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# Immunotherapy for Treatment of Cancer

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## Abstract

Cancer is known to be second cause of death worldwide despite aggressive therapeutic measures such as surgical resection of tumors, radiation therapy, and chemotherapy. The failure of currently available therapeutics for cancers, has led to increasing interest in alternative approaches including immunotherapy. Immunotherapy for cancer treatment is enhancing immune responses to fight cancer cells. Monoclonal antibodies, immune checkpoint blockades, targeted therapy, adoptive cell therapy, CAR T cells, and cancer vaccines are the most current and efficient parts of immunotherapy armamentarium. Immunotherapy has tremendous success in the treatment of cancers and is considered as a standard care of treatment or recurrence preventive therapy for variety of cancers. In this chapter, we discuss different types of immunotherapy for cancer treatment in detail.

**Keywords:** immunotherapy, immune checkpoint blockades, cancer vaccines, adoptive cell therapy, CAR T cell, personalized immunotherapy

## 1. Introduction

Cancer is the second most common cause of death in the world that has threatened health for thousands of years. Several aggressive measures such as surgical resection of tumors, chemotherapy, and radiotherapy are used to cure cancers. Although these therapeutics can minimize and inhibit cancer cells proliferation and metastasis, they have not been able to effectively defeat cancers until now. The efficacy of conventional treatments for cancer management is limited by factors such as recurrence of tumors and severe toxicities induced by therapeutics. Immunotherapy has become a tempting approach a long time after William Coley described the first immune stimulation by live bacteria for the treatment of cancer in 1893 [1]. Immunotherapy harnesses patients' own immune system to kill cancer cells thereby reducing toxic effects of traditional chemotherapy and radiotherapy. Immune cells can identify cancer cells by recognizing tumor-associated antigens. The ability of cancer cells to escape from immune system has limited the efficacy of immunotherapy. Current novel approaches have been involved in immunotherapy to stop immune evasion of cancer cells.

Immunotherapy includes several therapies such as monoclonal antibodies, tumor cell vaccines, immune cell vaccines, and adoptive cell therapy. Monoclonal antibodies, which block cytotoxic T lymphocyte-associated protein-4 (CTLA-4), programmed cell death-1 (PD-1), dendritic cell vaccines, and chimeric antigen receptor (CAR) T cells have shown a tremendous success in clinical trials for several

cancers. It is shown that immunotherapy has the potential to move to the front-line of therapeutic options in most cancers. Despite the benefits of immunotherapy, some treatments have severe side effects such as nausea, fever, and diarrhea [2]. The aim of this chapter is to study the concept of immunotherapy for cancer treatment and to provide a thorough review on immunotherapy's developments for both oncologists and cancer immunologists.

## **2. Monoclonal antibodies**

One of the mechanisms of immune system to defeat pathogens or cancers is to identify foreign substances or malignancies and generate antibodies against them. These antibodies can recognize pathogens and cancer cells by the antigens expressed on their surface. Antibodies have the ability to attach to the specific antigens and destroy foreign particles or malignancies. In the laboratory, scientists can generate many copies of antibodies that are specific to certain antigens on cancer cells. These are known as monoclonal antibodies. In 1997, the first monoclonal antibody, rituximab, was approved for treatment of non-Hodgkin's lymphoma. Beneficial outcomes of rituximab treatment resulted in emergence and development of monoclonal antibodies as a therapeutic approach for various hematological and solid cancers [3]. The most important step in generating monoclonal antibodies for cancer treatment is identifying right antigens on cancer cells. High mutation capacity of cancer cells and existence of various antigens make this task challenging. So far, monoclonal antibodies therapy has been more beneficial against some cancers than others.

Monoclonal antibodies can defeat cancer in different ways. Some monoclonal antibodies can recognize antigens expressed by cancer cells and mark them as a target that should be destroyed by immune system. This monoclonal antibody treatment is also known as targeted therapy [4]. Some of monoclonal antibodies cause apoptosis in cancer cells by directly attaching to the cancer cells. Preventing cell proliferation, destroying cell membrane, delivering radiation or chemotherapy to cancer cells, and inhibiting blood vessel growth are other functions of monoclonal antibodies to stop cancer cells. Monoclonal antibodies can robust, mimic or maintain the immune system's response on cancer cells in different ways, and some particular monoclonal antibodies act by more than one function [3]. Monoclonal antibodies can be categorized to three groups such as naked monoclonal antibodies (**Table 1**), conjugated monoclonal antibodies (**Table 2**), and bispecific monoclonal antibodies. Naked monoclonal antibodies act by just a single function. This single function can either be directly affecting cancer cells or by improving immune system against cancer cells. Trastuzumab is an example of monoclonal antibodies with direct effect on cancer cells. Trastuzumab can identify and block HER2 antigen, which is highly expressed on breast and stomach cancer cells. HER2 antigen is responsible for growth and proliferation of cancer cells. By blocking HER2 antigens, cancer cells are not able to expand and proliferate and spread in the body [5]. Immune check point inhibitors are monoclonal antibodies which improve immune system function. This group of antibodies will be discussed in detail later on this chapter. Some monoclonal antibodies can trigger immune system by attaching to immune cells and activating immune cells to destroy cancer cells. Alemtuzumab, which is a monoclonal antibody to treat chronic lymphocytic leukemia, binds to CD25 marker on the surface of lymphocytes and attracts immune cells to destroy cancer cells [6]. Conjugated monoclonal antibodies, also known as tagged antibodies or loaded antibodies, are antibodies that are being used to deliver either chemotherapy drugs or radioactive particles to cancer cells. These monoclonal

