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Challenges and Strategies for Developing Effective Neoantigen-Based Dendritic Cell Vaccines for Cancer Immunotherapy: A Literature Review

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ABSTRACT

Dendritic cells (DCs) are pivotal in the field of cancer immunotherapy due to their unique ability to initiate and modulate robust immune responses. Therefore, they represent a promising strategy for cancer vaccine development. Nonetheless, the efficacy of DC vaccines is hampered by the immunosuppressive microenvironment that is frequently present in tumors, which poses significant challenges to their effectiveness. Recent research has focused on two primary approaches to enhance DC vaccine outcomes. The first strategy involves the synergistic use of DC vaccines along with immune checkpoint inhibitors, traditional chemotherapy, or monospecific/bispecific antibodies to bolster immune activation. The second strategy emphasizes the identification and selection of tumor antigens that are not only specific and immunogenic but also manifest safety and stability characteristics. Among these, personalized neoantigens, specific antigens that arise from the tumor microenvironment, have garnered particular attention in clinical trials and have emerged as ideal candidates for DC vaccine targeting. This literature review comprehensively discusses these challenges and strategically explores the pathways to develop effective and safe neoantigen-based DC vaccines for cancer immunotherapy.

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Introduction

Cancer immunotherapy alters or amplifies one's immune system to fight against cancer cells (American Cancer Society). Cancer immunotherapy has several advantages. Compared to conventional therapies, such as chemotherapy and radiotherapy, immunotherapies are designed to target a patient's specific cancer antigen, resulting in fewer adverse effects. Therefore, it did not damage other tissues or cells. Moreover, it can be combined with other therapies such as surgery and chemotherapy to improve patient outcomes (1). In addition, some types of cancer do not respond well to chemotherapy or radiotherapy; however, studies have shown that immunotherapy is effective. The immune system can remember and respond vigorously to antigens previously encountered (2). There are numerous methods of cancer immunotherapy, of which cellular immunotherapy (CI) and immune checkpoint inhibitor (ICI) therapy are the most widely used (3, 4). CI of comprises two main therapeutic approaches: adoptive cell therapy (ACT) and dendritic cell (DC) vaccination. ACT and DC vaccinations are promising approaches for cancer treatment. ACT uses T cell populations such as tumor-infiltrating lymphocytes (TILs), TCR-engineered T cells, and chimeric antigen receptor (CAR) T cells. DC vaccination involves isolating DCs from patients and priming them with cancer antigens to

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stimulate T cells (5).

The co-inhibitory receptors programmed cell death 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) are expressed on the surface of T cells and negatively regulate T cell-mediated immune responses. Unfortunately, cancer cells exploit these inhibitory molecules to induce exhaustion and tolerance in T cells, thereby promoting their survival and growth (6).

Consequently, ICIs, such as anti-CTLA-4, anti-PD-1, and anti-programmed cell death ligand (anti-PD-L1), can target co-inhibitory receptors and restore the immune response against cancerous cells (4, 7). ICIs can result in durable responses and improved survival rates in patients with certain types of cancers, such as melanoma, non-small cell lung, and bladder cancer (7-9). ICIs effectively treat certain types of cancers, including melanoma, non-small cell lung cancer, and bladder cancer. The FDA has authorized seven ICIs, including three PD-1 and three PD-L1 inhibitors (10).

DCs play a crucial role in the immune response, and they are ideal for cancer vaccine research and clinical use due to their ability to capture and process antigens, migrate to lymphoid organs, and activate T cells (11). DCs are a top choice for cancer vaccine research despite challenges like cost, feasibility, and uncertain efficacy due to their unique qualities (11-13).

Preclinical and clinical studies have been conducted to test cancer vaccination. It has been shown that their efficacy is related to many factors, for instance, the type of cancer antigen that is targeted, the adjuvant that is used to boost its eligibility, and its ability to promote T cells (especially CD8+ T cells) to act reasonably in the immunosuppressive niche of the tumor (14-16).

Genetic alterations during tumorigenesis create new peptides expressed via MHC on the tumor cell surface as tumor-specific antigens (TSAs) or neoantigens, which the TCR of T cells can recognize and boost antitumor immune responses (17). Neoantigens are excellent candidates for designing cancer vaccines thanks to their high immunogenicity (18). Hence, considering the exceptional abilities of DCs to trigger an immune reaction against cancer antigens, coupled with the fact that neoantigens are top contenders for developing cancer vaccines, it is clear that neoantigen-based DC vaccines are viable options in the battle against cancer (19, 20). The purpose of the study is to review the challenges and strategies involved in developing effective DC vaccines for cancer immunotherapy using neoantigens.

2. Neoantigens and their formation in the cancer microenvironment

2.1. Tumor antigens

Tumor antigens are pivotal in cancer immunotherapy, categorized by origin and expression. These antigens are essential for eliciting targeted T cell responses against cancer cells. Traditionally, these antigens are broadly categorized into TSAs and tumor-associated antigens (TAAs). TSAs, including viral antigens (e.g., HPV E6/E7) and mutated neoantigens (shared or patient-specific from driver/carry-on mutations), are unique to tumor cells, minimizing off-target effects. Other shared tumor antigens include cancer-testis antigens (e.g., MAGE, BAGE, GAGE), although their strict tumor specificity is debated. TAAs, encompassing differentiation antigens (e.g., Melan-A/MART-1, PSA) and overexpressed antigens (e.g., survivin, Bcl-2), are also present in normal tissues. Overexpressed antigens exhibit elevated expression in cancer cells and are important for tumor survival and growth. Due to their unique expression in tumors and the expectation that tolerance mechanisms will not inhibit immune responses, TSAs are increasingly favored in immunotherapy development. Identifying and characterizing these antigens, particularly TSAs, remains a primary focus for creating effective anti-cancer immunotherapies (21, 22).

