REVIEW

Editorial Process: Submission:02/09/2025 Acceptance:08/15/2025 Published:08/23/2025

Personalized Cancer Vaccines in Combination Therapies: Current Status and Future Prospects

Fnu Rukhayya[1], Lahari Katta[2], Hana Khan Ghori[3], Shreya Kattela[4], Maahin Parvez[2], Sarojini Posani[5], Mihirkumar P. Parmar[6]*, Fnu Jatin[7], Sweta Sahu[8], Salma Younas[9]

Abstract

Personalized cancer vaccines represent a promising advancement in cancer immunotherapy, designed to target tumor-specific mutations unique to individual patients. By stimulating a tailored immune response, these vaccines aim to enhance antitumor immunity while minimizing off-target effects. However, cancer is a complex disease, and single-modality treatments often face challenges such as immune evasion and tumor heterogeneity. To address these limitations, personalized cancer vaccines are increasingly being explored in combination with other therapeutic strategies, including immune checkpoint inhibitors, cytokine therapies, oncolytic viruses, and traditional chemotherapies. This review provides a comprehensive overview of the current status of personalized cancer vaccines, focusing on their development, clinical trials, and early outcomes. It also discusses the synergistic potential of combination therapies, offering insights into how these strategies could overcome immunosuppressive tumor microenvironments and improve patient outcomes. Finally, we explore future prospects, addressing challenges such as vaccine production, patient selection, and regulatory frameworks to outline the path forward for the successful integration of personalized vaccines into standard oncological care.

Keywords: Quality Improvement- Therapeutics Prevention- Future Prospects- Current Status- Cancer Vaccine

Asian Pac J Cancer Prev, **26 (8)**, 2741-2754

Introduction

Immunotherapy is a treatment that uses the body's immune systems to fight diseases, especially cancer. It works by enhancing the immune system's ability to identify and destroy abnormal cancer cells. Different types of immunotherapy include monoclonal antibodies, checkpoint inhibitors, cytokines, and cancer vaccines, each targeting specific aspects of the disease or boosting the immune response in many ways [1]. Cancer immunotherapy builds on the principle to specifically target and eradicate cancerous cells. Unlike traditional treatments like chemotherapy and radiation, which kill cancer cells directly and tend to affect healthy cells as well, cancer immunotherapy aims to enhance the immune system's natural ability to fight cancer. This approach includes various methods. Monoclonal antibodies are a type of targeted drug therapy. These drugs target and bind to specific proteins on cancer cells. Similarly, checkpoint inhibitors, such as PD- 1/PD-L1 inhibitors (e.g., nivolumab, pembrolizumab), work by blocking inhibitory signals that prevent immune cells from attacking cancer cells, allowing the immune system to target and kill tumors. For instance, pembrolizumab has demonstrated improved survival rates in patients with non-small cell lung cancer (NSCLC), where overall survival increased by 40% in comparison to standard chemotherapy [2].

Cancer vaccines aim to help an individual's immune system recognize cancer antigens and attack and destroy the cancer cells that have them [3]. Checkpoint inhibitors are a type of immunotherapy that blocks proteins that stop the immune system from attacking the cancer cells [4]. Adoptive cell therapies, including CAR-T (Chimeric Antigen Receptor T-cell) therapy, represent another promising advancement. This approach modifies a patient's own T cells to express a receptor that recognizes and targets tumor-specific antigens. CAR-T therapies have already shown impressive results, especially in hematologic cancers like leukemia and lymphoma, where complete response rates exceed 80% in certain patient populations [5].

By focusing on boosting an individual's immune

*[1]Dr VRK Women's Medical College, India. [2]Osmania Medical Colleg, India. [3]JSS Medical College, India. [4]Bhaskar Medical College India. [5]Sri Devraj Urs Medical College, India. [6]Gujarat Medical Education and Research Society, Vadnagar, India. [7]Maharaja Agrasen Medical College, India. [8]JJM Medical College, India. [9]University of the Punjab, Pakistan. *For Correspondence: mmihir981@gmail.com*

response or altering how the immune system interacts with cancer cells, cancer immunotherapy represents a significant advancement in the fight against cancer, offering more targeted, effective, and personalized treatment options [6]. Personalized cancer vaccines are a tailored approach to immunotherapy designed to target the unique characteristics of an individual's cancer. Unlike standard cancer vaccines, which aim to provoke a broad immune response against common cancer antigens, personalized vaccines are customized based on the specific mutations and neoantigens present in a patient's tumor [7].

They operate in the following manner: a tumor sample is collected and sequenced to identify specific genetic mutations or neoantigens expressed by the cancer cells. Based on this analysis, a vaccine is developed to include these unique antigens or mutated proteins. The vaccine aims to stimulate the immune system to recognize and attack cells that express these specific markers. The personalized vaccine is administered to the patient, prompting the immune system to target and destroy cancer cells that carry identified antigens. The patient undergoes monitoring, evaluation, close follow-up, and maintenance with education and support. The data is collected, analyzed, and integrated with other therapies [7,8]. Personalized cancer vaccines offer the advantage of targeting the specific characteristics of an individual's cancer, increasing the effectiveness of the treatment, and minimizing damage to healthy cells. This approach shows potential for improving outcomes in cancer therapy by providing a more specific and precise method of exploiting the immune system against cancer [9].

Cancer's ability to evolve and become resistant to treatment is one of the biggest concerns that arises today when creating effective cancer therapies. It has been shown that combination therapy works better than monotherapy because it targets key pathways in a way that is more likely to work together, covers more areas, reduces side effects by using lower doses of each drug or therapy together, and lowers resistance. Cancer cells may develop resistance to one treatment, but combining treatments can make it harder for the cells to survive [10,11].

The objective of this literature review is to offer a comprehensive and detailed understanding of the incorporation of personalized cancer vaccines in combination therapy regimens. This review aims to evaluate the present situation of customized cancer vaccines and focuses on their role in enhancing the efficacy of combination therapies. It seeks to provide a thorough discussion of how personalized vaccines are developed and used alongside other treatment modalities, like chemotherapy, targeted therapies, and immunotherapies, and to assess their overall impact on treatment outcomes and patient quality of life. This review aims to identify the current strengths, limitations, and clinical implications of these combined approaches by examining recent advancements and ongoing research.

Review

Overview of Customized Cancer Vaccines

Dendritic cells are a type of antigen-presenting cells (APCs) that effectively stimulate T and B lymphocytes. They have both MHC (Major Histocompatibility Complex) class I and II on their surface, through which they activate cytotoxic T lymphocytes and T helper cells, respectively. When tumour antigens are present in the body, immature dendritic cells first find them, process them, show the MHC-antigen complex on their surface, and activate cytotoxic T-cell responses. Dendritic cells stimulate T and B lymphocytes by presenting antigens and play a crucial role in antitumor immunity. Cytotoxic T-cells by themselves cannot recognize tumour neoantigens due to the immunosuppressive tumour microenvironment [12].

By activating natural killer cells and cytotoxic T-cells that target tumour cells, dendritic cell vaccines aim to enhance both innate and adaptive immunity against tumours. A systematic review by Anguille et al. in 2014 showed that dendritic cell vaccination therapy had an objective response rate of 8.5% in melanoma patients, which was similar to dacarbazine, 7.1% in prostate cancer, 15.6% in malignant glioma, and 11.5% in advanced renal cell carcinoma. This study also highlighted the dissociation between the objective response rate and the survival benefit achieved by dendritic cell vaccination in solid cell tumours, indicating the need for alternative endpoints in assessing the efficacy of immunotherapies [13]. The steps used in preparing dendritic cell vaccines are the collection of dendritic cells, cell maturation, antigen loading, injection procedures, and immune and clinical response monitoring. Improving vaccine formulation protocols and combining the vaccine with other immunotherapeutic agents can enhance the efficiency of dendritic cell vaccines. Mature dendritic cells are more effective in activating cytotoxic T-cell and generating an immune response compared to immature dendritic cells. Using a single tumour antigen or antigens that do not effectively stimulate the immune system results in an ineffective vaccine formulation. We should use highly immunogenic tumour antigens for antigen loading [14].

Neoantigen Vaccines

Tumour-associated antigens are the proteins expressed by tumour cells in higher quantities, but they are present in normal tissues as well. Tyrosinase and HER2 are some of the examples. Therapies targeting tumour-associated antigens were unable to produce a satisfactory clinical effect compared to the standard therapies. Neoantigens, in contrast, are proteins expressed only in cancer cells and they are produced by somatic mutations. Only tumour cells express these proteins, demonstrating their high immunogenicity, effective binding to MHC complexes, and improved safety profiles. Neoantigens are used to make synthetic long peptide vaccines, RNA vaccines, DNA vaccines, or dendritic cell vaccines [15]. The identification of neoantigens has become easier now with the rapid development of bioinformatics and sequencing technology, including whole-genome sequencing and whole-exon sequencing. The first step in neoantigen identification is comparing the whole genomes of normal cells and tumor cells. We identify mutated DNA sequences, and whether these mutated sequences form tumour neoantigens depends on many factors, such as the

mutated sequence's translation ability, the processing of the formed protein into peptides and their presentation through MHC complexes, the affinity of the mutated peptides to MHC molecules, and their further interaction with cytotoxic T cells [16].

