Therapeutic Cancer Vaccines: Mechanism and Clinical Studies

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Abstract: Cancer, a genetic disease involved in abnormal cell growth and division, is a major cause of mortality worldwide for centuries. Among various existing cancer treatments, the development of cancer immunotherapy has been one of the most popular subjects in the field of oncology. Therapeutic cancer vaccine, an exciting innovation in cancer immunotherapy, has effectively improved the clinical outcome in patients by overcoming cancer treating barriers that other cancer treatments such as chemotherapy and radiation cannot achieve, in which tumor cells that are resistant to traditional cancer treatments continue to proliferate uncontrollably and invade other tissues causing disease relapse or metastases, thus resulting in toxicity and collateral destruction to normal tissues and affecting patient's quality of life. The development of therapeutic cancer vaccines involves numerous factors and requires prudent choice for each step of the design. This review provides an overview of basic components of therapeutic cancer vaccines including target antigens and vaccine platforms and analysis of FDA approved therapeutic cancer vaccines as well as those currently undergoing clinical trials.

1 INTRODUCTION

Cancer is a disease in which body cells abnormally grow and proliferate and generally develop into tumors. It is caused by genetic mutations due to cell division malfunctions, damages to DNA, or genetic inheritance. Researchers have identified three major cancer driver genes including proto-oncogenes involved in normal cell growth and division (Romei et al, 2016), tumor suppressor genes involved in regulating cell division and replication (Wang et al, 2019), and DNA repair genes involved in fixing damaged DNA (Ronen et al, 2001).

The study of cancer therapy has been one of the most important and popular subjects in the field of oncology since the 1930s. However, according to the World Health Organization, there were approximately 10 million cancer deaths worldwide in 2020 (WHO, 2021). Thus, the development of more effective cancer treatments is still in urgent need. Cancer immunotherapy, also known as immuno-oncology, is one of various existing cancer treatments that has significantly developed during the past decades. It aims to prevent, control, and eradicate cancer by restoring the activity of the patient's own immune system in which the immune system is educated to identify and attack specific cancer cells, immune cells are enhanced to assist cancer elimination, and the body is provided with additional components to boost immune responses. Types of cancer immunotherapy include cancer vaccines (therapeutic and prophylactic), adjuvants, tumor-infecting viruses, targeted antibodies, cytokines, adoptive cell transfer, and checkpoint inhibitors (CRI, 2020). Among the aforementioned cancer immunotherapies, cancer vaccines development has been a rapidly growing field of cancer immunotherapy research since 1990 DeMaria and Bilusic, 2019).

Cancer vaccines are classified into two categories: prophylactic and therapeutic cancer vaccines. Prophylactic cancer vaccines, or preventive cancer vaccines, are designed to reduce incidence and morbidity of cancers caused by oncoviruses and has mechanism similar to normal infectious disease vaccines in which an inactivated or weakened form of the disease is introduced to the immune system in order to educate the immune system to recognize and eradicate the disease based on their specific antigens, thus preventing the patient from the disease (Vanderbilt, 2020). Since prophylactic cancer vaccines work best in the preventive setting, patients must receive the vaccine before viral infection. Two types of prophylactic cancer vaccines are widely

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used: HPV vaccine (Cervarix, Gardasil, and Gardasil-9) which protects against the human papillomavirus and prevents cervical, vaginal, vulvar, and anal cancer in women; HBV vaccine (Heplisav-B) which protects against the hepatitis B virus and prevents liver cancer (DeMaria and Bilusic, 2019).