2.1.1. Tumor-associated antigens

The TAAs are a category of normal antigens mutual between normal and malignant cells. TAAs are often altered versions of normal proteins overexpressed, mutated, or aberrantly glycosylated in cancer cells. Some examples of this group are cancer differentiation antigens, cancer germline, and cancer testis antigens (23, 24).

TAAs can be targeted by the immune system for destruction, making them attractive targets for cancer immunotherapy. However, there are several challenges associated with targeting TAAs in cancer immunotherapy. An obstacle in cancer treatment is that TAAs are frequently not exclusive to cancer cells and may be expressed at minimal levels in healthy tissues, resulting in collateral effects and injury to non-cancerous tissues. Another challenge is that TAAs may be subject to immune evasion mechanisms cancer cells use. The expression of TAAs may be reduced or altered by cancer cells to avoid being detected by immunotherapies. Additionally, cancer cells may inhibit the activity of immune cells that recognize TAAs or secrete factors that suppress the immune response (25, 26) (Table 1).

Researchers are developing novel approaches to address these challenges to enhance the immune recognition and targeting of TAAs. One approach combines TAA-targeting therapies with other immune modulators, such as ICIs or cytokines, to boost the antitumor immune response (27). Another approach is to engineer T cells or other immune cells to express TAA-specific receptors, such as CAR T cells, to enhance their targeting of

cancer cells (28).
The prerequisite for using CAR T cells to treat large tumors is TAAs that are highly expressed in tumor tissues and low or absent in normal tissue. After much exertion by researchers, a few particular antigens against solid tumors (e.g., HER2, MUC1, GD2, etc.) are connected to CAR T cells for solid tumor treatment (28).

2.1.2. Tumor Specific Antigens

TSAs refer to a set of antigens exclusively expressed by tumor cells that are not found in normal cells (23). TSAs are formed from genetic mutations or abnormal protein expression in tumor cells. These abnormal protein expressions may cause them to be present on the surface of tumor cells, which allows for recognition by immune cells (29) (Table 1).

Table 1. Characteristic of target tumor antigens for dendritic cell-based vaccines

Characteristic	Interpretation
Specificity	For the immune response to target only cancer cells and not healthy tissues, target antigens that are absent in healthy cells must be specific for cancer cells.
Immunogenicity	Measuring the expression level of a target antigen, its ability to be processed and presented by DCs, and its capacity to elicit T cell activation can determine immunogenicity.
Heterogeneity	High numbers of target antigens in cancer cells are necessary to achieve an efficient immune response against various cancer cells.
Safety	No undesirable effects on healthy tissues and organs should occur with the target antigens.
Stability	The target antigens are not subject to rapid degradation or mutation.
Accessibility	The target antigens should be easily accessible to DCs for processing and presentation to T cells.

Cancer neoantigens are TSAs that result directly from genetic alterations unique to each patient (23). Genomic codon mutations, editing, usage, antigen processing, and presentation create neoantigens. Several processes produce neoantigens that alter the open reading frame acronym ORF. Changes in ORF that encode novel amino acid sequences not present in the standard genome can also be produced through missense mutations, fusion transcripts, frameshifts, and stop losses(30).
Neoantigens are a desirable focus for immunotherapeutic intervention as they exhibit specificity towards tumors and are not present in normal cells, thus minimizing the risk of non-specific autoimmunity (31). However, neoantigens vary among populations, from patient to patient, and even inside the bulk of tumor cells of a single individual; hence, they must be prepared individually (32). Another criterion that influences the possibility of generating neoantigens is the tumor mutational burden (TMB), which is related to the amount of gene mutations within the genome of a cancer cell (33, 34).
The use of neoantigens to generate and produce personalized cancer vaccines has some benefits. These antigens are expressed solely on cancer cells and not on normal cells; therefore, they can induce strong responses in T cells because there is no central tolerance to them. In addition, they can be recognized and screened by mass spectrometry, machine learning tools, and computational algorithms, such as those performed by artificial intelligence, so it is not complex to choose the best candidate for developing personalized cancer vaccines. However, the production of personalized cancer vaccines for each patient is complicated and expensive (14, 32).
A mature and efficient synthesis system is crucial for creating personalized neoantigens for each patient. This process represents the initial step in neoantigen production and must be rapid and straightforward. Personalized neoantigens are a distinct category of neoantigens tailored to individual patient (35).