Neoantigens are of two types: shared and personalized. Shared neoantigens are proteins expressed by a specific tumor type and are common among certain tumor types/patients, whereas personalized neoantigens are specific to an individual [17]. Tumour heterogeneity refers to the presence of a diverse set of cancer cells within the same tumour or between different tumours in the same patient. This means all the cancer cells do not express the same neoantigens and eliminating cells expressing one neoantigen may lead to overgrowth of other cells expressing different neoantigens. This warrants targeting multiple neoantigens in a single vaccine for complete tumour eradication [18]. In a clinical trial, Ott et al. demonstrated a significant T-cell response against neoantigens used in vaccinating melanoma patients [19].

Peptide Vaccines

The cytotoxic T-cell response is crucial for suppressing tumour growth. For sustained and enhanced cytotoxic T-cell response, T-helper cell activation is also necessary. So ideally, a highly immunogenic peptide molecule should have epitopes to activate both these cells. The whole protein is beneficial for vaccination because it contains multiple epitopes that stimulate both CD4 and CD8 cells. However, because these proteins are self-antigens, the thymus may have deleted the T cells that attack them during the developmental process. Rationally designed peptide vaccines containing multiple epitopes combined with an appropriate adjuvant are the key to creating a better vaccine [20].

DNA/RNA-Based Vaccines

DNA and RNA vaccines are gene-based vaccines. The DNA vaccines deliver genes encoding various tumour antigens via plasmids. Different delivery strategies, such as sonoporation, electroporation, gene gun, or DNA tattooing, transfer these plasmids into the nucleus. MHC complexes express the antigen in the nucleus, transfer it to the cytosol, and present it to the immune cells. DNA vaccines failed in clinical trials for a number of reasons, including not being able to stimulate the immune system, T-cells getting tired, and the production of cytokines that weaken the immune system. Animal models find that chimeric DNA vaccines coding xenogeneic antigens are more effective than autologous antigens [21].

The development process of personalized cancer vaccines from tumor profiling to vaccine formulation is shown in Figure 1.

To explain the meaning of combined therapy, it involves combining a personalized cancer vaccine, specifically tailored to the targeted antigens, with various treatment regimes such as radiotherapy and chemotherapy to improve patient outcomes. This approach involves the use of specifically designed vaccines in conjunction with various strategies such as targeted therapies, immune

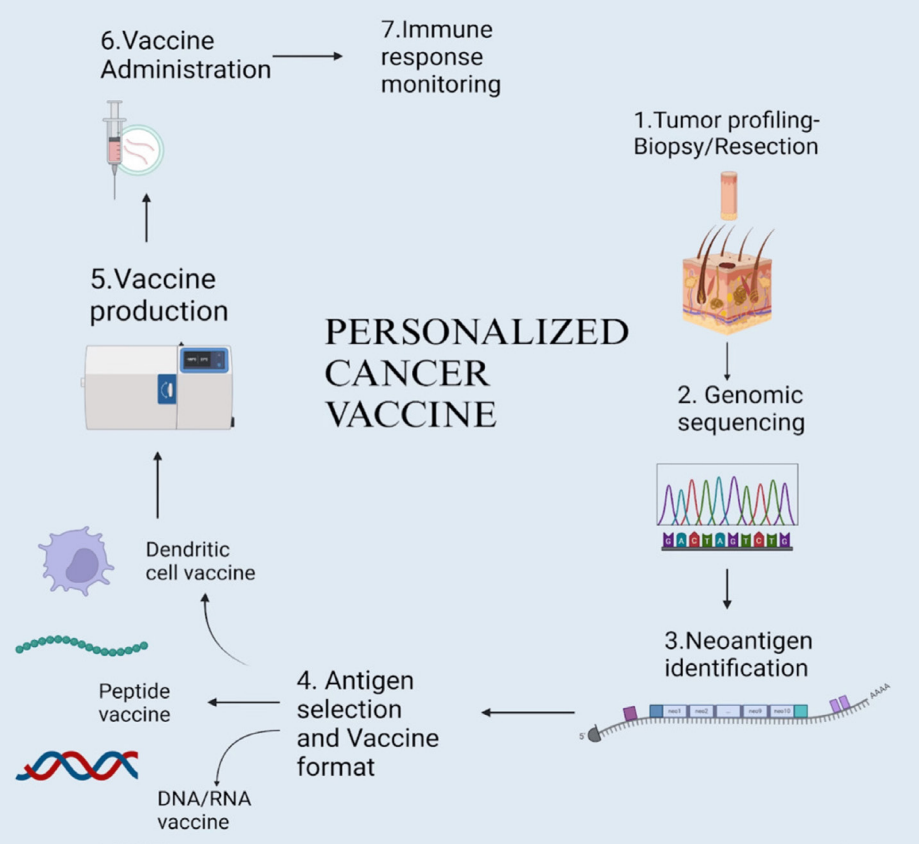

Figure 1. The Development Process of Personalized Cancer Vaccines from Tumor Profiling to Vaccine Formulation. Image Credits: Fnu Rukhayya and Lahari Katta

checkpoint inhibitors, or conventional treatments. The implementation of such combined regimes has numerous effects, including but not limited to improved immune system activation and overcoming tumour resistance. Additionally, they address the various biological aspects of cancer [22].

Combination Therapies

Combination with Immune Checkpoint Inhibitors

Checkpoint inhibitors have now made cancer immunotherapy useful in clinical practice [23]. They are known to improve the survival rates for various types of cancer, including metastases [24]. There are specialized immune cells that are very important for triggering an immune response; they are known as dendritic cells [25,26]. We use these to create cancer vaccines. Dendritic cells directly activate new T cells and thereby help in strengthening immune memory against some tumor - related proteins in cancer cells. Checkpoint inhibitors further enhance the immune response that the vaccine triggers against tumors. Some drugs such as Pembrolizumb and Ipilimumab are currently testing this approach [27-30].

Combining a cancer vaccine (like GVAX) with anti-CTLA-4 checkpoint inhibitors yields better results in mouse models of melanoma and prostate cancer. Give anti-CTLA-4 checkpoint inhibitors after the vaccine to ensure its effectiveness; administering it too early could hinder its ability to effectively target T cells. Some of the cancer vaccines, like DNA- or peptide-based ones, work by directly targeting dendritic cells in the lymph nodes. However, due to varying levels of antigen expression, these vaccines may not be effective in all patients [28]. In the CT26 mouse model of colorectal cancer, the combination of GVAX with dual PD-1 and CTLA-4 checkpoint inhibitors resulted in all the mice rejecting their tumors [29]. People often combine these vaccines with other treatments like chemotherapy to enhance their effectiveness. Hence, this combination approach is now considered the best for making cancer vaccines more effective [31].

Combination with Targeted Therapies

Targeted therapies have the principle of blocking specific processes or some abnormal proteins that tumors require for their survival [32]. They slow the growth of tumors, resulting in shrinkage [33]. The important proteins include epidermal growth factor receptors (EGFR), BRAF, KIT, HER2, and ALK [34]. Clinical trials in phase ll have also demonstrated the success of Sipuleucel-T and Ipilimumab [23]. Ipilimumab is a monoclonal antibody with a short-term response; hence, the disease might recur after a period of time [35]. Research has developed pathways that tumours use to grow and survive, which can aid in the development of targeted drug therapy [34]. Trastuzumab and Cetuximab are the monoclonal bodies that target HER2 and EGFR receptors [36]. By forming immune complexes, these antibodies also enhance the presentation of tumour antigens [37, 38].

Targeted therapies have the potential to enhance immune responses, but they can also lead to immunosuppressive responses. For instance, HSP90 inhibitors have the potential to destroy tumours by enhancing MHC class L presentation, but they can also hinder the process by reducing the activity of dendritic cells and macrophages [39, 40]. Combining therapies also raises the question of whether they can enhance anti-tumor effects without increasing dangerous side effects. For instance, hypophysitis is a side effect of Ipilimumab [41].

Combination with Chemotherapy

Various cells and processes are responsible for a successful immune response to a cancer vaccine, which can also interact with chemotherapy in many ways [42]. Dendritic cells first process the antigen when it enters and present it to the T cells with the help of MHC molecules, thereby activating both CD4+ and CD8+ T cells. Then they destroy tumour cells with the help of certain cytokines and antibodies. Chemotherapy is helpful in enhancing this immune response [43]. The primary problem with chemotherapy is that it weakens the immune response, making patients more susceptible to infections [44].