In contrast to prophylactic cancer vaccines, therapeutic or curative cancer vaccines are administered to patients with existing malignancy. Therapeutic cancer vaccine comes in two forms, and its mechanism involves utilizing the adjuvant vaccination strategies (Melief et al, 2015) (Figure 1). In one type, malignant cells are removed from a patient's tumor. Antigens will then be isolated and mixed with an adjuvant and made into a vaccine given back to the patient. By administering the cancer antigen this way, the patient's immune system is primed to recognize the malignant cells as a threat and thus eradicate the cancer. Another form of therapeutic cancer vaccines involves removing the dendritic cells (DCs) from the patient's blood via leukapheresis and loading them with cancer antigens ex vivo. Such antigen-riched dendritic cells will then be infused back into the patient and trigger an immune response to the malignant cells (Vanderbilt, 2020) (Melief et al, 2015). To date, three therapeutic cancer vaccines have been approved in the United States: BCG for treating early-stage bladder cancer, Provenge for treating prostate cancer, and T-VEC for treating melanoma (DeMaria and Bilusic, 2019).

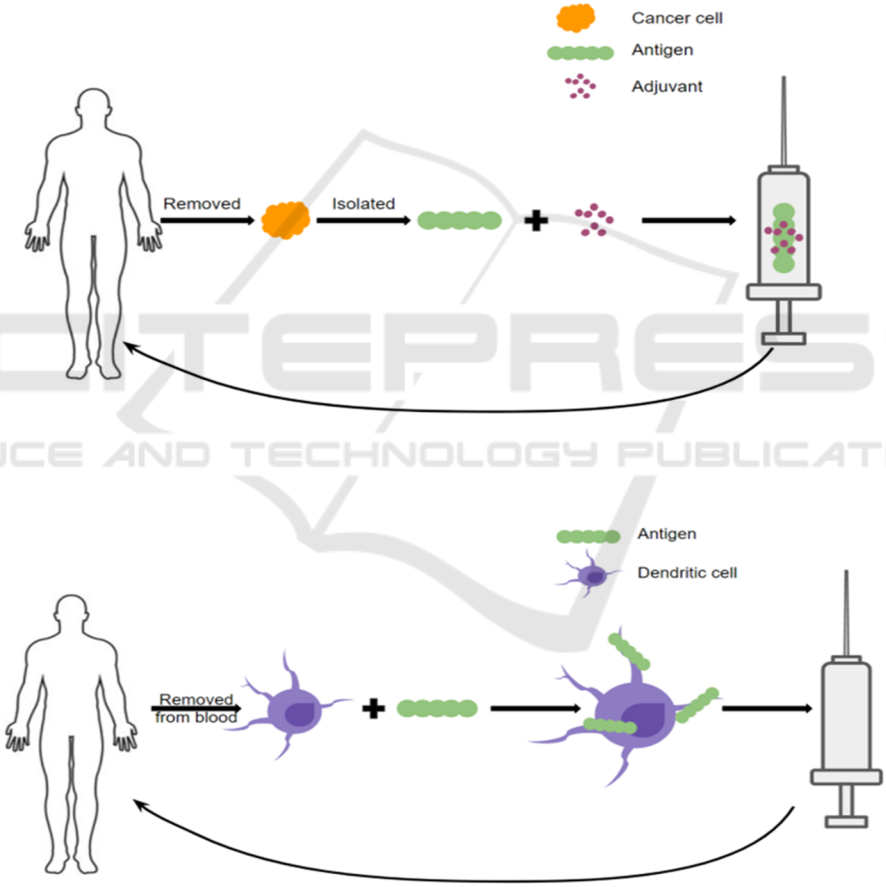

Figure 1: Mechanisms of Therapeutic Cancer Vaccines (CRI, 2020).

This review elucidates the essential factors in therapeutic cancer vaccine development including target antigens and vaccine platforms. Tumor vaccination targets can be subclassified as either tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs), and depending on different causes of cancer or location of tumor expression, the choice of target antigens can be varied. Moreover, therapeutic cancer vaccines can be developed via different vaccine platforms including cellular vaccines, viral vector-based vaccines, or molecular vaccines, and each of the platforms contributes to the development of therapeutic cancer vaccines uniquely. Additionally, this review introduces four current FDA

approved therapeutic cancer vaccines including BCG, Provenge, and T-VEC and provides a summary of latest cancer vaccines in clinical trials againsting different cancers including prostate cancer, breast cancer, pancreatic cancer, colorectal cancer, renal cell carcinoma, and hematological malignancies.