2.2. Identifying Tumor Neoantigens for Cancer Immunotherapy

A few mutations can terminate T-cell activation against cancer cells. To better understand the roles of tumor neoantigens in tumor progression or control and their potential to be used in generating vaccines or therapies, there is an urgent need to identify the epitopes identified by CD8+ and CD4+ T cells (36).
The methods used to identify neoantigens are broadly expressed by Schumacher et al.. However, to put it in a nutshell, the process includes some common steps: 1. The whole genome of tumor cells was sequenced using next-generation sequencing and contrasted against the genome derived from normal healthy cells of the same patient (2. RNA sequencing was performed to determine any possible alternative splicing, any expression of mutant genes in the tumor cells, and the expression frequency of abnormal alleles, 3. Computational algorithms are used to predict expressed tumor variants, known as neoantigens, by analyzing the peptide cleavage product within the intracellular proteasome. The binding affinity of the resulting peptide to MHC was also evaluated using tools such as NetMHC, SMMPMBEC, and SMM. In addition, the mutated peptides were compared to self-peptides to assess their potential as neoantigens. Various software programs, including pVAC-Seq, TSNAD, CloudNeo, Tlminer, MuPeXI, Neopepsee, and INTEGRATE-Neo, have been utilized for the analysis of single nucleotide variants (SNVs), insertions and deletions (INDELs), and gene fusion at the genomic level. These computational methods

aid in identifying neoantigens that exhibit specificity towards tumors and minimize the risk of non-specific autoimmunity. 4. Mass Cytometry can be used to directly analyze the MHC ligandome (immunopeptidome) to overcome the limitations of in silico predictions (low accuracy for low-frequency HLAs). 5. A direct T cell-based assay was used to determine whether a patient's T cell repertoire has detected MHC-presented neoantigens (15, 35, 37).

Identifying and recognizing tumor neoantigens is crucial in developing effective cancer vaccines and therapies. The process involves sequencing the tumor genome, analyzing expressed tumor variants, and predicting the binding affinity of the neoantigens to the patient's MHC. In silico predictions can be complemented by Mass-spectrometry and T cell-based assays to increase accuracy. Identifying neoantigens provides an excellent option to treat patients with individual cancer and also indicates the importance of understanding the immune system's response to tumor cells. Further research is needed to improve the accuracy and efficiency of neoantigen identification methods (38, 39).

2.2.1. Manufacturing Neoantigen-Based Cancer Vaccines

Pennington et al. have thoroughly investigated the commercial manufacturing process and the large-scale production of peptides, including neoantigens (1). In any order, there are three main steps to produce neoantigens for developing neoantigen-based cancer vaccines or immunotherapies. The first step is the synthesis of neoantigen. The neoantigen must be carefully synthesized uniquely for each individual, so the process must be rapid, simple, mature, and safe. In addition, for individual neoantigens to be soluble and stable, it is necessary to normalize their formulation by buffering agents and surfactants. The subsequent phase involves the refinement of the neoantigen via Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC), as well as the utilization of flash-like schemes or mechanized methods, including auto-sampling systems and Ultra-Performance Liquid Chromatography (UPLC) for expediting productivity and sustaining quality. The final course of action involves lyophilizing the neoantigen to enable easy transportation and storage until the point of need (35).

Combining neoantigen vaccines and immunotherapy, such as ICIs, can prevent partial immune evasion from cancer cells. However, the exact mechanisms behind this combination remain unclear (40). A new approach involves using transfected monocyte-derived DCs that contain neoantigen-encoding mRNA to prime autologous naive CD8+ T-cells in healthy individuals (41). Nevertheless, identifying and validating neoantigens is expensive and time-consuming, so vaccine preparation from tissue samples can take three to five months. Overcoming technical challenges could be improved, such as the high demand for tumor tissue during identification and the low yield of peptides after immunoaffinity purification. To overcome technical challenges related to neoantigen prediction, further optimization of the prediction algorithm is necessary, as it should accurately predict potential neoantigens that are generated by gene fusion, indels, and other changes (20, 40, 42).

2.2.2. Challenges and Strategies for Neoantigen-Based Cancer Vaccines

Neoantigens hold great promise for cancer immunotherapy, but several challenges and problems must be addressed for their widespread use. The main challenges include the time-consuming and expensive process of identifying and verifying neoantigens, which usually takes several months, technical obstacles in preparing vaccines from tissue samples, and the need for further optimization of the neoantigen prediction algorithm (43, 44).

Additional challenges include the limited availability of effective antigens, the lack of effective screening methods for neoantigens, the long development cycle and high development costs of neoantigen vaccines, the difficulty in preparing and delivering vaccines, the heterogeneity of tumors, and the high cost of personalized therapies based on neoantigens. In addition, negative T-cell regulators and immune-suppressive cells within the tumor microenvironment can increase the probability of immune escape of tumor cells following immunotherapy with neoantigens. Addressing these challenges will be critical to the successful and widespread use of neoantigens in cancer immunotherapy. (20, 45, 46).

Several strategies can be employed to increase the efficiency and effectiveness of immunotherapy with neoantigens. These include combining neoantigen vaccines with other therapies such as ICIs, monoclonal antibodies targeting neoantigens to DCs, and drugs targeting immunosuppressive factors in the tumor microenvironment. Multi-epitope vaccination can also increase the breadth and diversity of neoantigen-specific T cells. Adjuvants and delivery systems such as nanoparticles and Toll-like receptors (TLRs) agonists can improve antigen presentation efficiency and vaccination antitumor activity (47, 48). Combination with conventional cellular immunotherapies such as the DC vaccine based on neoantigens and TCR-engineered T cell targeting

neoantigens can generate a robust immune response against tumor cells (49, 50). Finally, the merger of established therapeutic modalities, chemotherapy, and radiotherapy may amplify the effectiveness of immunotherapy via heightened antigen emergence, enhanced antigen demonstration, boosted T-cell reactivity, and local generation of a vaccine (51, 52).