Mostly, chemotherapy drugs cause mild lymphopenia or none [45]. Some chemotherapy drugs could also increase beneficial cytokines, thereby helping reduce the size of the tumor [46]. Alkylating agents, such as Cyclophosphamide and Busulfan, can stop cell growth before or after it is exposed to an antigen. Antimetabolites, such as 6-Mercaptopurine and Methotrexate, can stop cell growth after an antigen has been activated [47, 48]. Some of the studies suggest that Cyclophosphamide and Paclitaxel work well if given before the vaccine [49]. Researchers have proven that cyclophosphamide reduces the immune response of a cancer vaccine when administered after or at the same time as vaccination, but Paclitaxel is only effective when administered before the vaccine [50]. There is only limited data proving the effectiveness of immunotherapy and chemotherapy when combined [51].

Combined with Radiotherapy

About 70% of cancer patients opt for radiotherapy as a common treatment regime. Radiotherapy (RT) works by causing irreversible changes to the DNA of cancer cells in the targeted tissue, thereby controlling tumour growth. Over the years, there have been many significant advancements in RT [52, 53]. However, RT can also stimulate specific immune cells, leading to the release of substances such as myeloid-derived suppressor cells (MDSCs), regulatory T-cells (Tregs), M2-like tumour-associated macrophages (M2-like TAMs), N2 neutrophils, and immunosuppressive cytokines like TGF-b and IL-10. These substances suppress the immune system and create an increasingly immune-suppressed area around the tumour [54, 55]. One of the major issues in the current research area is the inadequate response of tumours to radiation therapy, which can be attributed to low oxygen levels in certain areas of the tumour [56].

In contrast to the other disease prevention vaccines, the goal of the tumour vaccine is to enhance the response of tumour-specific T-cells for targeted action on tumour

cells and therefore tumour control. This type of targeted response makes the tumour vaccine a promising option for cancer treatment [57, 58]. Most of the current tumor vaccines, by themselves, cannot fully eliminate tumors because a good immune response requires CD4+ T cells, tissue-resident memory T cells (TRM), and other immune cells in addition to CD8+ cells. Most of the current tumour vaccines lack the ability to produce such a response and primarily target only CD8+ T cells. Therefore, a combination of tumour vaccines with other treatment modalities like radiotherapy can aid in the enhancement of the efficacy of vaccines. The targeted use of radiotherapy increases the expression of certain key molecules on tumour cells, making them more receptive to the vaccines and hence boosting the immune response and overall outcome [59-61].

Enhancing Immune Responses

Many cancer drugs alter the properties of tumors, making them more susceptible to the actions of immune cells. These drugs work by impairing DNA or altering the idiosyncrasy of the tumor [62, 63]. Chemotherapy drugs can alter the immune system in many ways. A few of these drugs include 5-FU, topoisomerase inhibitors, platinum compounds, gemcitabine, and taxanes [64-66]. The immune system damages the cancer cells while sparing the surrounding unaffected tissue and cells, which opens up the possibility of cancer vaccines as a viable and promising treatment. There have been limitations on the clinical success of such vaccines; however, recent studies have identified methods to increase the efficacy of vaccines and overcome the immune suppression by using chemotherapy drugs alongside vaccines. These drugs render the cancer cells more susceptible to the action of the immune system and thereby have a significant potential for improving the outcome of vaccine use [67].

Overcoming Resistance

When single treatments are applied, tumours can become resistant, leading to increased heterogeneity in patients and disease, which limits the available treatment modalities and increases the possibility of worse outcomes. This raises the need to use treatment regimes and strategies that can tackle the many different aspects of cancer simultaneously. One such modality is the use of effective combination therapies that target the specific genetic as well as epigenetic details of the tumour cells. The effectiveness of vaccines depends on various factors like inhibitory molecules, T-cell metabolism, and immune cells. Despite the challenging tumour environment, we can significantly enhance the effective response of vaccine-stimulated T-cells by adjusting these factors. Identification of reliable biomarkers, standardisation of side effect monitoring, and precise understanding of timing, dosage, and administration are crucial for achieving a favourable outcome of the treatment [31].

The cancer cells have the ability to develop resistance to the treatments. A variety of available drugs can provide relief to patients with metastatic cancer, but frequently, they cannot completely treat the disease due to the development of resistance. Beyond the resistance to the administered drug, cancer cells can also develop resistance to other drugs, even those with different mechanisms of action [68]. One of the major drawbacks of cancer treatment is the development of resistance to chemotherapy and radiotherapy due to problems with cell death processes [69]. The standardized treatment regimes can target most cancer cells, whereas those with high levels of specific antigens are unaffected. Vaccine-activated T-cells can effectively target these unaffected cells. A combination therapy can therefore be more efficacious instead of a single treatment plan, improving the overall outcome [70].

Figure 2 is representing the synergistic effects of personalized cancer vaccines with other therapeutic

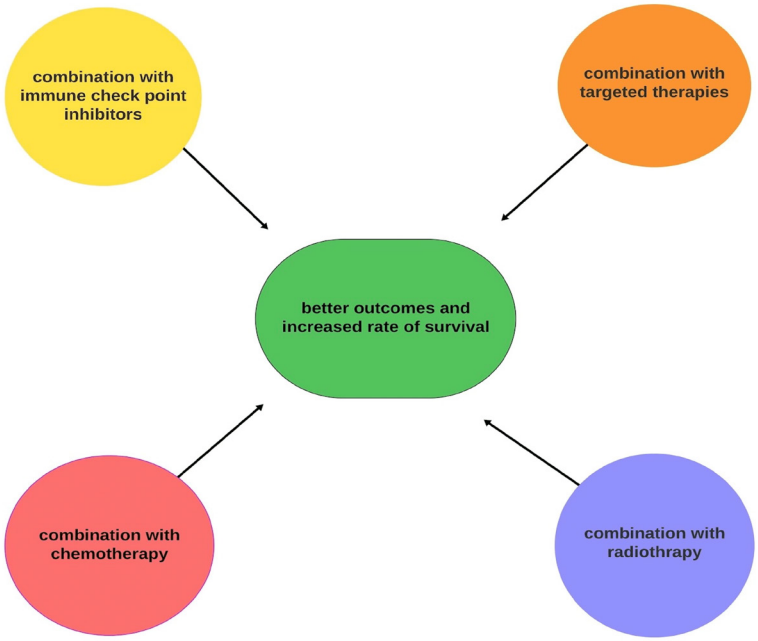

Figure 2. Synergistic Effects of Personalized Cancer Vaccines with Other Therapeutic Modalities. Image Credits: Hana Khan Ghori and Shreya Kattela

modalities.

The Current Status of Personalized Cancer Vaccines in Combination Therapies

Recent Clinical Trials and Studies

Personalized cancer vaccines, particularly those targeting neoantigens, have emerged as a transformative approach in oncology, offering the potential to generate highly specific and individualized immune responses. Neoantigens, which are tumour-specific antigens arising from mutations, are not present in normal cells, making them ideal targets for cancer immunotherapy. Recent clinical trials have underscored the potential of personalized vaccines when combined with other therapies, such as immune checkpoint inhibitors (ICIs), chemotherapy, and radiation therapy. These combination approaches aim to enhance the immune system's ability to detect and destroy cancer cells by addressing the tumor's complex immune evasion mechanisms. For example, mRNA-based neuroantigen vaccines mixed with ICIs, like anti-PD-1 or anti-CTLA-4, have been shown to help people with melanoma. In these trials, patients demonstrated improved immune responses, with some achieving partial or complete tumour regression. However, the efficacy of these vaccines is variable across different cancer types, and response rates remain suboptimal in more complex malignancies like pancreatic and colorectal cancers. This variation suggests the need for further optimization of vaccine design, antigen selection, and combination strategies to improve therapeutic outcomes [57].

Key Clinical Trials

Several key clinical trials have been instrumental in advancing our understanding of personalized cancer vaccines in combination with other therapies. BioNTech's Phase 1 trial of BNT122, a personalised mRNA vaccine, in combination with ICIs for patients with advanced melanoma is one such trial. This trial demonstrated encouraging early outcomes, with some patients achieving durable responses, indicating the potential of this combination to boost the immune response against cancer. Additionally, trials exploring the synergy of mRNA vaccines and immune checkpoint blockades have shown enhanced T cell activation, increased tumor infiltration by effector T cells, and, in some cases, significant tumor regression. Beyond melanoma, other trials have tested similar combinations in lung cancer and renal cell carcinoma, with varying degrees of success. These early trials show how complicated the relationship is between the body's immune system and cancer. They also suggest that while using vaccines and ICIs together shows promise, the best treatment plan may be different for different types of cancer and for each patient [71].