2 TARGET ANTIGENS

A wide variety of antigens expressed by tumor cells can be targeted by therapeutic cancer vaccines (DeMaria and Bilusic, 2019), yet the most imperative factor when it comes to designing cancer vaccines is the choice of antigen (Jou et al, 2021) with the ideal antigens being expressed only by cancer cells, presented on all cancer cells, highly immunogenic, and indispensable for ensuring the survival of cancer cells (Hollingsworth and Jansen, 2019). Tumor vaccination targets are subclassified as either tumor-associated antigens (TAAs) (Alatrash et al, 2019) or tumor-specific antigens (TSAs) (Apavaloaei et al, 2020). Table 1 provides a summary of the differences between TAAs and TSAs (Wang et al, 2019).

Table 1: TAAs VS. TSAs.

	Tumor-associated antigens (TAAs)	Tumor-specific antigens (TSAs)
Expressed in tumor cells?	Yes	Yes
Expressed in normal cells?	Yes	No
Most common cause	Post-translational modifications/Genetic amplification	Oncogenic driver mutations that produce novel peptide sequences
Target types	Overexpressed antigens Differentiation antigens cancer/testis antigens	Oncogenic viral antigens Shared neoantigens Private neoantigens

2.1 Tumor-Associated Antigens (TAAs)

TAAs are self-antigens expressed abnormally in malignant cells and at low levels in normal cells (Alatrash et al, 2019). TAAs target types include: overexpressed antigens, cell lineage differentiation antigens, and cancer/testis antigens (CT antigens) (Table 1). Overexpressed antigens are a broad category that encompasses any protein discovered in higher concentrations in tumors than in healthy cells and tissues (Bright et al, 2014). Examples of antigens that are overexpressed in malignant cells include MUC-1, mesothelin, HER2, hTERT. Cell lineage differentiation antigens such as glycoprotein 100 (gp100), prostatic acid phosphatase (PAP), prostate-specific antigen (PSA), and melanoma antigen detected by T-cell 1 (MART-1) are generally not expressed in adult tissue. CT antigens are usually only seen in male germ cells, examples including human melanoma antigen A1 (MAGE-A1), human melanoma antigen A3 (MAGE-A3), and New York esophageal carcinoma antigen 1 (NY-ESO-1) (DeMaria and Bilusic, 2019) (Hollingsworth and Jansen, 2019).

Several obstacles must be overcome in order to develop effective therapeutic cancer vaccines against TAAs. Foremost, growth and activation of self-antigen-reactive T cells, particularly low-affinity T cells, must be boosted through utilization of strong adjuvants, co-stimulators, or repeated vaccination because the high-affinity B cells and T cells for recognizing these self-antigens may be inadequate to trigger immune responses due to central and peripheral tolerance mechanisms. Therefore, therapeutic cancer vaccines utilizing TAAs must elicit the remaining low affinity T cells for the purpose of "breaking" the tolerance mechanisms (Jou et al, 2021) (Hollingsworth and Jansen, 2019).

2.2 Tumor-Specific Antigens (TSAs)

TSAs are exclusively expressed by malignant cells, and because of such tumor-specific properties, unlike TAAs, TSAs are able to strongly trigger high-affinity T cells and are less likely to be impacted by central tolerance and autoimmunity. TSAs consist of antigens expressed by neoantigens and oncoviruses (Table 1) due to genetic modifications, nonsynonymous mutations, or virally transmitted genetic information in malignant cells (Jou et al, 2021).

Examples of oncogenic viral antigens include the cervical cancer's antigens, E7 and HPV E6. An estimated 10-15 percent of human cancers worldwide arise from viral infection (Liao, 2006), and such highly immunogenic alien antigens are indeed the cause of oncogenesis. Various highly effective prophylactic antiviral vaccines have been developed for preventing infections including HPV and HBV vaccines; however, such vaccines have not proven to be beneficial in the treatment of cancer that has already developed, mainly due to the incapability of humoral immunity to effectively eradicate vast numbers of virus-infected malignant cells thus

requiring cell-mediated immune response (Hollingsworth and Jansen, 2019).