The use of neoantigen-based DC vaccines has demonstrated significant potential in cancer immunotherapy. Studies have indicated that DC vaccines loaded with antigens lead to a more robust immune response than those generated using adjuvants and antigens. Extensive research has been undertaken on the efficacy of neoantigen-based DC vaccines, and encouraging clinical outcomes have been observed in treating melanoma and solid tumors. These vaccines can induce long-term immunity by increasing neoantigen presentation, activating host antigen-specific T cells, and accelerating T cell homing (19, 50, 53, 54). Research progress and more detailed evidence of neoantigen-based DC vaccines in cancer immunotherapy have been investigated.

2.3. Dendritic Cell Subsets and Their Functions

DCs are the most potent and efficient APCs, which can collect antigens from the body and, after processing, present them effectively to naïve T and other immune cells and lead to different responses from regulation or tolerance by inducing regulatory T cells (Tregs) or activate immunity like innate immunity, Th1, Th2, Th17, T follicular helper (Tfh) cells, CTL (55-57).

DCs result from hematopoietic stem cell (HSC) differentiation in the bone marrow. Their categorization relies on three main subsets: plasmacytoid DCs (pDCs), conventional DCs (cDCs), and monocyte-derived DCs (MoDCs). These can be differentiated according to their morphology, geographical location, developmental process, growth mechanisms, and specialized function markers that are regulated by specific transcription factors (58).

pDCs can be described as plasma cell-like cells found in lymphoid tissues, blood, mouse lungs, and human tonsils. Their development depends on growth factors Fms-related tyrosine kinase three ligands (Flt3L) and the transcription factor IRF7 from HSC and common DC progenitor (CDP). Their primary markers recognize these cells in humans, including CD11c-, HLA-DRlow, CD123+, CD303+, CD304+, CCR2+, and CXCR3+. PDCs can cross-present antigens to DC8+ naïve T cells and activate them, and they are reported to correlate with poor prognosis of cancer (58).

cDCs are classified into cDC1 and cDC2 subpopulations according to their growth, transcription factors, markers, and primary functions. Their resemblance is the same so that they are stellate-shaped with extensive cell membrane processes, and their location is not different. They are located mainly in lymphoid tissues found in blood, peripheral tissues, and lymph nodes. Their migratory subsets are present can be found. Their first difference is in their dependence on various growth and transcription factors, so that cDC1 depends on Flt3L, GM-CSF/BATF3, IRF8, BCL-6, ID2, ZBTB46, NFIL3, and Notch signaling, while cDC2 needs Flt3L, GM-CSF/IRF4, ID2, RBPJ, NOTCH2, KLF4, ZBTB46 to be derived from HSCs, CDPs, and pDC. Moreover, their markers are quite different, cDC1 expresses CD11c low, HLA- DR+, CD141+, XCR1+, CLEC9A+, DEC205+, but cDC2s express CD11c+, HLA-DR+, CD1c+, CD11b+, CD172a+, CD1a+. The main difference between these two subpopulations is their functions. cDC1 are responsible for cellular immunity against tumors, specialized cross-presentation, TCD8+ and Th1 immunity, producing IFN type I and III and IL-12, and good prognosis of cancer. On the other hand, cDC2s are responsible for maintaining Th17, gut homeostasis, and producing anti and pro-inflammatory cytokines (58, 59).

MoDCs are a subtype of DCs derived from monocytes in inflammatory environments and conditions in peripheral tissues and remain there. Also, they can be derived from monocytes in vitro. Their derivation from monocytes depends on CSF1R, in vitro GM-CSF and IL-4/MAFB, KLF4, and ZBTB46. They can be evaluated by many markers including CD11c+, HLA- DR+, CD1c+, CD11b+, CD14+, CD64+, CD206+, CD209+, CD172a+, CD1a+, CCR2+. MoDCs stimulate and regulate CD8+ T cell, Treg, Th1, Th2, and Th17 cell type immunity (58, 60) (Figure 1).