Outcomes and Efficacy Data

Clinical trials combining personalized cancer vaccines with ICIs have produced mixed, but promising results. Some studies, like those that used neoantigen vaccines along with PD-1 inhibitors, found strong T cell responses that were specific to the neoantigens. However, clinical benefits, such as significant tumour shrinkage, have been inconsistent across patients and cancer types. In a trial for melanoma patients, a subset of individuals exhibited durable tumour regression, yet many did not respond to the treatment, underscoring the challenges of tumour heterogeneity and immune escape mechanisms. Trials focusing on other cancer types, such as non-small-cell lung cancer (NSCLC), have shown that combining personalized vaccines with ICIs can induce an immune response, but the correlation between immune activation and clinical outcomes remains unclear. These findings indicate that while personalized vaccines can effectively prime the immune system, their success in controlling cancer may depend on additional factors, including the tumor's immunogenicity and its microenvironment [72].

Case Studies

A notable Phase 1 case study involving a patient with metastatic melanoma demonstrated the potential of combination therapy. In this case, a neoantigen-based mRNA vaccine combined with an anti-PD-1 checkpoint inhibitor resulted in disease stabilization for over 12 months, a significant outcome for such an advanced-stage cancer. However, many patients in the same trial did not achieve the same benefit, highlighting the variability in patient responses and the importance of identifying predictive biomarkers for response to therapy. This case study emphasizes the need for improved patient selection criteria, possibly based on factors such as tumor mutational burden (TMB) and pre-existing immune infiltration [73].

Approved and Experimental Combination Therapies

Currently, Sipuleucel-T, an autologous cellular vaccine, remains one of the few cancer vaccines approved by the FDA for use in prostate cancer. Its success in improving survival when combined with standard treatments underscores the potential of immunotherapy in cancer. In contrast, clinical trials are testing experimental personalised cancer vaccines, particularly mRNA-based vaccines, in combination with ICIs, chemotherapy, and radiation for cancers like melanoma, NSCLC, and glioblastoma. These combination approaches aim to elicit stronger and more durable immune responses than either therapy alone [74].

Challenges and Limitations

Despite the promising potential of personalized cancer vaccines, significant challenges remain. Tumour heterogeneity, which refers to the diversity of mutations within a tumour, makes it difficult to identify a comprehensive set of neoantigens for vaccine development. Additionally, the suppressive tumor microenvironment, characterized by regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and inhibitory cytokines, presents a substantial barrier to the effectiveness of both vaccines and ICIs. Researchers have proposed tumour mutational burden (TMB) as a predictor of response, but its correlation with clinical outcomes is not always straightforward, which complicates patient selection for personalised therapies [75].

Safety and Adverse Effects

Personalized cancer vaccines, particularly those used in combination with ICIs, are generally well-tolerated, but adverse effects can occur. The most common side effects include injection site reactions and mild flu-like symptoms. Reports have indicated the occurrence of more severe immune-related adverse events, like cytokine release syndrome (CRS) and autoimmune reactions, especially in cases of excessive immune system activation. There are limited long-term safety data, and the risk of autoimmune disorders continues to be a concern, particularly for combination therapies that further stimulate the immune system [73].

Cost and Accessibility

One of the major limitations of personalized cancer vaccines is their high cost, driven by the individualized nature of their treatment. The process involves sequencing the patient's tumour, identifying neoantigens, and manufacturing the vaccine-a time-consuming and expensive process. When combined with ICIs, which are themselves costly, the overall expense of treatment becomes prohibitive, particularly in low-resource settings. Addressing these financial barriers is critical to making these therapies more accessible to a broader population of cancer patients [75].

Regulatory Hurdles

Regulatory approval for customized cancer vaccines presents significant challenges. The application of the traditional drug approval pathway, which relies on large-scale, standardised trials, is challenging due to the tailored nature of each vaccine for each patient. Moreover, establishing consistent manufacturing practices and demonstrating the reproducibility of vaccine efficacy across different patient populations are additional hurdles. Large-scale trials and the accumulation of long-term safety and efficacy data will be essential to overcome these regulatory challenges [18]. Table 1 is depicting the summary of current approved and experimental combination therapies for personalised cancer vaccines.

Sipuleucel-T (Provenge®), the only personalised cancer vaccine approved by the FDA for prostate cancer, has shown a small increase in survival rates. mRNA-4157 + Pembrolizumab has shown significant immune responses in unresectable solid tumours, suggesting potential when combined with immune checkpoint blockade. BNT122 + Atezolizumab is being studied for colorectal cancer, but the trial results have not yet been released. NEO-PV-01 + ICI has shown some efficacy across a number of solid tumours, with a 13% conversion rate from disease progression to response, highlighting the potential for personalised vaccines used with ICIs.

Mechanism of Action of Personalised Cancer Vaccines

Personalised cancer vaccines aim to specifically target the tumour cells of that patient by focusing on antigens that are unique or overexpressed in their cancer cells. Tumor antigens and a potent adjuvant capable of directly stimulating T-cells combine to prepare these vaccines. To create a unique 'cancer vaccine' that boosts the patient's immune system to attack specific tumour antigens, researchers take a tumour biopsy from the patient for whole-exome and RNA sequencing. Intra-tumoural dendritic cells identify the vaccine containing neoantigens, prime naive T cells to kill antigen-specific tumour cells, release more antigens, and further enhance the immune response [76]. The immunological mechanism involved in this process involves the presentation and recognition of immunogenic tumour antigens by antigen-presenting cells (APCs), their recruitment, maturation, and interaction with the adaptive immune system. This interaction primes and activates cytotoxic T-cells, leading to tumour cell death and immunological memory [75-78]. These cells aid in long-term surveillance and can identify and respond to tumour cells if they reappear. They stimulate both innate and adaptive immune responses with the use of an adjuvant and antigen, respectively [78]. Antigen selection for the development of vaccines is the most important and critical step. Next-generation sequencing aids in this process by identifying neo-antigens [79]. The antigens presented by the tumor cells could be tumor-associated or tumor-specific. Enhancing antigen presentation and T cell activation in cancer vaccines is a crucial area of research. Adjuvants, improved antigen formulations, dendritic cell vaccines, genetic modification of tumour cells, and immune checkpoint inhibitors can enhance antigen presentation [80].

Interaction with Immune Checkpoint Inhibitors

Combining cancer vaccines with checkpoint inhibitors can activate T cells by overcoming the immunosuppressive tumour microenvironment. Tumour cells contain a protein (PD-L1) that binds to its corresponding protein (PD-1) on T-cells (immune checkpoints), thereby suppressing the immune response. Immune checkpoint inhibitors (ICI) prevent the tumour protein from binding to the T-cell receptor, thereby triggering a T-cell-mediated immune response against the tumour cell. But many cancer patients, due to their immunocompromised nature, do not show an effective response with immune checkpoint inhibitors. Therefore, researchers proposed the synergistic

Table 1. Current Approved and Experimental Combination Therapies

Therapy Name	Type	Targeted Cancer	Combination	Outcomes
Sipuleucel-T (Provenge)	Approved	Prostate Cancer	None	4.1 months survival benefit
mRNA-4157 + Pembrolizumab	Experimental	Unresectable solid tumors	Pembrolizumab	Immune response observed in 60% of patients
BNT122 + Atezolizumab	Experimental	Colorectal cancer	Atezolizumab	Trial ongoing, results pending
NEO-PV-01 + Immune Checkpoint Inhibitor (ICI)	Experimental	Various solid tumors	Immune Checkpoint Inhibitor (ICI)	13% conversion rate from progression to response

use of personalised cancer vaccines and immune checkpoint inhibitors [81]. Researchers propose combined therapy for patients with advanced cancer, especially those with multiline therapy, multiple drug resistance, and immune deficiency [75]. Cancer vaccines enhance the body's immune system by increasing the effector T-cell, leading to T-cell infiltration into the tumors Additionally, the increased number of T-cells leads to an increase in immune checkpoints, providing opportunities for the ICI to act and trigger an effective T-cell response. Several studies, including those by Karyampudi et al. [82], Li et al. [27], and Soares et al. [83], have shown that combination therapy works in breast, colon, and pancreatic cancer, respectively. Figure 3 is showing the interaction between personalized cancer vaccines and immune checkpoint inhibitors within the tumor microenvironment.

The Role of the Tumour Microenvironment

Tumour microenvironment (TME) includes a variety of non-cancerous cells, molecules, and structural components that interact with tumour cells and form an effective barrier, thereby protecting the tumour cell from host immune response. Understanding the role of the TME in cancer vaccines is crucial for designing effective immunotherapies. There are a lot of T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs) in the TME. These cells create an immunosuppressive environment by stopping effector T cells from activating. This means that cancer vaccines don't work. The TME also helps the tumour grow and spread by getting into the bloodstream and surrounding tissues by changing the extracellular matrix and releasing proteolytic enzymes [84]. It can also develop resistance to therapies by altering drug delivery, promoting repair pathways, and inducing adaptive resistance mechanisms [85].