Even if oncogenic viral antigens are unique to specific tumor types, they are prevalent across many patients. Comparably, some neoantigens may occur in many tumor types and in many patients, hence the so-called shared neoantigens; whereas, most neoantigens are exclusively expressed in an individual patient's tumor, and they are referred to as private neoantigens (Hollingsworth and Jansen, 2019). Thus, generation of personalized therapy is essential for developing a cancer vaccine against an individual patient's private neoantigens. The process of such personalized approach includes sequencing the patient's tumor genome, recognizing and identifying the mutations, predicting neoantigens utilizing computer-operated algorithms, developing a personalized vaccine with the predicted neoantigen, and eventually delivering the vaccine to the patient (Kreiter et al, 2015).

3 VACCINE PLATFORMS

Anticancer therapy has been tested on a variety of vaccine designs. These vaccines aim to induce activation, proliferation, and maturation of T and B cells by introducing tumor-associated peptides complexed with major histocompatibility complex (MHC) molecules to cognate receptors on T and B cells. Antitumor immune responses are effective with the present of T cells as tumor antigens are often generated from intracellular proteins. Improved understanding of T cell activation and activity has aided recent developments in therapeutic cancer vaccine innovations (Hollingsworth and Jansen, 2019). Generally, platforms of therapeutic cancer vaccines are classified as: cellular vaccines, viral vector-based vaccines, and molecular vaccines (Peptide, DNA, or RNA) (Jou et al, 2021).

3.1 Cellular Vaccines

Cellular vaccines refers to cell-based vaccines that are developed utilizing autologous patient-derived tumor cells or allogeneic tumor cell line-derived cells (Jou et al, 2021) (Le et al, 2010) and can be administered to patients utilizing cell lysates or irradiated whole-tumor cells (Srivatsan et al, 2014). GVAX vaccine is an example of cellular vaccine utilizing genetically modified whole-tumor cells (Jou et al, 2021) to secrete Granulocyte-macrophage colony-stimulating factor (GM-CSF), which is a cytokine that boost the activation of dendritic cells and facilitates antigen presentation to both T and B cells thus stimulating the immune system against malignant cells (Nemunaitis, 2005). GVMAX vaccines have shown promising efficacy in stimulating immune system responses and inducing tumor regression, yet several clinical studies demonstrate that GVAX vaccines have limited effectiveness in prostate cancer, pancreatic cancer, lung cancer, and melanoma (Hollingsworth and Jansen, 2019). Autologous dendritic cells (DCs) are also utilized for cellular cancer vaccine development as they act as tumor antigen consumers, processors, and presenters (Jou et al, 2021), and they are either pulsed with peptide antigen or infected with a viral vector. Sipuleucel-T (Provenge) is a conventional cancer vaccine for treating metastatic castration-resistant prostate cancer (mCRPC) (DeMaria and Bilusic, 2019). Researchers are currently developing and inspecting other DC vaccines with one instance being the adenovirus MART-1-engineered autologous DC vaccine for treating metastatic melanoma (Butterfield et al, 2008). Other cellular vaccines utilized microorganisms to deliver tumor antigens and elicit immune responses (Jou et al, 2021) (DeMaria and Bilusic, 2019) (Hollingsworth and Jansen, 2019).

3.2 Viral Vector-Based Vaccines

Several viruses have been utilized to develop therapeutic cancer vaccines. Such viral vector-based vaccines exploit genetically modified versions of different viruses as vectors and are constructed to eliminate and replicate within malignant cells (Jou et al, 2021). An advantage for viral vector-based vaccines is that the patient's immune system is able to respond and recognize viruses efficiently, with both adaptive and innate immune systems collaborating to produce robust and substantial responses. Pattern recognition receptors (PRRs) will activate antigen-presenting cells in response to viral pathogen-associated molecular patterns (Hollingsworth and Jansen, 2019). However, repeat vaccination will be limited due to the fact that such viral vectors are neutralized by antiviral immune response. A common approach to address this advantage is the application of a heterologous prime-boost strategy in which one virus vector delivers a tumor antigen first, followed by a boost with the same tumor antigen carried by a different viral vector (Pan et al, 2020).