Monoclonal antibody	Target	Type	Approval year	Cancer
Rituximab	CD20	Chimeric IgG1	1997	B cell non-Hodgkin lymphoma
Trastuzumab	EGF	Humanized IgG1	1998	Breast cancer
Gemtuzumab Ozogamicin	CD33		2000	Acute myeloid leukemia
Alemtuzumab	CD52	Humanized IgG1	2001	B cell chronic lymphocytic leukemia
Ibritumomab Tiuxetan	CD20		2002	B cell non-Hodgkin lymphoma
Cetuximab	VEGFR	Chimeric IgG1	2004	Merkel cell carcinoma
Bevacizumab	VEGF	Humanized IgG1	2004	Colon cancer
Panitumumab	EGFR	Human IgG2	2006	Colorectal Ca
Catumaxomab	CD3	Chimeric mouse-rat hybrid	2009	Malignant ascites
Ofatumumab	CD20	Human IgG1	2009	B cell chronic lymphocytic leukemia
Ipilimumab	CTLA-4	Human IgG1	2011	Melanoma
Brentuximab Vedotin	CD30		2011	Hodgkin lymphoma
Pertuzumab	HER2	Humanized IgG1	2012	Breast cancer
Ado-Trastuzumab Emtansine	HER2	Humanized IgG1	2013	Breast cancer
Obinutuzumab	CD20		2013	B cell chronic lymphocytic leukemia
Denosumab		Human IgG2	2013	Osteoclastoma
Ramucirumab	VEGFR2	Human IgG1	2014	Gastric Ca
Pembrolizumab	PD-1	Humanized IgG1	2014	Melanoma
Nivolumab	PD-1	Human IgG1	2014	Melanoma
Dinutuximab	GD2	Chimeric IgG1	2015	Neuroblastoma
Daratumumab	CD38	Human IgG1	2015	Multiple myeloma
Necitumumab	EGFR	Human IgG1	2015	Lung cancer
Elotuzumab	SLAMF7	Humanized IgG1	2015	Multiple myeloma
Atezolizumab	PD-L1	Humanized IgG1	2016	Urothelial cancer
Avelumab (14)	PD-L1	human IgG1 monoclonal antibody	2017	Metastatic merkel cell carcinoma
Durvalumab	PD-L1	human IgG1 kappa monoclonal antibody	2018	Urothelial carcinoma/ non-small cell lung cancer

**Table 1.**  
*Unconjugated monoclonal antibodies currently approved by the Food and Drug Administration (FDA) for cancer therapy.*

antibodies reduce the toxic effects of systemic chemotherapy and radiotherapy by directly homing the toxic drugs to tumor microenvironment [7, 8]. Ibritumomab tiuxetan is a radio-immunotherapeutic drug which directly delivers radio isotopes to cancerous B cells in non-Hodgkin lymphoma. Ibritumomab tiuxetan is a radio-labeled monoclonal antibody against CD20 antigen, which is expressed on B cell surface. By attaching Ibritumomab tiuxetan to CD20 on the B cells and killing cancer cells, the drug is able to eliminate lymphoma [7]. Chemolabeled antibodies are monoclonal antibodies that are attached to chemotherapy drugs. Brentuximab

Monoclonal antibody	Target	Type	Approval year	Cancers
Ibritumomab tiuxetan	CD20 Radionucleotide (Yttrium <sup>90</sup> or Indium <sup>111</sup> )	Murine IgG1	2002	B cell non-Hodgkin's lymphoma/ lymphoproliferative disorder
Ositumomab	CD20 Radionucleotide (Iodine <sup>131</sup> )	Murine IgG2a	2003	Non-Hodgkin lymphoma
Brentuximab vedotin	CD30	Chimeric IgG1 Drug (auristatin E)	2011	Hodgkin lymphoma and systemic anaplastic large cell lymphoma
Trastuzumab emtansine	Trastuzumab DM1	Humanized IgG1 Drug (mertansine)	2013	Breast cancer
Tositumomab; Iodine I 131 Tositumomab	CD19+ CD3	Murine IgG2a	2014	Acute lymphoblastic leukemia
Arcitumomab	Diagnostic	Murine IgG1		Colorectal cancer
Capromab pendetide	Diagnostic	Murine IgG1		Prostate cancer