Modifying the tumour microenvironment, improving vaccine delivery, and using combination therapies can evade the challenges faced by TME. Anti-angiogenic drugs, antitumor inflammatory drugs, or hypoxia inhibitors can modify TME and improve the overall outcome [86]. Checkpoint inhibitors, like anti-PD-1/PD-L1 or anti-CTLA-4, and immunomodulators, which target Tregs or MDSCs and make vaccines work better, are both parts of combination therapy [87]. Using nanoparticles in vaccines and target delivery systems could help get around the problems that TME causes and make vaccines work better [88].

Future Prospects and Innovations in Personalized Cancer Vaccines

Advances in Genomic and Proteomic Technologies

The growth of genomic and proteomic technologies has been essential for developing personalized cancer vaccines. These tools allow researchers to sequence tumors and identify neoantigens, which are unique mutations found only in cancer cells. By targeting these specific molecules, vaccines can stimulate a patient's immune system to mount a precise and effective attack against cancer, reducing the risk of off- target effects. The NeoVax peptide vaccine is a good example. It has shown promise in clinical trials for glioblastoma by improving the immune response through targeted neoantigen recognition [89].

Novel Adjuvants and Delivery Systems

DNA origami-based vaccines, among other new vaccine delivery systems, offer precise control over the delivery of antigens and adjuvants to immune cells. For instance, the DoriVac platform arranges CpG adjuvants in a pattern that optimizes immune cell activation, leading to stronger and more targeted anti- tumour responses. These innovations not only improve vaccination efficacy but also minimize the toxic side effects associated with traditional adjuvants. These systems have shown success in preclinical models, where vaccines based on DNA origami improved tumor suppression in both melanoma and lymphoma mice [90].

The Integration of Artificial Intelligence and Machine Learning

AI and ML technologies are becoming integral to the design of personalized cancer vaccines. They facilitate the prediction of neoantigens that are most likely to trigger an immune response, accelerating vaccine development and improving clinical outcomes. AI algorithms can also analyze patient data and tailor treatment protocols dynamically, enhancing vaccine effectiveness by selecting biomarkers that predict immune responses [89, 90]. As researchers refine these tools, AI-driven platforms will play a crucial role in personalizing vaccines and predicting therapeutic responses more accurately [89].

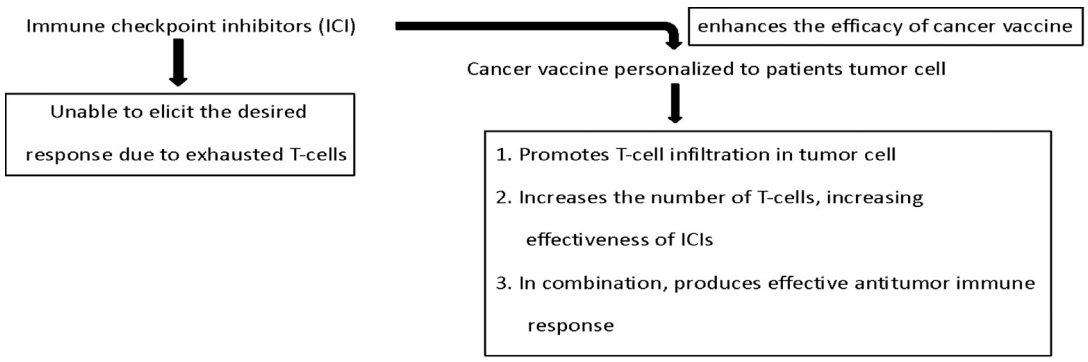

Figure 3. The Interaction between Personalized Cancer Vaccines and Immune Checkpoint Inhibitors within the tumor microenvironment. Image Credits: Maahin Parvez and Sarojini Posani

Emerging Biomarkers for Response Prediction

Biomarkers are pivotal in monitoring how patients respond to cancer vaccines and adjusting treatments accordingly. Recent studies focus on immune markers such as cytokine profiles to predict patient outcomes, ensuring real-time adjustments to therapy as needed. Identifying these biomarkers helps stratify patients who are most likely to benefit from vaccines, increasing the overall success rate of clinical trials [89].

Furthermore, research into novel tumour-specific biomarkers continues to expand, offering more precise ways to monitor immune responses during treatment [91].

Potential for Personalized Vaccines across Cancer Types

Multiple cancer types, including glioblastoma, melanoma, and solid tumours like breast and ovarian cancers, are undergoing testing for personalised vaccines. For glioblastoma, personalized peptide vaccines have shown promise for improving immune responses and prolonging patient survival [89]. In situ vaccination, which directly activates immune responses at the tumour site, has demonstrated systemic tumour regression, thereby expanding the reach of personalised immunotherapy approaches [89, 90]. Combining these vaccines with immune checkpoint inhibitors, such as PD-1 blockers, has shown synergistic effects, leading to more durable and effective treatments [91].

Clinical Implications and Personalized Medicine

Personalised medicine considers the genetic makeup of each person, the impact of their environment on them, and how they live. Personalized medicine holds significant promise for better health outcomes and improved therapeutic interventions. Studies have indicated that cancer vaccines can improve a patient's chances of surviving certain types of cancer, especially when conventional therapies are less effective. For instance, individuals with advanced metastatic castration-resistant prostate cancer have experienced better overall survival with the use of Sipuleucel-T (Provenge), an FDA-approved cancer vaccine. An overall survival analysis of a phase II, randomized, controlled trial of patients with mCRPC showed a 44% reduction in the death rate and an 8.5-month improvement in median overall survival [92].

Similarly, studies have found that melanoma-targeting vaccines like Talimogene Laherparepvec (T-VEC) also extend survival. Patients who received this vaccine in clinical trials lived longer than those who received a placebo by several months. The FDA and EMA approved T-VEC, the first genetically modified herpes simplex virus-1-based oncolytic immunotherapy, for the treatment of unresectable, cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma after initial surgery [93, 94]. Trials have tested GVA Pancreas and CRS-207 for pancreatic cancer and Gardasil and Cervarix for cervical cancer, significantly reducing the cancer risk.

Personalisation of treatment in the context of cancer vaccines involves tailoring the vaccine to target specific characteristics of a patient's tumor. This approach aims to increase treatment effectiveness while minimizing side effects. Integrating personalized medicine into routine medical practice may raise ethical issues around patient privacy, data protection, and the fairness of access to these treatments.

Proper Communication

Cancer-related treatment modalities might be confusing to the patient because of the complex nature of the mechanisms and genetics behind them. Patients might not always understand the nature of vaccines and their benefits. Proper communication channels need to be in place for patients to understand these vaccines and their benefits.

Transparency

Transparency of clinical trial information is essential to scientific advancement. The clinical utility of personalized vaccines depends on earlier scientific work focused on identifying genotype-phenotype associations among population groups. However, racial and ethnic minorities have been significantly under- represented in the studies that serve as the 'inputs' for translational efforts [95, 96]. Clinical trials for many of these vaccines may be in their initial phases, and it is crucial to maintain proper transparency among patients about their pros and cons.

Privacy

We need to take steps to prevent miscreants from misusing an individual's genetic and confidential information, which personalised vaccines require access to. Privacy is a condition of limited access to or information regarding an individual [97]. In this article, we focus on informational health privacy, although there are several other types of privacy, including physical, decisional, proprietary, and relational or associational privacy [98]. The related concept of confidentiality is a condition under which information obtained or disclosed within a confidential relationship is not redisclosed without the permission of the individual [97].The development of EHRs and EHR networks would increase the privacy risk because EHRs are typically comprehensive and instantaneously distributed to multiple parties. Therefore, anyone with access to the EHR can view even sensitive information that is part of an individual's record.

Accessibility

Information technologies, which enable patients to access their own health records, are crucial in the development of personalised vaccines. In this way, personalised medicine reflects broader trends in healthcare by encouraging patients to use information technologies to take responsibility for their own health needs [99, 100].

Physician-Patient Relation

Personalized vaccines are likely to have major effects on the physician-patient relationship. The first issue is whether these physicians have adequate training to provide the essential services of personalised medicine. Besides physicians' lack of training [101], another issue is a shortage of time. Personalized vaccines will often involve the use of genome sequencing or other laboratory techniques, which is likely to increase the time needed

for clinical tasks. For instance, performing a genetic test necessitates pre-test genetic counselling to ascertain the patient's comprehension of the test's implications and potential social ramifications. After receiving the test results, the physician must interpret the information and design a treatment plan. In any event, it is likely that personalized vaccines will change the physician-patient relationship.