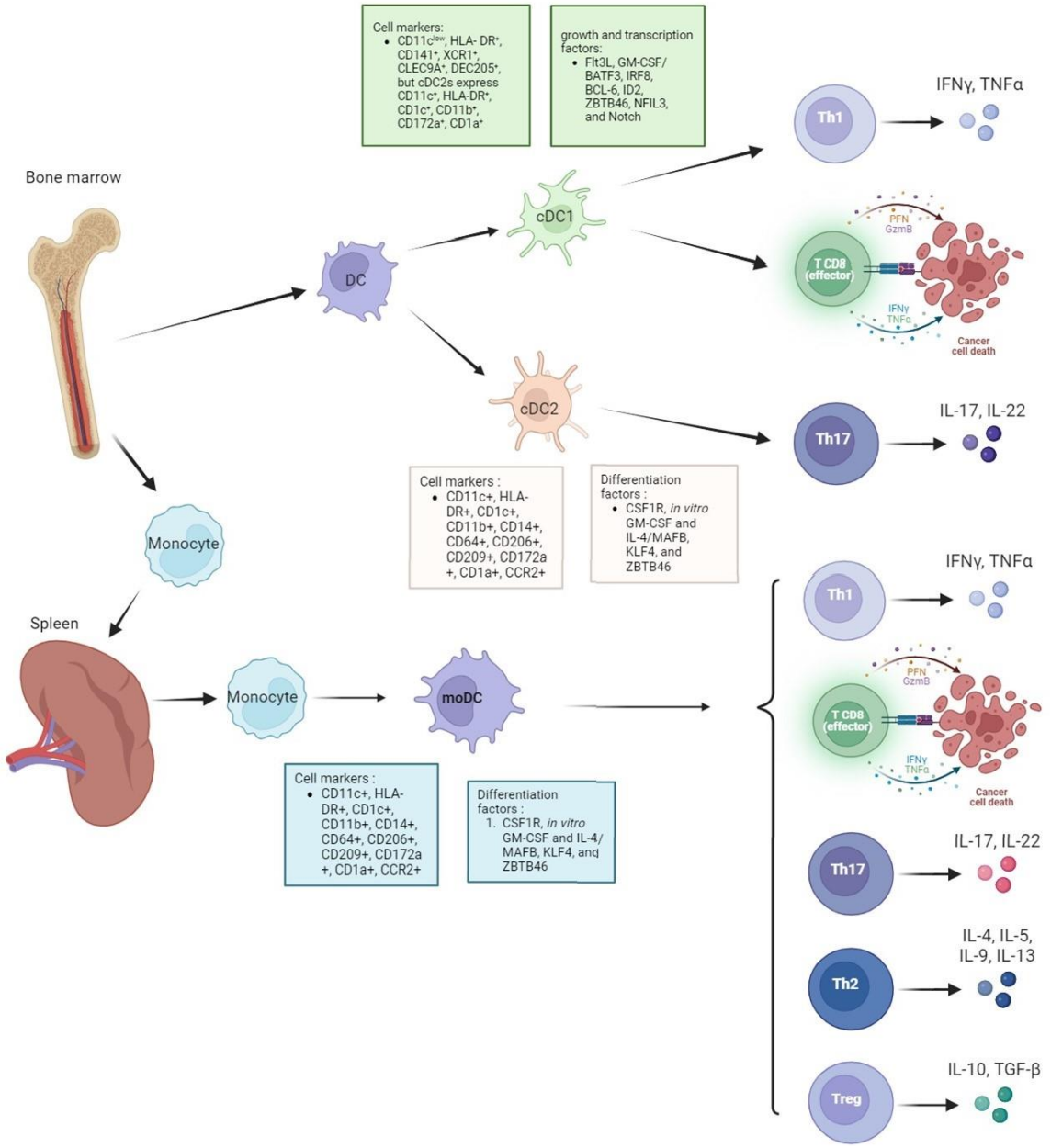

Figure 1. Dendritic cell subtypes maturation and derivation: Dendritic cells originate from HSCs located in the bone marrow (not depicted). These cells undergo a series of changes leading to the formation of cDC1 and cDC2, which the presence of specific cell markers, growth factors, and transcription markers can identify. The remarkable maturation of cDC1s enables them to help Th1 cells, facilitating the production of IFN-γ and TNF-α to bolster cellular immunity. In the immune system, cDC1s are crucial in assisting T CD8+ cells to eliminate malignant tumor cells, while cDC2s support Th17 cells in releasing potent cytokines IL17 and IL22, which enhances immune response. Bone marrow monocytes become moDCs in the spleen with distinct markers and factors. Remarkably versatile, moDCs serve diverse functions akin to their cDC counterparts, including assistance to Th1 cells, T CD8+ cells, and Th17 cells. moDCs help Th2 cells produce important cytokines and promote IL10 and TGF-β production by Treg cells, showcasing their diverse immunoregulatory abilities.

2.3.1. Dendritic Cell Vaccines and Selection of Tumor Antigens

DC vaccines mean using autologous self-mature DCs or ex vivo MoDCs, which are cultured along with TSAs or TAAs and cytokine cocktail, and finally, reinjection of antigen-loaded DCs with proper adjuvants into the same patient. As soon as the tumor antigens to lymph nodes, DCs present them with MHC I and II to CD8+ T and CD4+ T cells, respectively, to induce cellular and humoral immunity against cancer cells (61, 62). Characteristic of target tumor antigens for DC-based vaccines described in table 2.

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Table 2. Comparison of tumor-associated antigens and tumor-specific antigens properties for use in cancer vaccines.

Characteristic	Comparison
Expression in various types of cancer	TAAs* > TSAs**
Using to produce broad-spectrum cancer vaccines	TAAs > TSAs
Immunogenicity	TAAs < TSAs
Risk of inducing autoimmune responses	TAAs < TSAs
Ease of isolation or production in large quantities	TAAs > TSAs
Cost of production *in vitro*	TAAs < TSAs

* Tumor-associated antigens
** Tumor-specific antigens

DC vaccines can be administered in combination with chemotherapy and other immunotherapies, like ICIs, to elevate the efficacy of cancer therapies (62-65). The only FDA-approved autologous DC-based cancer vaccine is Sipuleucel-T. Recombinant prostate acid phosphatase (PAP) and GM-CSF are used to treat patient DCs in ex vivo before reinfusion to the patient. It has demonstrated positive prospects in therapeutic approaches for prostate cancer patients; no toxic effect has been reported from using it (58, 62).

There are certain limitations to DC vaccines, including the heterogeneous population of ex vivo cultured DCs from HSCs may lead to the hardship and complicatedness of standardization, and term ex vivo culture can result in the decrease of the capacity of migratory and functionality to induce strong T cell response of reinfused DCs (12).