**Table 2.** Conjugated monoclonal antibodies currently approved by the Food and Drug Administration (FDA) for cancer therapy.

vedotin is a chemolabeled monoclonal antibody specific for CD30 antigen on lymphocytes that delivers monomethyl auristatin E chemotherapy to cancer cells for treatment of Hodgkin lymphoma and anaplastic large cell lymphoma [9]. Ado-trastuzumab emtansine is another chemolabeled antibody attached to Mertansine (DM1) chemotherapy with ability to target HER2 molecules on breast cancer cells [10]. Immunotoxin monoclonal antibodies are a new class of monoclonal antibodies that are attached to highly toxic protein molecules of a plant or bacteria. Immunotoxins can specifically bind to their target and deliver potent toxins to cancer cells [11]. The most recent group of antibodies is bispecific monoclonal antibodies that consist of two separate antibodies targeting different specific antigens. Blinatumomab is a bispecific monoclonal antibody with the ability to bind to CD19 on lymphoma and leukemia cells and CD3 on T cells. This antibody is usually used for treatment of acute lymphocytic leukemia. By binding to two antigens on separate cells, Blinatumomab is able to bring immune cells and cancer cells together and ease the pathway for immune cells to find, attack, and kill cancer cells [12].

Based on the genetically engineering techniques, four groups of monoclonal antibodies have been developed. Murine monoclonal antibodies, which were derived from mice, were the first generation of antibodies. They were quickly eliminated from clinical studies as they were not able to interact with human immune system. Chimeric monoclonal antibodies are another category of monoclonal antibodies, consist of constant regions mostly derived from human source and variable regions entirely derived from murine source [13]. There is a subtype of chimeric non-humanized monoclonal antibodies also known as rat-mouse hybrid monoclonal antibodies with murine Fc portion that have specificities for binding to three different tumor cells, T cells and also accessory cells [14]. On the other hand, chimeric humanized monoclonal antibodies, that comprise human Fc portion, are



developed with more efficient interaction with human immune system and less immunogenicity [15]. Less immunogenic and more efficient monoclonal antibodies have been developed as humanized monoclonal antibodies, which predominantly originated from human source excluding Fab portion which is derived from murine source. Human monoclonal antibodies that are fully human and are derived from transgenic mice known to be the most efficient and the least immunogenic [16].

Although monoclonal antibodies are being used for treatment of cancer, they may increase the risk of immune reactions or adverse effects. The immune reactions including acute anaphylactic reaction, serum sickness, or cytokine release syndrome (CRS) generally occur after first infusion of monoclonal antibodies. Adverse effects of monoclonal antibodies are the result of immunodeficiency mediated by blockade of specific targets. Infections such as reactivation of tuberculosis or progressive multifocal leukoencephalopathy, autoimmune diseases such as lupus and thyroid disease, cancer, dermatitis, and organ-specific adverse effects are other risks of monoclonal antibodies administration [13]. The other problem of monoclonal antibodies are constant mutation of cancer cells which results in formation of different or neoantigens that already available antibodies cannot function against them. Generation of different or neoantigens lead to absence of responsiveness to monoclonal antibodies. Developed genome sequencing techniques is promising for identifying neoantigens and producing monoclonal antibodies against this targets [3]. Monoclonal antibodies have been proven to remarkably shrink solid tumors, suppress malignancies, diminish metastasis, and increase overall survival in patients [17, 18]. Monoclonal antibodies are promising for treatment of cancers in both monotherapy and in combinatorial therapeutic approaches.

### **3. Immune checkpoint blockades**

It was believed that cancer cells were completely resistant to immune system till 1800s when researchers reported regression or total elimination of some solid tumors in patients who had streptococcal skin infections or were infused with bacterial extracts [1, 19]. These studies were not continued until Sharma and Allison noticed that blocking of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) enhances tumor killing capacity of T cells [20]. This hypothesis pops up that some bacterial or organisms' extracts have the ability to block molecules on immune cells, known as checkpoints, which promote immune cells' functionality against cancer cells. These observations led to more in-depth studies to identify immune checkpoints which their blockade can trigger robust anticancer immune responses.

One type of monoclonal antibodies that bind to immune check points is referred as immune checkpoint blockades. Checkpoints or coinhibitory receptors are molecules on immune cells that bind to their ligands expressed on normal cells. Under normal circumstances, immune checkpoints recognize healthy cells as non-pathogenic by binding to the ligands on normal cells and prevent activity of the immune system against its own tissue. Some cancer cells express check points ligands which help them to escape from recognition and elimination by immune system. By blocking immune checkpoints, immune cells gain a robust response against cancer cells. Immune check point blockades have been proven to be effective in many cancers and are promising because they are targeting immune cells by removing inhibitory pathways [21].