Cost-Effective Analysis

Another set of challenges that threaten to exacerbate health disparities are economic barriers. Studies pertaining to clinical applications of personalised vaccines may necessitate larger study samples compared to conventional approaches, potentially delaying the emergence of an evidence base for these applications [102, 103]. Patients who can overlook the cost factor for health benefits are more likely to accept a customised vaccine that can enhance QALY (quality life years).

Long-Term Benefits

Vaccines eliminate the need to undergo repeated psychologically draining treatments; this in turn will reduce the burden on the healthcare system and the economic savings of the population.

Ethical and Access Considerations

As personalized cancer vaccines advance, they raise important ethical, privacy, and access issues. Patients must receive clear communication about the complex mechanisms, potential benefits, and risks of these therapies. Ensuring privacy around genetic data, improving equitable access across socioeconomic groups, addressing physician training needs, and managing the high costs of vaccine development and delivery will all be crucial for integrating these treatments into routine care. Thoughtful regulatory frameworks and health policies will be needed to balance innovation with fairness and long-term healthcare sustainability. Figure 4 is showing the pathway from personalized cancer vaccine development to patient outcomes.

Conclusions

Personalized cancer vaccines with other combined therapies offers a promising advance in cancer treatment, leveraging tailored immune responses for enhanced efficacy. Early evidence shows that these vaccines, particularly when paired with immune checkpoint inhibitors and targeted therapies, may improve outcomes. However, challenges remain, including optimizing biomarkers, managing side effects, and refining delivery. Future progress will rely on continued research, innovation, and supportive regulations to bring safe, effective, and personalized therapies to patients, marking a significant step forward in cancer care.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

None.

Conflicts of interest

In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work.

References

1. Mukherjee AG, Wanjari UR, Namachivayam A, Murali R, Prabakaran DS, Ganesan R, et al. Role of immune cells and receptors in cancer treatment: An immunotherapeutic approach. Vaccines (Basel). 2022;10(9):1493. https://doi.org/10.3390/vaccines10091493.
2. Zahavi D, Weiner L. Monoclonal antibodies in cancer therapy. Antibodies (Basel). 2020;9(3). https://doi.org/10.3390/antib9030034
3. Liu D, Che X, Wang X, Ma C, Wu G. Tumor vaccines: Unleashing the power of the immune system to fight cancer. Pharmaceuticals (Basel). 2023;16(10). https://doi.org/10.3390/ph16101384

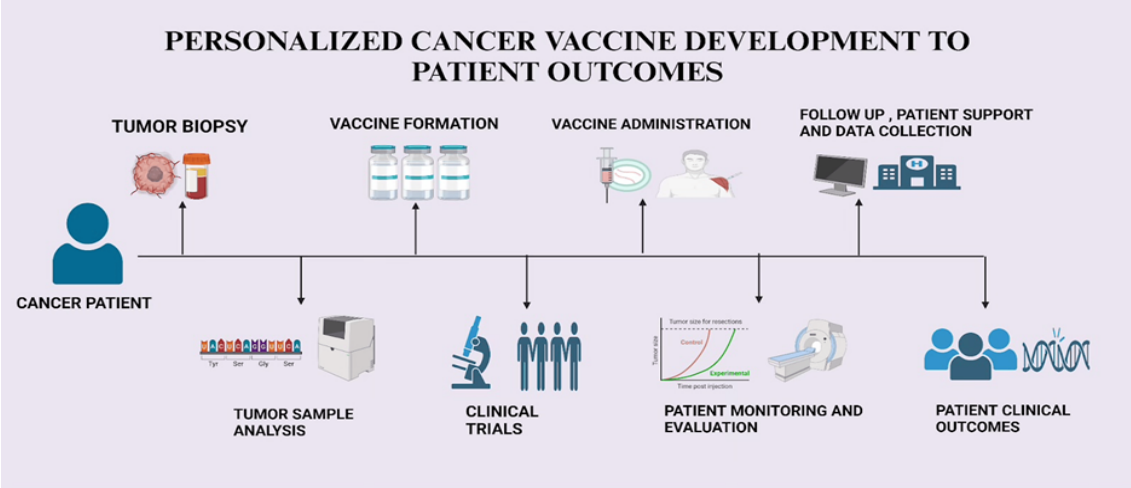

Figure 4. The Pathway from Personalized Cancer Vaccine Development to Patient Outcomes. Image Credits: Mihirkumar P. Parmar, Fnu Jatin, and Sweta Sahu

4. Shiravand Y, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, Sadeghirad H, et al. Immune checkpoint inhibitors in cancer therapy. Curr Oncol. 2022;29(5):3044-60. https://doi.org/10.3390/curroncol29050247.
5. Uscanga-Palomeque AC, Chávez-Escamilla AK, Alvizo-Báez CA, Saavedra-Alonso S, Terrazas-Armendáriz LD, Tamez-Guerra RS, et al. Car-t cell therapy: From the shop to cancer therapy. Int J Mol Sci. 2023;24(21). https://doi.org/10.3390/ijms242115688.
6. Kciuk M, Yahya EB, Mohamed Ibrahim Mohamed M, Rashid S, Iqbal MO, Kontek R, et al. Recent advances in molecular mechanisms of cancer immunotherapy. Cancers (Basel). 2023;15(10). https://doi.org/10.3390/cancers15102721.
7. Seclì L, Leoni G, Ruzza V, Siani L, Cotugno G, Scarselli E, et al. Personalized cancer vaccines go viral: Viral vectors in the era of personalized immunotherapy of cancer. Int J Mol Sci. 2023;24(23). https://doi.org/10.3390/ijms242316591.
8. Lang F, Schrörs B, Löwer M, Türeci Ö, Sahin U. Identification of neoantigens for individualized therapeutic cancer vaccines. Nat Rev Drug Discov. 2022;21(4):261-82. https://doi.org/10.1038/s41573-021-00387-y.
9. Kaczmarek M, Poznańska J, Fechner F, Michalska N, Paszkowska S, Napierała A, et al. Cancer vaccine therapeutics: Limitations and effectiveness-a literature review. Cells. 2023;12(17). https://doi.org/10.3390/cells12172159.
10. Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, et al. Drug resistance in cancer: An overview. Cancers (Basel). 2014;6(3):1769-92. https://doi.org/10.3390/cancers6031769
11. Bayat Mokhtari R, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, et al. Combination therapy in combating cancer. Oncotarget. 2017;8(23):38022-43. https://doi.org/10.18632/oncotarget.16723.
12. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature. 1998;392(6673):245-52. https://doi.org/10.1038/32588
13. Anguille S, Smits EL, Lion E, van Tendeloo VF, Berneman ZN. Clinical use of dendritic cells for cancer therapy. Lancet Oncol. 2014;15(7):e257-67. https://doi.org/10.1016/s1470-2045(13)70585-0
14. Hato L, Vizcay A, Eguren I, Pérez-Gracia JL, Rodríguez J, Gállego Pérez-Larraya J, et al. Dendritic cells in cancer immunology and immunotherapy. Cancers (Basel). 2024;16(5). https://doi.org/10.3390/cancers16050981.
15. Li L, Goedegebuure SP, Gillanders WE. Preclinical and clinical development of neoantigen vaccines. Ann Oncol. 2017;28(suppl_12):xii11-xii7. https://doi.org/10.1093/annonc/mdx681.
16. Peng M, Mo Y, Wang Y, Wu P, Zhang Y, Xiong F, et al. Neoantigen vaccine: An emerging tumor immunotherapy. Mol Cancer. 2019;18(1):128. https://doi.org/10.1186/s12943-019-1055-6.
17. Aldous AR, Dong JZ. Personalized neoantigen vaccines: A new approach to cancer immunotherapy. Bioorg Med Chem. 2018;26(10):2842-9. https://doi.org/10.1016/j.bmc.2017.10.021.
18. Blass E, Ott PA. Advances in the development of personalized neoantigen-based therapeutic cancer vaccines. Nat Rev Clin Oncol. 2021;18(4):215-29. https://doi.org/10.1038/s41571-020-00460-2
19. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature. 2017;547(7662):217-21. https://doi.org/10.1038/nature22991
20. Pietersz GA, Pouniotis DS, Apostolopoulos V. Design of peptide-based vaccines for cancer. Curr Med Chem. 2006;13(14):1591-607. https://doi.org/10.2174/092986706777441922.
21. Lopes A, Vandermeulen G, Préat V. Cancer DNA vaccines: Current preclinical and clinical developments and future perspectives. J Exp Clin Cancer Res. 2019;38(1):146. https://doi.org/10.1186/s13046-019-1154-7.
22. Melief CJM, van der Burg SH, Aranda F, et al. Personalized cancer vaccines and combination therapies . Immunotherapy. 2022;14:183-199.
23. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480(7378):480-9. https://doi.org/10.1038/nature10673
24. Farkona S, Diamandis EP, Blasutig IM. Cancer immunotherapy: The beginning of the end of cancer? BMC Med. 2016;14:73. https://doi.org/10.1186/s12916-016-0623-5.
25. Jung S, Unutmaz D, Wong P, Sano G, De los Santos K, Sparwasser T, et al. In vivo depletion of cd11c+ dendritic cells abrogates priming of cd8+ t cells by exogenous cell-associated antigens. Immunity. 2002;17(2):211-20. https://doi.org/10.1016/s1074-7613(02)00365-5
26. Mempel TR, Henrickson SE, Von Andrian UH. T-cell priming by dendritic cells in lymph nodes occurs in three distinct phases. Nature. 2004;427(6970):154-9. https://doi.org/10.1038/nature02238
27. Li B, VanRoey M, Wang C, Chen TH, Korman A, Jooss K. Anti-programmed death-1 synergizes with granulocyte macrophage colony-stimulating factor--secreting tumor cell immunotherapy providing therapeutic benefit to mice with established tumors. Clin Cancer Res. 2009;15(5):1623-34. https://doi.org/10.1158/1078-0432.Ccr-08-1825.
28. Wada S, Jackson CM, Yoshimura K, Yen HR, Getnet D, Harris TJ, et al. Sequencing ctla-4 blockade with cell-based immunotherapy for prostate cancer. J Transl Med. 2013;11:89. https://doi.org/10.1186/1479-5876-11-89.
29. Duraiswamy J, Kaluza KM, Freeman GJ, Coukos G. Dual blockade of pd-1 and ctla-4 combined with tumor vaccine effectively restores t-cell rejection function in tumors. Cancer Res. 2013;73(12):3591-603. https://doi.org/10.1158/0008-5472.Can-12-4100.
30. Santos PM, Adamik J, Howes TR, Du S, Vujanovic L, Warren S, et al. Impact of checkpoint blockade on cancer vaccine–activated CD8+ T cell responses.J Exp Med. 2020;5:217(7):e20191369.
31. Kerr MD, McBride DA, Chumber AK, Shah NJ. Combining therapeutic vaccines with chemo- and immunotherapies in the treatment of cancer. Expert Opin Drug Discov. 2021;16(1):89-99. https://doi.org/10.1080/17460441.2020.1811673.
32. Druker BJ. David a. Karnofsky award lecture. Imatinib as a paradigm of targeted therapies. J Clin Oncol. 2003;21(23 Suppl):239s-45s. https://doi.org/10.1200/jco.2003.10.589.
33. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003;348(11):994-1004. https://doi.org/10.1056/NEJMoa022457
34. Haber DA, Gray NS, Baselga J. The evolving war on cancer. Cell. 2011;145(1):19-24. https://doi.org/10.1016/j.cell.2011.03.026
35. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clin Cancer Res. 2009;15(23):7412-20. https://doi.org/10.1158/1078-0432.Ccr-09-1624.
36. Dougan M, Dranoff G. Immune therapy for cancer. Annu Rev Immunol. 2009;27:83-117. https://doi.org/10.1146/annurev.