A variety of cancer-related antigens can be used in designing DC vaccines. Differentiation antigens, such as MART1, GP100, tyrosinase, PAP, and CEA, are the first group of TAAs that are used to produce DC vaccines. Their high prevalence makes them easily recognized and cheaply used, but their lower specificity might lead to side effects. The second group includes overexpressed antigens such as WT1, MUC1, and ERBB2, which are related to the normal antigens highly expressed by malignant cells. As a result, they are easy to detect and inexpensive. However, as in the previous group, non-specific side effects may occur (66, 67). Viral antigens are another source of antigens for dendritic cell (DC) vaccines. They are antigens related to oncoviruses, such as HPV- and EBV-derived proteins, but the prevalence of virus-associated tumors is limited (58). Cancer-germ line or cancer-testis antigens, e.g., NY- ESO-1, MAGE (like MAGEA3), GAGE, and BAGE protein families, are TAAs that can induce T cell responses and are not expensive in clinical use. However, because they are not exclusive to cancer, they may result in side effects. Whole-tumor antigens can also be used as sources of DC vaccine antigens. Lysates of autologous or allogeneic dead cancer material (e.g., GVAX, Melacine, and OncoVAX) are examples of whole tumor antigens. However, they are complicated to be allogenically matched, difficult to standardize, and susceptible to side effects due to variable specificity because they contain additional DC activating material. They are inexpensive and commonly used (66, 68).

Neoantigens, as the last source of cancer DC vaccine antigens, result from a mutation in malignant cell DNA, so they have the highest possible specificity. As a result, the efficacy is high, and their side effect is the least. Personalized neoantigens are isolated, identified, and selected from a patient's tumor and then loaded onto DCs *ex vivo*, enabling efficient presentation to T cells, which can have an antitumor effect. On the other hand, the recognition and preparation of the product are labor-intensive, time-consuming, and expensive (44, 69). Neoantigen-based DC vaccines in cancer treatment have shown promising results, especially in melanoma and other solid tumors (Table 3). Lung cancer, which has a high level of tumor neoantigens, may also benefit from this therapy (35, 50, 58).

2.3.2. Neoantigen-Based Dendritic Cell Vaccines

The first step in generating neoantigen-based DC vaccines is isolating DCs or their precursors from patients, culturing *ex vivo* and encountering the prepared neoantigen, and finally re-injecting them into the same patient's bloodstream. DCs migrate into lymph nodes and activate T cells against specific cancer antigens *in vivo* (35). However, a vaccine based on neoantigens cannot eliminate cancer cells. This is because cancer patients often have impaired immune cells despite the importance of considering neoantigen antigenicity. Antigen-presenting cells (APCs) do not function correctly and cannot initiate an effective T cell response against tumors. As a result, there is a deficiency in the ability of the immune system to respond to malignant cells (30, 70) (Figure 2).