3.3 Molecular Vaccines

There are three types of molecular vaccines based on the source of tumor antigen delivery: peptide, DNA, and RNA. And each of these three vaccine platforms have the ability to elicit significant T cell responses as well as therapeutic effects against established diseases (Li et al, 2014). Figure 2 provides a simplified illustration of the three different therapeutic cancer vaccine delivery types.

Peptide-based vaccines, also known as synthetic long peptide (SLP) vaccines, relies on usage of exact MHC class I-binding short peptide fragments to design the elicitation of high targeted immunological responses thus avoiding reactogenic sequences (Bijker et al, 2008). However, single antigen-based short peptides may fail to overcome loss of antigen expression within the tumor or fail to encode sufficient antigenic material to stimulate potent immune responses, thus immune adjuvant is usually required for developing peptide vaccines (DeMaria and Bilusic, 2019). Short peptides, usually less than fifteen amino acids, can bind toMHC class I molecules and do not necessitate processing by antigen-presenting cells. Nevertheless, T cell dysfunction and tolerogenic signal might occur if such short peptides bind to other cells that do not provide correct co-stimulation (Overwijk, 2017). Moreover, C4 helper T cells will not be activated by short peptides. Researchers have put effort into improving peptide vaccines' quality by utilizing amphiphilic peptides and combining them with other immune modulators (Lysén et al, 2020).

DNA vaccines have built-in adjuvants such as CpG (TLR9) (Li et al, 2014) and represent a condensed conformation of TAAs, yet they require additional transcriptional and translational steps before being cross-represented on DCs (Sahin et al, 2017). Furthermore, DNA vaccines can be electroporated at the injection location directly. When administered at high dosages by intramuscular injection combined with electroporation, DNA vaccines are the most efficient in generating sufficient antigen processing and presentation to induce CD8+ T and CD4+T responses (Li et al, 2014). A further innovation of CD8+ T cell induction is a technique in neoepitope-specific vaccines in which antibody response and T cells are boosted due to co-expression of DNA and chemokines for targeting specific dendritic cell subsets (Ewer et al, 2016).

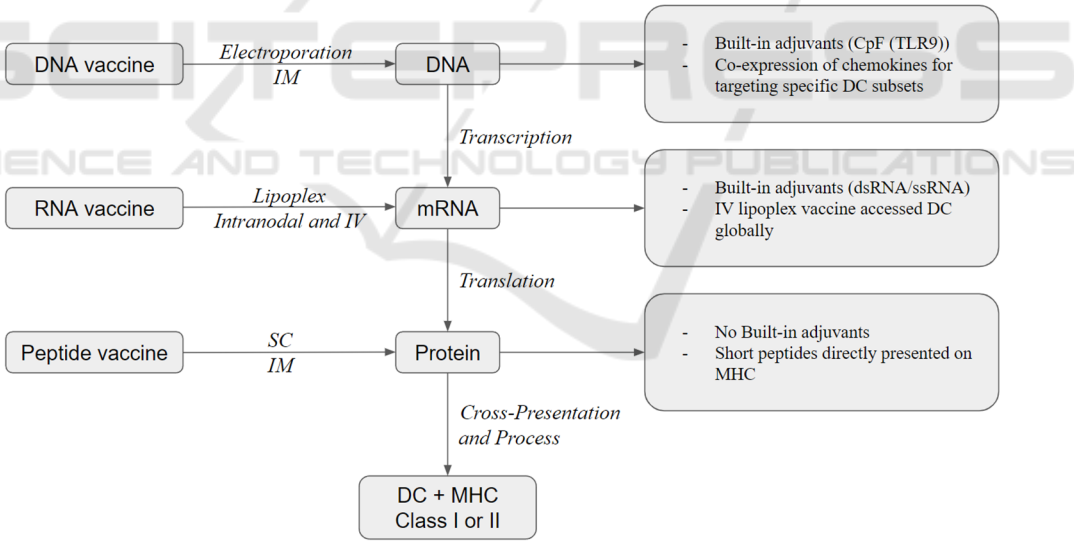

Figure 2: Simplified illustration of three therapeutic cancer vaccine delivery types (Li et al, 2014).