immunol.021908.132544.
37. Correale P, Botta C, Cusi MG, Del Vecchio MT, De Santi MM, Gori Savellini G, et al. Cetuximab ± chemotherapy enhances dendritic cell-mediated phagocytosis of colon cancer cells and ignites a highly efficient colon cancer antigen-specific cytotoxic t-cell response in vitro. Int J Cancer. 2012;130(7):1577-89. https://doi.org/10.1002/ijc.26181.
38. Wolpoe ME, Lutz ER, Ercolini AM, Murata S, Ivie SE, Garrett ES, et al. Her-2/neu-specific monoclonal antibodies collaborate with her-2/neu-targeted granulocyte macrophage colony-stimulating factor secreting whole cell vaccination to augment cd8+ t cell effector function and tumor-free survival in her-2/neu-transgenic mice. J Immunol. 2003;171(4):2161-9. https://doi.org/10.4049/jimmunol.171.4.2161
39. Bae J, Mitsiades C, Tai YT, Bertheau R, Shammas M, Batchu RB, et al. Phenotypic and functional effects of heat shock protein 90 inhibition on dendritic cell. J Immunol. 2007;178(12):7730-7. https://doi.org/10.4049/jimmunol.178.12.7730.
40. Yun TJ, Harning EK, Giza K, Rabah D, Li P, Arndt JW, et al. Ec144, a synthetic inhibitor of heat shock protein 90, blocks innate and adaptive immune responses in models of inflammation and autoimmunity. J Immunol. 2011;186(1):563-75. https://doi.org/10.4049/jimmunol.1000222.
41. Dranoff G. Experimental mouse tumour models: What can be learnt about human cancer immunology? Nat Rev Immunol. 2011;12(1):61-6. https://doi.org/10.1038/nri3129
42. Blattman JN, Greenberg PD. Cancer immunotherapy: A treatment for the masses. Science. 2004;305(5681):200-5. https://doi.org/10.1126/science.1100369.
43. Lake RA, Robinson BW. Immunotherapy and chemotherapy--a practical partnership. Nat Rev Cancer. 2005;5(5):397-405. https://doi.org/10.1038/nrc1613.
44. Tsimberidou AM, Younes A, Romaguera J, Hagemeister FB, Rodriguez MA, Feng L, et al. Immunosuppression and infectious complications in patients with stage iv indolent lymphoma treated with a fludarabine, mitoxantrone, and dexamethasone regimen. Cancer. 2005;104(2):345-53. https://doi.org/10.1002/cncr.21151.
45. Sfikakis PP, Gourgoulis GM, Moulopoulos LA, Kouvatseas G, Theofilopoulos AN, Dimopoulos MA. Age-related thymic activity in adults following chemotherapy-induced lymphopenia. Eur J Clin Invest. 2005;35(6):380-7. https://doi.org/10.1111/j.1365-2362.2005.01499.x.
46. Tsavaris N, Kosmas C, Vadiaka M, Kanelopoulos P, Boulamatsis D. Immune changes in patients with advanced breast cancer undergoing chemotherapy with taxanes. Br J Cancer. 2002;87(1):21-7. https://doi.org/10.1038/sj.bjc.6600347
47. Mitchell MS. Combinations of anticancer drugs and immunotherapy. Cancer Immunol Immunother. 2003;52(11):686-92. https://doi.org/10.1007/s00262-003-0427-2.
48. Turk JL, Parker D. Effect of cyclophosphamide on immunological control mechanisms. Immunol Rev. 1982;65:99-113. https://doi.org/10.1111/j.1600-065x.1982.tb00429.x.
49. Nowak AK, Robinson BW, Lake RA. Synergy between chemotherapy and immunotherapy in the treatment of established murine solid tumors. Cancer Res. 2003;63(15):4490-6.
50. Nigam A, Yacavone RF, Zahurak ML, Johns CM, Pardoll DM, Piantadosi S, et al. Immunomodulatory properties of antineoplastic drugs administered in conjunction with gm-csf-secreting cancer cell vaccines. Int J Oncol. 1998;12(1):161-70. https://doi.org/10.3892/ijo.12.1.161.
51. Lissoni P, Brivio F, Fumagalli L, Messina G, Ghezzi V, Frontini L, et al. Efficacy of cancer chemotherapy in relation to the pretreatment number of lymphocytes in patients with metastatic solid tumors. Int J Biol Markers. 2004;19(2):135-40. https://doi.org/10.1177/172460080401900208
52. Allen C, Her S, Jaffray DA. Radiotherapy for cancer: Present and future. Adv Drug Deliv Rev. 2017;109:1-2. https://doi.org/10.1016/j.addr.2017.01.004.
53. Ghaemi B, Mashinchian O, Mousavi T, Karimi R, Kharrazi S, Amani A. Harnessing the cancer radiation therapy by lanthanide-doped zinc oxide based theranostic nanoparticles. ACS Appl Mater Interfaces. 2016;8(5):3123-34. https://doi.org/10.1021/acsami.5b10056
54. Ahn GO, Tseng D, Liao CH, Dorie MJ, Czechowicz A, Brown JM. Inhibition of mac-1 (cd11b/cd18) enhances tumor response to radiation by reducing myeloid cell recruitment. Proc Natl Acad Sci U S A. 2010;107(18):8363-8. https://doi.org/10.1073/pnas.0911378107.
55. Shevtsov M, Sato H, Multhoff G, Shibata A. Novel approaches to improve the efficacy of immuno-radiotherapy. Front Oncol. 2019;9:156. https://doi.org/10.3389/fonc.2019.00156
56. Rodríguez-Ruiz ME, Vanpouille-Box C, Melero I, Formenti SC, Demaria S. Immunological mechanisms responsible for radiation-induced abscopal effect. Trends Immunol. 2018;39(8):644-55. https://doi.org/10.1016/j.it.2018.06.001
57. Sahin U, Türeci Ö. Personalized vaccines for cancer immunotherapy. Science. 2018;359(6382):1355-60. https://doi.org/10.1126/science.aar7112
58. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Löwer M, et al. Personalized rna mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature. 2017;547(7662):222-6. https://doi.org/10.1038/nature23003.
59. Chakraborty M, Abrams SI, Camphausen K, Liu K, Scott T, Coleman CN, et al. Irradiation of tumor cells up-regulates fas and enhances ctl lytic activity and ctl adoptive immunotherapy. J Immunol. 2003;170(12):6338-47. https://doi.org/10.4049/jimmunol.170.12.6338.
60. Chakraborty M, Abrams SI, Coleman CN, Camphausen K, Schlom J, Hodge JW. External beam radiation of tumors alters phenotype of tumor cells to render them susceptible to vaccine-mediated t-cell killing. Cancer Res. 2004;64(12):4328-37. https://doi.org/10.1158/0008-5472.Can-04-0073.
61. Ferrara TA, Hodge JW, Gulley JL. Combining radiation and immunotherapy for synergistic antitumor therapy. Curr Opin Mol Ther. 2009;11(1):37-42.
62. Zitvogel L, Kroemer G. Anticancer immunochemotherapy using adjuvants with direct cytotoxic effects. J Clin Invest. 2009;119(8):2127-30. https://doi.org/10.1172/jci39991.
63. Emens LA, Middleton G. The interplay of immunotherapy and chemotherapy: Harnessing potential synergies. Cancer Immunol Res. 2015;3(5):436-43. https://doi.org/10.1158/2326-6066.Cir-15-0064.
64. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell. 2015;28(6):690-714. https://doi.org/10.1016/j.ccell.2015.10.012
65. Galetto A, Buttiglieri S, Forno S, Moro F, Mussa A, Matera L. Drug- and cell-mediated antitumor cytotoxicities modulate cross-presentation of tumor antigens by myeloid dendritic cells. Anticancer Drugs. 2003;14(10):833-43. https://doi.org/10.1097/00001813-200311000-00010.
66. Nowak AK, Lake RA, Marzo AL, Scott B, Heath WR, Collins EJ, et al. Induction of tumor cell apoptosis in vivo increases tumor antigen cross-presentation, cross-priming