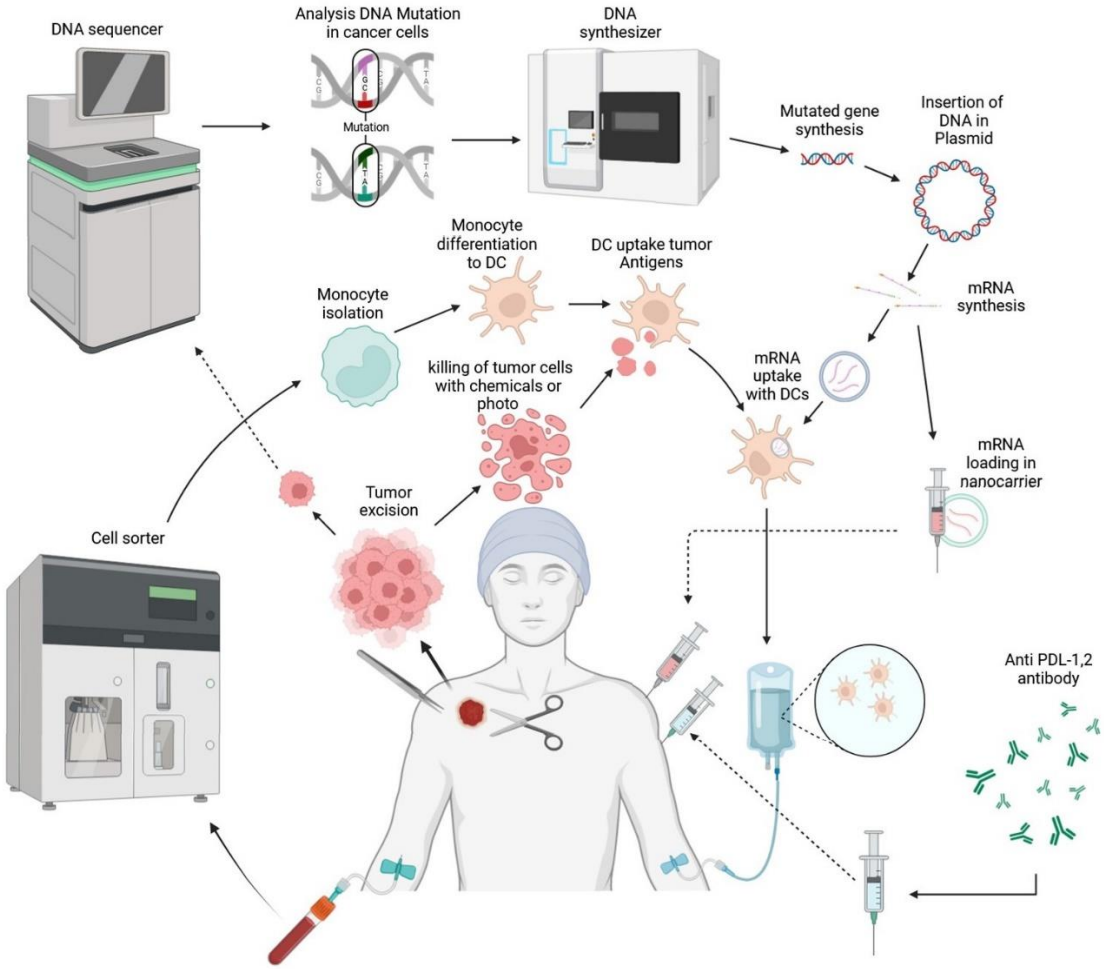

Figure 2. Schematic representation of the generation of neoantigen-based dendritic cell vaccines for cancer immunotherapy: Peripheral blood mononuclear cells (PBMCs) are isolated from the patient's whole blood, and then monocytes that are purified using a cell sorter are differentiated into DCs. The tumor bulk is excised from the same patient and utilized in two ways. Firstly, tumor cells are killed using chemical agents or photos, and the prepared DCs internalize the resulting tumor antigens. Secondly, the excised tumor cells undergo DNA sequencing to identify mutations. The identified mutations are synthesized and inserted into plasmids to produce mRNA, which can be taken up by DCs or loaded into nano-carriers for direct injection into the patient's body. The patient is administered DCs containing tumor antigens or mRNA, followed by immune checkpoint inhibitors like anti-PD1 or anti-PDL1 antibodies, to enhance immune responses against the tumor.

Some approaches have been employed in order to address the problem of the antitumor efficacy of neoantigen-based DC vaccines. Chemotherapy can improve antigen production and presentation and induce T cell immune response. So, it is helpful to combine immunotherapy and tumor vaccination, though it can cause some side effects (35, 52). Zhou *et al*. reported that colorectal cancer patients enrolled in four clinical trials experienced significantly higher overall survival (OS) and disease-free survival (DFS) when they took chemotherapy combined with the DC vaccine and cytokine-induced killer cells. They showed that combining these therapies is feasible and effective in these patients (71).

Furthermore, ICIs play a crucial role in inhibiting the immune response of T cells, particularly cancer cells. Combining anti-ICIs, such as anti-PD1, anti-PDL1, and anti-CTLA4, with DC vaccines is advisable to produce a potent T cell immune response against cancerous cells, resulting in their more effective elimination (35). Studies assessed the effectiveness of combining ICIs and DC vaccines. Hannan *et al*. found that combining DC vaccines and anti-PD1 drug products *in vitro* could enhance the growth of antitumor CD8+ T cells in melanoma patients (19). Ott *et al*. utilized the neoantigen vaccine NEO-PV-01 in combination

with anti-PD1 in melanoma, non-small cell lung cancer (NSCLC), or bladder cancer patients. After vaccination, CD4+ T cells and cytotoxic CD8+ T cells were observed in the tumor site, killing malignant cells. They demonstrated that this combination was safe, and no side effects were observed (72).

Ipilimumab (anti-CTLA4) is another ICI used in clinical trials in combination with neoantigen vaccines. Palmer *et al.* administered a neoantigen vaccine consisting of heterologous chimpanzee adenovirus (ChAd68) and self-amplifying mRNA (samRNA), along with nivolumab (anti-PD1) and ipilimumab, to patients with colorectal cancer. After using this therapy, they reported an overall survival of 8.7 months (18).

2.3.3. Challenges Neoantigen-Based Dendritic Cell Vaccines

Numerous neoantigens are encoded by passenger gene mutations that occur only in some tumor clones (subclonal epitopes). These mutations do not provide a selective survival advantage for patients with cancer. Therefore, they can be lost during clonal evolution even though they can induce an immune response against cancer cells. Targeting mutations of clonal epitopes to eradicate tumor cells is ideal for the design of neoantigen-based DC vaccines; however, due to the high rate of mutations in malignant cells, especially in late stages, it is quite complex, labor, time, and resource intensive to identify a proper clonal mutation for each individual (36).

Furthermore, the immune escape mechanisms of tumors are another obstacle to the use of neoantigen-based DC vaccines. Decreased antigen presentation, expression of immunosuppressive molecules such as PD-1 and CTLA-4, and the antitumor microenvironment of tumors are examples of tumor escape mechanisms from the immune system that can reduce the efficacy of neoantigen-based DC vaccines. A combination of neoantigen-based DC vaccines with conventional chemotherapy and ICIs are solutions for this problem that is being used in some clinical trials (36). Various clinical trials testing neoantigen-based DC vaccines, combined with ICIs and anti-angiogenic factors, are currently being conducted in different parts of the world to treat different types of cancer. Some clinical trials in Table 3 have provided promising preliminary results for improved cancer immunotherapy.