CTLA-4 is a coinhibitory receptor on T cells that prevent T cells activation. During T cells activation, antigen-presenting cells (APCs) present processed antigens on their major histocompatibility complex (MHC) molecules to T cell receptors. After the initial phase of activation, B7-1 or B7-2 molecules of APCs

attach to CD28 on T cells. TCR signal and costimulatory B7-CD28 induce complete T cell activation that result in cytokine release from activated T cells [22]. Besides, inhibitory signals induce by CTLA-4 act in an opposite way [23]. CTLA-4 molecule expressed on T cells has a higher affinity to bind to B7 compare to CD28. In a competition between CD28 and CTLA-4, CTLA-4 predominantly binds to B7 and generates an inhibitory signal during T cells activation. Inhibitory signals of CTLA-4 halt T cells activation and induce immune tolerance. Blocking of CTLA-4 by Ipilimumab (CTLA-4 blockade) was first approved by FDA due to success of CTLA-4 blockade in treatment of melanoma patients [24]. Ipilimumab boosts immune responses to cancer cells mediated by T cells activation. Most of patients experience Ipilimumab-related side effects like diarrhea, vomiting, skin rashes, nausea, and even life-threatening effects. All patients receiving this drug are always monitored closely and side effects are managed by corticosteroids [25].

In cancer, T cells are constantly exposed to antigen stimulation which result in gradual deterioration of their function by losing cytokine production ability and persistent increase in expression of inhibitory receptors. Defects in T cell activation, cytokine production, and proliferation is defined as exhaustion. Inhibitory receptors are highly expressed on exhausted T cells. Cancer cells have a high expression of inhibitory ligands that increase the chance of exhaustion in T cells. Programmed cell death-1 (PD-1) is an inhibitory molecule known as the receptor for cell death and have regulatory inhibitory role in activation of T cells. Physiologically, PD-1/PD-1 ligand (PD-L1) signaling pathway is a way to control excessive inflammation to protect normal tissues by induction of immune tolerance [26]. Interaction of PD-1 and PD-L1, which is highly expressed on tumor cells, causes exhaustion and dysfunctionality in T cells that avoid immune response against cancer cells. PD-1 or PD-L1 inhibitors pharmacologically prevent interaction of these molecules and efficiently maintain T cells function and facilitate them to kill tumor cells. Both PD-1 and PD-L1 immune checkpoint blockades have been proven to be effective for many malignancies but still it is not obvious that whether blocking of PD-1 on T cells or PD-L1 on tumors is more effective for cancer treatment. Patients' characteristics such as type of tumor, mutation burden of tumor, and metastases of tumor affect efficacy of PD-1/PD-L1 inhibitors [27]. PD-L1 is not constantly expressed on different tumors and even in different stages of tumor growth. Therefore, efficacy of PD-L1 blockade depends on the type of tumor, stage of tumor, location of the tumor, and many other factors [28, 29]. Atezolizumab, the first FDA-approved PD-L1 blockade, has been used as the first-line treatment of metastatic non-small lung carcinoma and cisplatin-resistant metastatic urothelial carcinoma. Avelumab, is another FDA-approved PD-L1 blockade for metastatic merkel cell carcinoma that lack efficient response to chemotherapy [30]. Nivolumab and Pembrolizumab are PD-1 blockers and are successfully used in Phase I clinical trial on patients with non-small-cell lung cancer and renal cell carcinoma. Nivolumab was approved by FDA for treatment of advanced melanoma patients after significant improved response in phase III trial. Also, Pembrolizumab is the first-line immune checkpoint blockade for the treatment of metastatic melanoma and metastatic non-small cell lung cancer [31]. These drugs have significantly increased survival of patients with minimal side effects in other solid tissue tumors. To improve benefits from immune checkpoint blockades, combinatorial strategies are under study. Combination regimens include administration of two immune checkpoint blockades together or a monoclonal antibody with chemotherapy or radiotherapy [32]. Combinatorial strategies enhance anticancer responses because each treatment works through targeting different pathways. Combination therapy of Ipilimumab/Nivolumab is approved by FDA for treatment of melanoma [33]. Pembrolizumab plus chemotherapy (pemetrexed/carboplatin) is approved for

treatment of non-small cell lung carcinoma [34]. Several combination therapies including either two different checkpoint blockades or with chemo/radiotherapy are under investigation [32].

Immune checkpoint blockades have changed the treatment strategies for cancer with dramatic improves in many cancers. PD-1, PD-L1, and CTLA-4 inhibitors are able to change immune responses and it may cause adverse immune reactions. These immune reactions are usually better tolerated than chemotherapy drugs but still recognition and proactive treatments should be included in the treatment strategy for patients receiving immune checkpoint blockades [35].