Similar to DNA vaccines, RNA vaccines have built-in adjuvants such as dsRNA and ssRNA. Nonetheless, in contrast to DNA vaccines, RNA vaccines do not require an extra transcriptional process. Thus, they are closer to protein antigen expression and presentation on MHC molecules (Li et al, 2014). RNA vaccines can be injected into lymph nodes directly or intravenously injected with the help of recently created nanoparticles (lipoplexes) (Fletcher, 2019). The majority of RNA vaccines in clinical studies nowadays have utilized mRNA while the use of RNA replicon is also being investigated (Plosker, 2012).

4 APPROVED THERAPEUTIC CANCER VACCINES

To date, only three therapeutic cancer vaccines have been approved and utilized in the United States: BCG for treating early-stage bladder cancer, Provenge for treating prostate cancer, and T-VEC for treating melanoma (DeMaria and Bilusic, 2019).

4.1 BCG (Baciile Calmette-Guerin; Sanofi Pasteur)

BCG live, also known as TheraCys and TICE, was approved by the FDA in 1990 as a cancer immunotherapy for the treatment of early-stage bladder cancer. Concretely, it is developed for intravesical utilization for treating and preventing urothelial carcinoma in situ of the urinary bladder and primary Ta or T1 urothelial carcinoma after transurethral resection (DeMaria and Bilusic, 2019). Healthcare professionals will administer BCG as a liquid drug into the patient's bladder via a catheter. Such an approach enables direct contact of the drug and the cancer cells in the bladder thus ensuring the right target for the patient's immune system. However, BCG immunotherapy can cause various side effects which include urinary tract infection, blood in the urine, discomfort in the bladder, etc (Anassi and Ndefo, 2011). According to research, in patients with superficial bladder cancer who undergo maintenance treatment, intravesical BCG remarkably lowers the likelihood of progression following transurethral resection (DeMaria and Bilusic, 2019).

4.2 Provenge (Sipuleucel-T; Dendreon Corporation)

Provenge, also known as Sipuleucel-T, was approved by the FDA in 2010 as an autologous cellular immunotherapy for treating metastatic castration-resistant prostate cancer (mCRPC), which is a form of advanced prostate cancer (DeMaria and Bilusic, 2019). Provenge is developed to activate T cell response against prostatic acid phosphatase (PAP), which is an antigen expressed in most prostate cancers yet not in non-prostate tissues. It is an effective personalized vaccine therapy in which each treatment dose is designed specifically for each individual patient utilizing the patient's own immune system. Patient's immune cells, concretely autologous peripheral blood mononuclear cells, will be collected through leukapheresis, and these immune cells will be combined with a protein (Conry et al, 2018) that triggers the immune cells to detect prostate cancer. Provenge only has mild to moderate side effects that usually last one to two days. Researches have shown with the help of provenge, men with prostate cancers are able to live longer, and the risk of death due to prostate cancer has been reduced (The ASCO Post, 2019).

4.3 T-VEC (talimogene laherparepvec; Amgen)

Imlygic, also known as talimogene laherparepvec or T-VEC, was approved by the FDA in 2015 for treating advanced melanoma. It is also the first oncolytic viral therapy in the United States (DeMaria and Bilusic, 2019) in which an oncolytic herpes virus, a virus that only infects cancer cells, is utilized. Such oncolytic virus is genetically modified to ensure its replication within tumors and production of the granulocyte-macrophage colony stimulating factor (GM-CSF). Usually, talimogene laherparepve is injected directly into the detected lymph nodes, subcutaneous lesions, or skin lesions that surgery cannot remove. Talimogene laherparepvec injected into the tumor will break down the tumor cells and release tumor-derived antigens. Such tumor-derived antigens together with GM-CSF can stimulate the immune response against the tumor. Side effects of this therapy include fatigue, chills, fever, nausea, vomiting, diarrhea, constipation, abdominal pain, dizziness, injection site pain or inflammation, etc (Melero et al, 2014). According to research, talimogene laherparepvec has effectively treated approximately 40% of patients with surgically unremovable tumors (Geary and Salem, 2013).