Recent developments in DC-based vaccines for cancer therapy have highlighted their potential, particularly through the use of neoantigen-targeted approaches. Clinical trials are currently exploring various methods to optimize DC maturation and antigen delivery, utilizing agents like TNF-α, CD40 ligand, and cytokine cocktails to enhance immune responses. The integration of DC vaccines with conventional therapies such as chemotherapy and radiation, as well as immunotherapies like checkpoint inhibitors and TLR agonists, is being investigated to achieve synergistic effects (73).

Additionally, the use of adjuvants, nanoparticles, and peptides in vaccine formulations aims to improve efficacy. Tailoring antigens to tumor-specific neoepitopes is a key focus, with ongoing trials assessing optimal dosing, frequency, and treatment duration to ensure sustained disease control and improved survival rates. Notably, a trial involving a human anti-DEC-205 monoclonal antibody fused with the tumor antigen NY-ESO-1 demonstrated promising humoral and T cell responses without toxicity (74).

Despite the challenges of high costs and lengthy production times, advancements in whole exome sequencing and neoantigen prediction algorithms are paving the way for personalized neoantigen-based DC vaccines. Combining these strategies with biomarker research is essential for enhancing immunotherapy outcomes across various cancers, including those with traditionally low mutational burdens like pancreatic cancer (75).

Table 3. List of immunotherapy clinical trials using neoantigen-based dendritic cell vaccines registered in Clinical Trials.gov between 2018 and 2023.

Study Title	NCT Number/ Study Start	Status	Conditions	Interventions
Personalized Neoantigen Derived Dendritic Cell-Based Immunotherapy as Cancer Treatment	NCT05767684 /2023-06-01	Recruiting	Refractory Tumor, Solid Tumor	Biological: Dendritic Cell Vaccine Drug: Lenvatinib (anti-VEGF) Drug: Nivolumab (anti-PD-1)
Neoantigen Dendritic Cell Vaccine and Nivolumab in Hepatocellular Carcinoma and Liver Metastases from Colorectal cancer	NCT04912765 /2021-04-15	Recruiting	Hepatocellular Carcinoma, Hepatocellular Cancer, Colorectal Cancer	Biological: Neoantigen Dendritic Cell Vaccine Drug: Nivolumab (anti-PD-1)
Breast Cancer Neoantigen Vaccination with Autologous Dendritic Cells	NCT04105582 / 2019-08-01	Completed	Breast Cancer, Triple Negative Breast Cancer	Biological: Neo-antigen pulsed Dendritic cell
A Study Combining Personalized Neoantigen-based Dendritic Cell Vaccine	NCT03674073 /2018-10-15	Unknown status	Hepatocellular Carcinoma	Biological: Neoantigen Vaccines

With Microwave Ablation for the Treatment of Hepatocellular Carcinoma			Liver Cancer, Adult	Procedure: Microwave Ablation
Using Neoantigen Peptide Vaccine/Neoantigen-based DC to Treat Advanced Malignant Solid Tumors	NCT05749627 /2023-04-01	Recruiting	Advanced Malignant Solid Tumors	Drug: Neoantigen peptide vaccine Biological: Neoantigen-based DC immune preparation
Neoantigen-primed DC Vaccines Therapy for Refractory Lung Cancer	NCT03871205 /2019-04-01	Unknown status	Carcinoma, Non-Small Cell Lung Carcinoma, Small Cell Lung	Biological: Neoantigen-loaded DC vaccine
Ability of a Dendritic Cell Vaccine to Immunize Melanoma or Epithelial Cancer Patients Against Defined Mutated Neoantigens Expressed by the Autologous Cancer	NCT03300843 /2018-04-11	Terminated	Melanoma, Gastrointestinal Cancer, Breast Cancer	Biological: Peptide-loaded dendritic cell vaccine

Finally, the cost and time of preparing, using, and delivering a neoantigen-based cancer vaccine is still a significant problem in its development. Needs more collaboration between private and government sectors to provide enough budget and focus for these research projects as the future solution to cancer (36, 70).

3. Conclusion

In conclusion, neoantigen-based DC vaccines have shown promising results in inducing a robust immune response against tumors by targeting highly specific personalized tumor neoantigens. However, the effectiveness of personalized neoantigens vaccine depends on the efficient uptake and processing of APCs, which may be inhibited in patients with malignant tumors. Neoantigen-based DC vaccines have been found to increase the number of central and effector memory T cells and induce effector CD8+ T cells to secrete IFN-γ while decreasing the number of immunosuppressive regulatory T cells in tumor tissues (76). Advances in whole exome sequencing and neoantigen prediction algorithms present an opportunity to improve the development of neoantigen-based DC vaccines despite limitations such as high costs and low efficiency of DC migration (53). The combination of immunotherapies based on neoantigen-based DC vaccines, chemotherapy, and ICIs has also shown promising therapeutic benefits for different types of cancer. The feasibility, safety, and immunogenicity of personalized neoantigen-based autologous DC vaccines have been demonstrated in patients with advanced non-small-cell lung cancer. (50), and may have implications in a wide range of solid tumors. Further research and clinical trials are necessary to optimize and evaluate the efficacy of neoantigen-based DC vaccines for different cancers, which may lead to precise treatment options for more cancer patients.

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During the preparation of this literature review, we used ChatGPT (OpenAI) in order to improve the quality and accuracy of writing by identifying grammar mistakes and introducing new words and phrases.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Disclosure statement

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Author contributions

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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