#### **4. Cancer vaccines**

Cancer vaccines are a new generation of vaccines different to traditional prophylactic vaccines which were administered to healthy people. Cancer vaccines are administered to either prevent cancer in high-risk individuals or to treat cancer in patients with malignancies. Therapeutic cancer vaccines are able to enhance immune system to attack cancer cells. Two prophylactic vaccines were approved for cancers that are caused by virus infections. One of the prophylactic vaccines is for hepatitis B virus (HBV) infection that can cause liver cancers such as cirrhosis and hepatocellular carcinoma in those who suffer from chronic infections. Another prophylactic vaccine is against human papilloma virus (HPV) that mediates cervical, anal, vaginal, vulvar, and throat cancers as well as genital warts. Until now, preventive vaccines were only available for the cancers that are caused by infections. Therapeutic vaccines are meant to enhance immune system in order to interfere with cancer cells, stop their growth and proliferation, and kill cancer cells. Therapeutic cancers are divided to several categories of cell vaccines, peptide vaccines, and genetic vaccines.

Tumor cell vaccines are a type of cell vaccines including autologous tumor cell vaccines and allogenic tumor cell vaccines. Autologous tumor cell vaccines are isolated from patient-derived tumor cells and prepared in vitro for administration to the patient from whom the tumor cells were isolated. Preparation of tumor cells for vaccination includes irradiation of tumor cells or combining tumor cells with an immune stimulatory adjuvant such as recombinant granulocyte monocyte-colony stimulating factor (GM-CSF) [36]. Autologous cell vaccines are able to present a wide range of tumor-associated antigens to cytotoxic T cells, resulting in a robust antitumor activity. Modification of autologous tumor cells to induce higher levels of immune stimulation has been studied by many researchers. Autologous tumor cell vaccines in animal tumor models of lymphoma and melanoma were more potent when tumor cell vaccines were infected with Newcastle disease virus [37]. In another study, tumor cell vaccines were genetically modified to express higher levels of IL-2 which induced activation of T cells and natural killer (NK) cells [38]. Autologous tumor cell vaccines transduced with GM-CSF, named GVAX, are able to get involved with dendritic cells (DCs), and induce maturation of DCs. GVAX-mediated matured DCs activate cytotoxic T cells and improve T cells response to cancer [39]. Autologous tumor cell vaccines have been extensively investigated in clinical and preclinical studies on several cancers and approximately 20% of patients survived for a long time [40]. The advantage of autologous tumor cell vaccines is that the vaccines can target the patient's own tumor-associated antigens and excludes the step to select specific antigens. One major problem in preparing autologous tumor cell vaccines is the time-consuming process of harvesting sufficient amount of tumor cells, which is a restriction for certain tumors. Appose to autologous tumor cell vaccines, allogeneic tumor cell vaccines are easy and less



expensive to produce in large scales. Allogeneic whole tumor cell vaccines consist of at least two human tumor cell lines and have unlimited tumor-specific antigens. Canavaxin is an allogeneic tumor cell vaccine consisting of three irradiated allogeneic melanoma cell lines combined with adjuvant *Bacillus Calmette-Guérin* (BCG). Despite Canavaxin increased overall survival of melanoma patients in phase II of trials, clinical trials were terminated because of failure of the vaccine in stages III and IV [41]. Allogeneic GVAX vaccine has been studied for treatment of prostate cancer [42], breast cancer [43], and pancreatic cancer [44]. Combination of GVAX vaccine with CTLA-4 antibody (Ipilimumab) was approved by FDA for treatment of metastatic melanoma [45]. Belagenpumatucel-L is another allogeneic tumor cell vaccine formed from four non-small cell lung carcinoma (NSCLC) cell lines transfected with plasmid containing a transforming growth factor (TGF)-beta2 antisense transgene. This genetically modified vaccine secretes TGF-beta and is used for treatment of NSCLC [46].