5 CURRENT THERAPEUTIC CANCER VACCINES UNDERGO CLINICAL TRIALS

Researchers are currently investigating more possible therapeutic cancer vaccines for different types of cancer which include prostate cancer, breast cancer, pancreatic cancer, colorectal cancer, renal cell carcinoma, hematological malignancies, etc (Wittendorf et al, 2012).

As aforementioned, Provenge (sipuleucel-T) is a currently utilized therapeutic cancer vaccine for treating patients with spreaded prostate cancer. Recent studies are investigating and developing therapeutic cancer vaccines for early-stage prostate cancer treatments (Wittendorf et al, 2012) (Middleton

et al, 2013). Current clinical trials are investigating HER2-derived peptides along with additional immunostimulatory agents including Granulocyte-macrophage colony-stimulating factor (GM-CSF), cyclophosphamide, or poly-ICLC. Research has shown that directly against HER2-derived peptides via active immunotherapy have beneficial effects for women with breast tumors with low level HER2 (Wittendorf et al, 2012) (Cancer.NET, 2020). Telomerase peptide vaccine GV1001 and the allogeneic tumor-cell vaccine algenpantucel-L are the most commonly investigated cancer immunotherapies for pancreatic cancer treatment. Several phase III and II studies had promising early-phase trials yet failed in the later stage trials (Amin et al, 2013).

Current clinical studies on colorectal cancer treatments involves developing therapeutic cancer vaccines to educate the immune system to combat cells with antigens include carcinoembryonic antigen (CEA), MUC1, guanylyl cyclase C, and NY-ESO-1 (Wittendorf et al, 2012) (Keiholz et al, 2009). AGS-003 is a current immunotherapy development for treating renal cell carcinoma (RCC), it is a personalized therapy utilizing DCs transfected with patient-specific cancer cell RNA and a truncated, synthetic human CD40 ligand (Wittendorf et al, 2012).Current clinical studies on hematological malignancies treatments involve developing therapeutic cancer vaccines to educate the immune system to combat cells with antigens include WT1, MAGE, MUC1 and the preferentially expressed antigen of melanoma (PRAME) (Wittendorf et al, 2012).

6 CONCLUSION

The development of therapeutic cancer vaccines have improved the field of cancer immunotherapy tremendously. As a result of the development of three FDA approved therapeutic cancer vaccines, which include BCG, Provenge, and T-VEC, our understanding of the tumor biology as well as pathways of the immune system have reached the next level.

Despite the fact that therapeutic cancer vaccine development has had promising achievement and considerable results in most phase I and some phase II clinical trials, the vast majority of therapeutic cancer vaccines have failed to exhibit clinical improvements in phase III trials over the past years due to low immunogenicity of tumor antigens, difficulty in targeting established tumor, and immunosuppressive tumor microenvironment. Thus, testing therapeutic cancer vaccines in early stages of cancer to minimize the disease burden and immune tolerance should be prioritized. Moreover, it's essential to establish better strategies of incorporating therapeutic cancer vaccines into the standard treatment such that immune tolerance is less formidable or combining therapeutic cancer vaccines with other cancer treatment therapies thus promoting synergistic treatment effects.

Developing personalized therapeutic cancer vaccines is a difficult task overall. Fortunately, researchers are still indefatigably investigating potential solutions to the aforementioned challenges and examining more therapeutic cancer vaccines in clinical trials. It is undoubtedly that more therapeutic cancer vaccines can be approved in the future.

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