follows:
Kreuder LA. Current immunotherapy techniques for cancer treatment: A scoping review. URNCST Journal. 2023 Mar 10: 7(3). https://urncst.com/index.php/urncst/article/view/449
DOI Link: https://doi.org/10.26685/urncst.449

URNCST Journal
"Research in Earnest"

Funded by the Government of Canada | Canada