## **5. Dendritic cell vaccines**

Dendritic cell (DC) vaccines emerged as a potent cancer vaccine. DCs are professional antigen-presenting cells (APCs) that act as a bridge between innate and adoptive immune system [47]. DCs uptake pathogens, process them, and present pathogen antigens on their MHC molecules. Processed antigens on DCs are directly recognized by T cells which induce antigen-specific immune responses. Different subtypes of DCs exist in human body based on CD8, CD103, or CD11b expressions. DCs are in both non-lymphoid organs and lymphoid organs such as lymph nodes, spleens, and bone marrow. Classical DCs (cDCs) are divided to CD8+, CD103+, and CD11b+ DCs. Non-classic DCs include monocyte-derived DCs, plasmacytoid DCs, and Langerhans cells. These categories are based on expression of molecules and the location of DCs in body [48]. Studies showed that different subsets of DCs can prime and expand various T cells. For example, CD8+ CD205+ DCs present antigens on both MHC-I and MHC-II and are able to prime CD4+ T cell and CD8+ T cells but CD8-33D1+ DCs present antigens just on MHC-II and prime CD4+ T cells [49]. DCs act as a double-edged sword that can induce both immune tolerance and immune activation depending on which receptors on DCs are engaged [50]. Maturation and migration of DCs play a critical role in characteristics of DCs [51]. Matured DCs migrate to lymphoid organs and prime T cells to enhance antitumor responses. Loading of MHC molecules with cancer antigens, up regulation of costimulatory molecules such as CD40, CD80, and CD86 on DCs, and cytokine production of DCs are critically required for activation of T cells DCs [52, 53]. DC vaccines include *ex vivo* generation of DCs from CD34+ hematopoietic progenitor cells or peripheral blood-derived monocytes (PBMC) [53]. *Ex vivo*-generated DCs are loaded with appropriate source of tumor antigens and are subsequently activated with adjuvants and are administered back to patients to kill tumors. Tumor antigens derived from total tumor [54], DNA/RNA virus [55], tumor proteins, or peptides [56, 57] are utilized for DC vaccines. Moreover, some DC vaccines are composed of fusion of tumor cells and *ex vivo*-generated DCs [58]. Autologous DC vaccine pulsed with HLA-A0201 peptide (prostate-specific antigen) was among the first dendritic cell vaccines used in clinical trials with promising results [56]. DC vaccines have been studied in many clinical trials on various cancers. FDA-approved Sipuleucel-T DC vaccine for the first time for the treatment of metastatic castrate-resistant prostate cancer [59]. Sipuleucel-T composed of PBMC-derived DCs loaded with PA2024 (prostatic acid phosphate) fused to GM-CSF, which significantly increased patients survival. Although DC vaccines were successful in prostate cancer treatment, their

efficacy in other cancers was modest. Researchers conduct studies to enhance DC vaccines potency by modulating stimulatory and inhibitory molecules on DCs. Modulation of costimulatory molecules such as CD40L, CD70, GITRL, CD137L, and OX40L [60–63] or inflammatory markers of IL-12p70, IL-18, IL-12, CXCL10, and CCR7 on DCs improve DCs maturation and T cell priming characteristics [64–68]. The other way to enhance anticancer T cell response by DCs is to suppress inhibitory molecules on DCs. Genetically silencing of ubiquitin-editing enzyme A20 [69], suppressor of cytokine signaling 1 (SOCS1) [70], and scavenger receptor SRA/CD204 [71] improve DCs function and subsequently enhance T cell response to cancer cells.

Two of the most important limitations of cancer cell vaccines and DC vaccines are limited source of specimen and complicated procedure to generate these vaccines. New vaccines generated by tumor-associated antigen peptides combined with an adjuvant seemed to solve the restrictions of cancer cell and DC vaccines. The first encoded human tumor-associated antigen peptide was named MAGE-1 [72]. Different types of tumor-associated antigen peptides are studied. Cancer testis antigens are a group of genes available in both healthy and cancerous tissues. These genes such as MAGE, BAGE, NY-ESO-1, and SSX-2 are scant in normal tissues but are highly expressed in tumors [73–75]. Tissue differentiation antigens are available and active in both healthy tissues and tumors-like PSA and PAP in prostate cancer [76, 77], gp100, Melan-A/Mart-1, and tyrosinase in melanoma [78–80], and mammaglobin-A in breast carcinomas [81]. Tumor-specific antigens or -mutated oncogenes are a group of antigens expressed on both normal tissues and tumors with a unique up regulation in tumors such as CEA [82], MUC-1 [83], HER2/Neu [84], and certain antiapoptotic proteins (i.e. livin and survivin) [85, 86]. Clinical trials mostly focused on effects of peptide vaccines that target cancer testis antigens, and differentiation-associated antigens. To produce an effective peptide vaccine, addition of immune stimulatory adjuvant is required for an efficient immune response as tumor-associated antigens are not immunogenic. Some adjuvants used for peptide vaccine generation are aluminum salt, pathogen-associated molecular patterns (PAMPs), TLR agonists [87], BCG [88], and monophosphoryl lipid A (MPL) [89]. Cervarix is the first peptide vaccine for human papillomavirus composed of MPL and aluminum salt [90]. The advantage of peptide vaccines to DC vaccines and cancer cell vaccines is that peptide vaccines are more cost effective, but they may also appear to be less potent because they only target one or few epitopes of tumor-associated antigens. Formulation of peptide vaccines, route of delivery, and selection of immunogenic adjuvants can influence efficacy of peptide vaccines [91].

## **6. Genetic vaccines**

Genetic vaccines are another approach for carrying tumor-associated antigens to patients by utilizing plasmid DNA vectors. Genetic vaccines transfect DCs and directly present tumor-associated antigens to cytotoxic T cells or they can transfect somatic cells and indirectly cross prime T cells. Each genetic vaccine can deliver many tumor-associated antigens to patients and induce a robust anticancer immunity [92]. DNA vaccines are composed of bacterial plasmids that carry genes of interest under the control of mammalian promoter. DNA vaccines are able to initiate innate immunity and based on the site of delivery, they can trigger cellular and humoral immunity [93]. Usually the transgene is cytomegalovirus (CMV) immediate early promoter and its intron A sequence [94]. Optimizing codon usage can increase the transduction of antigens. In the intra muscular administration of DNA

vaccines, DNA plasmids transfect both myocytes and DCs. The plasmids act as an immunogenic and activate T cells via toll-like receptors [95]. DNA sensors in cytosol of cells such as DAI, H2B, IFI16, DDX41, LRRFIP1, and cGAS are able to detect presence of DNA vaccines. DNA sensors send signal to STING-TBK1 signaling cascade and activate interferon regulatory factor 3 which results in expression of type I interferons. TLR9 recognizes unmethylated CpG DNA and activates interferon regulatory factor 7 that induce expression of interferons. DCs phagocytose antigen-expressing cell (myocytes) and cross present antigens on MHC-I to CD8 T cells. Moreover, interferons promote this pathway. If DNA vaccines directly transfect DCs, DCs are able to uptake, process, and present antigens on MHC-I to CD8 T cells [96]. Transfection of the vector with multiple gene sequences increases the immunization and induces humoral [97] and CD8 T cell response [98]. Combination of DC vaccines with other immune stimulatory agents such as TLR agonists [99], or monoclonal antibodies [100] increase anticancer immunity. RNA vaccines are safe vaccines compared to DNA vaccines as they degrade and clear quickly in body. Total tumor RNAs are isolated from tumor tissues and they can induce a potent immune response. RNA vaccines are composed of various tumor antigens which reduce the possibility of immune escape by tumor cells. The first use of RNA vaccines was to immunize patients with mRNAs that encode tumor-associated antigens. Furthermore, RNA vaccines can be produced for personalized cancer treatment. Patients' neoantigens can be identified by tumor exome analyzing and personalized RNA vaccine can be specifically generated. In addition to direct use of mRNAs for vaccine generation, RNAs are utilized in cell therapies. Transfecting patient-derived cells with RNAs and giving manipulated cells back to patients are another form of utilizing mRNAs. For example, transfection of patient-derived DCs with mRNA of tumor-associated antigens can induce an antigen-specific T cell response in cancer patients. Transfection of patient-derived T cells with mRNA of chimeric antigen receptors, triggers T cells to identify specific antigens on cancer cells which quickly deteriorate cancer [101]. Liposomes and protamine are adjuvants of RNA vaccines and help to stabilize RNAs [102].

## **7. Adoptive cell therapy**

Adoptive T cell therapy (ACT) is a treatment that enhances T cells' ability to kill cancer cells by transferring immune system-derived cells to patients. The cells used for ACT can originate from the same patient or another individual. In 1988, the first ACT reduced metastatic melanoma tumors with transferring of autologous CD4+ and CD8+ tumor infiltrating lymphocytes (TILs) to the patients [103, 104]. Both peripheral blood T cells and TILs extracted from tumors are utilized to generate specific T cells for ACT. These T cells can be modified and then transferred to patients or directly administered in their natural state. TILs by their own nature have an antitumor activity as they are specific for tumor cells. TILs can recognize tumor antigens such as cancer germline antigens, neoantigens, and viral proteins and kill cancer cells [104]. After tumors are resected, the tumor tissues digest into fragments and each fragment is cultured in the presence of IL-2. The T cells are expanded and each clone is monitored for its reactivity against tumor cells. Proliferating lymphocytes kill tumor cells and produce a pure population of T cells. Cancer reactive T cells are infused back to patients. Moreover, T cells that express a TCR specific for tumor antigens can be selected in vitro from peripheral blood and expanded. Antigen-specific T cells are selected by coculturing of T cells with APCs loaded with tumor particles such as RNAs. By expansion of antigen-specific T cells, a specific antitumor T cell clone can be generated [105]. T cells with TCR targeting



tumorigenic mutations such as Ras mutations have shown promise in cancer treatment. Ras is commonly mutated at the onset of tumorigenesis in the dominant population of tumor cells. Targeting Ras mutations and killing tumor cells with Ras-specific ACT may have profound effects on cancers with Ras mutations [106]. TCRs targeting KRAS G12D, a common proto-oncogene encoding GTPase, have anti-tumorigenic effects on patients with colorectal cancer [107]. Also, genetically modified antitumor T cell clones can be produced by infecting T cells with viruses that carry genetically engineered TCRs [108]. TCR-transduced T cells are generated by cloning specific TCRs into a retrovirus. Patients derived PBMCs are activated with CD3 and IL-2 and are transduced with the retrovirus encoding the antigen-specific TCR. The T cells are expanded and injected back to the individuals. Peripheral blood T cells transfected with retrovirus encoding MART-1 TCR regress tumors in melanoma [103]. Genetically engineering techniques can modify TCRs to target-specific antigens. For example, T cells with modified TCRs that target NY-ESO-1, a cancer germline antigen, were successfully used as ACT for treatment of patients with synovial cell sarcoma and melanoma [109]. One major limitation of ACTs is that they induce short-lasting responses in immune system. Administration of T cells after chemotherapy increases cancer regression due to repopulation of host T cells with antigen-specific T cells. Lymphodepletion induced by chemotherapy helps T cells from ACT to proliferate during hemostatic proliferative phase and persist for months after infusion [109]. It was also shown that high doses of IL-2 therapy contribute to expansion of the transferred cells [110, 111]. The first signal in T cell activation begins with binding of TCR to MHC molecules on APCs. Furthermore, MHC expression downregulates on APCs in cancers so that they can escape immunity [112]. In 1989, first chimeric antigen receptors (CARs) were developed to avoid interaction of T cells with MHC molecules. CAR T cells are designed to identify cancer cells and attack them without mediation of APCs. As a result, CARs act independent of any stimulatory and TCR signaling. CAR composed of a ligand-binding domain and a signaling domain. Ligand-binding domain is the extracellular part of CAR that includes B cell receptor derived single chain variable fragment. The signaling domain is made of costimulatory molecules and CD3 $\zeta$  and 1 [112]. CD19 CAR T cells were used in clinical trial for patients with refractory B cell lymphoma and hematological malignancies. No acute graft versus host disease (GVHD) has been reported in patients except for one mild chronic ocular GVHD that was observed 2 years after CAR T cells infusion [113]. In 2017, FDA-approved Tisagenlecleucel, CD19 CAR T cell, for the treatment of acute lymphoblastic leukemia (ALL). Excellent results with these trials, increased interests in CAR T cell immunotherapy approach [114, 115]. Cytokine release syndrome (CRS) is one of the side effects of CAR T Cells. CRS is a storm of inflammatory cytokines including IL-6, IL-10, and IFN- $\gamma$  that happens after the infusion of CAR T cells [2]. Patients may show symptoms such as hypotension, pulmonary edema, multi-organ failure, and even CRS-related death. Treatment of CRS includes administration of corticosteroids and IL-6 blockade. Using corticosteroids for treatment of CRS symptoms is controversial as corticosteroids dramatically decrease inflammatory cytokines and mitigate CAR T cells efficacy [116]. Another problem with CAR T cells is that they cannot penetrate into solid tumors. Studies are underway to alleviate limitations of CAR T cells and improve their efficacy for treatment of solid tumors [117].

## **8. Developing personalized immunotherapy**

Many cancer patients do not benefit from immunotherapies they are receiving. Recently, many studies are focusing on identifying predictive and prognostic



biomarkers in cancers as a beneficial guide for treatment decisions. This will stop administration of drugs for those patients who does not benefit from them and improve treatment in patients that are most likely respond to specific immunotherapies. Selecting the appropriate immunotherapy for each cancer patient is still a challenge. Scientists and oncologists are developing methods in genomic testing to discover cell signaling and biomarkers involved in responding to immunotherapy. It has been shown that cancers identified by specific quantity or pattern of mutations in the tumor microenvironment or surrounding area are more responsive to immune checkpoint blockades. Of note, scientists are trying to exploit other drugs to alter the tumor microenvironment of less immune responsive tumors, known as cold tumors, and turn them to check point blockades susceptible tumors that are defined as hot tumors [32]. Altering tumor microenvironment and surrounding tissues can increase the number of patients who can benefit from immune checkpoint blockades. Immunopharmacogenomics approach is providing a significant hope for personalized immunotherapy [118].

## 9. Conclusion

In summary, immunotherapy shows a tremendous potential in treatment of cancer. Different immunotherapies have been approved by FDA for prevention and treatment of cancers. Despite the breakthroughs achieved by immunotherapy, many cancers still do not respond to immunotherapy. Monotherapy of immune checkpoint blockades or other immunotherapies failed in treatment of some cancers. Finding the efficient treatment by combinatorial immunotherapies or combination of immunotherapy and traditional chemotherapy and radiotherapy are under investigation. Development of DCs and cancer vaccines, immune checkpoint blockades, CAR T cells, and ACT requires an in-depth understanding of tumor microenvironment and identifying tumor-specific antigens. More studies to develop immunotherapy can provide improved efficacy in cancer treatments.

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