rather than cross-tolerizing host tumor-specific cd8 t cells. J Immunol. 2003;170(10):4905-13. https://doi.org/10.4049/jimmunol.170.10.4905.
67. Andersen MH, Junker N, Ellebaek E, Svane IM, Thor Straten P. Therapeutic cancer vaccines in combination with conventional therapy. J Biomed Biotechnol. 2010;2010:237623. https://doi.org/10.1155/2010/237623.
68. Makin G, Hickman JA. Apoptosis and cancer chemotherapy. Cell Tissue Res. 2000;301(1):143-52. https://doi.org/10.1007/s004419900160.
69. Longley DB, Johnston PG. Molecular mechanisms of drug resistance. J Pathol. 2005;205(2):275-92. https://doi.org/10.1002/path.1706.
70. Andersen MH, Becker JC, Straten P. Regulators of apoptosis: Suitable targets for immune therapy of cancer. Nat Rev Drug Discov. 2005;4(5):399-409. https://doi.org/10.1038/nrd1717.
71. Seclì L, Leoni G, Ruzza V, et al. Personalized cancer vaccines go viral: Vectors in the era of personalized immunotherapy of cancer. Inter J Mole Sci. 2023, 4:1355-1360.
72. van der Burg SH. Correlates of immune and clinical activity of novel cancer vaccines. Semin Immunol. 2018;39:119-36. https://doi.org/10.1016/j.smim.2018.04.001
73. Ye T, Li F, Ma G, Wei W. Enhancing therapeutic performance of personalized cancer vaccine via delivery vectors. Adv Drug Deliv Rev. 2021;177:113927. https://doi.org/10.1016/j.addr.2021.113927.
74. Liu J, Fu M, Wang M, Wan D, Wei Y, Wei X. Cancer vaccines as promising immuno-therapeutics: Platforms and current progress. J Hematol Oncol. 2022;15(1):28. https://doi.org/10.1186/s13045-022-01247-x.
75. Janes ME, Gottlieb AP, Park KS, Zhao Z, Mitragotri S. Cancer vaccines in the clinic. Bioeng Transl Med. 2024;9(1):e10588. https://doi.org/10.1002/btm2.10588.
76. Chen DS, Mellman I. Oncology meets immunology: The cancer-immunity cycle. Immunity. 2013;39(1):1-10. https://doi.org/10.1016/j.immuni.2013.07.012
77. Makker S, Galley C, Bennett CL. Cancer vaccines: From an immunology perspective. Immunother Adv. 2024;4(1):ltad030. https://doi.org/10.1093/immadv/ltad030.
78. Shemesh CS, Hsu JC, Hosseini I, Shen BQ, Rotte A, Twomey P, et al. Personalized cancer vaccines: Clinical landscape, challenges, and opportunities. Mol Ther. 2021;29(2):555-70. https://doi.org/10.1016/j.ymthe.2020.09.038
79. Lin MJ, Svensson-Arvelund J, Lubitz GS, Marabelle A, Melero I, Brown BD, et al. Cancer vaccines: The next immunotherapy frontier. Nat Cancer. 2022;3(8):911-26. https://doi.org/10.1038/s43018-022-00418-6
80. Fan T, Zhang M, Yang J, Zhu Z, Cao W, Dong C. Therapeutic cancer vaccines: Advancements, challenges, and prospects. Signal Transduct Target Ther. 2023;8(1):450. https://doi.org/10.1038/s41392-023-01674-3.
81. Kleponis J, Skelton R, Zheng L. Fueling the engine and releasing the break: Combinational therapy of cancer vaccines and immune checkpoint inhibitors. Cancer Biol Med. 2015;12(3):201-8. https://doi.org/10.7497/j.issn.2095-3941.2015.0046.
82. Karyampudi L, Lamichhane P, Scheid AD, Kalli KR, Shreeder B, Krempski JW, et al. Accumulation of memory precursor cd8 t cells in regressing tumors following combination therapy with vaccine and anti-pd-1 antibody. Cancer Res. 2014;74(11):2974-85. https://doi.org/10.1158/0008-5472.Can-13-2564.
83. Soares KC, Rucki AA, Wu AA, Olino K, Xiao Q, Chai Y, et al. Pd-1/pd-l1 blockade together with vaccine therapy facilitates effector t-cell infiltration into pancreatic tumors. J Immunother. 2015;38(1):1-11. https://doi.org/10.1097/cji.0000000000000062.
84. Whiteside TL. The tumor microenvironment and its role in promoting tumor growth. Oncogene. 2008;27(45):5904-12. https://doi.org/10.1038/onc.2008.271
85. Son B, Lee S, Youn H, Kim E, Kim W, Youn B. The role of tumor microenvironment in therapeutic resistance. Oncotarget. 2017;8(3):3933-45. https://doi.org/10.18632/oncotarget.13907.
86. Jiang X, Wang J, Deng X, Xiong F, Zhang S, Gong Z, et al. The role of microenvironment in tumor angiogenesis. J Exp Clin Cancer Res. 2020;39(1):204. https://doi.org/10.1186/s13046-020-01709-5.
87. Chaudhary B, Elkord E. Regulatory t cells in the tumor microenvironment and cancer progression: Role and therapeutic targeting. Vaccines (Basel). 2016;4(3). https://doi.org/10.3390/vaccines4030028.
88. Fan Y, Moon JJ. Nanoparticle drug delivery systems designed to improve cancer vaccines and immunotherapy. Vaccines (Basel). 2015;3(3):662-85. https://doi.org/10.3390/vaccines3030662.
89. Cancer research institute (CRI). Impact Report of the Cancer Research Institute. Accessed: May 17. 2024. Available from: https://www.cancerresearch.org/impact2024.
90. Passaro A, Al Bakir M, Hamilton EG, Diehn M, André F, Roy-Chowdhuri S, et al. Cancer biomarkers: Emerging trends and clinical implications for personalized treatment. Cell. 2024;187(7):1617-35. https://doi.org/10.1016/j.cell.2024.02.041
91. DNA origami-based vaccines toward safe and highly-effective precision cancer immunotherapy. 2024. Accessed: May 17, 2024. Available from: https://wyss.harvard.edu/news/dna-origami-based-vaccines-toward-safe-and-highly-effective-precision-cancer-immunother.
92. Kantoff PW, Schuetz TJ, Blumenstein BA, Glode LM, Bilhartz DL, Wyand M, et al. Overall survival analysis of a phase ii randomized controlled trial of a poxviral-based psa-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol. 2010;28(7):1099-105. https://doi.org/10.1200/jco.2009.25.0597.
93. FDA. IMLYGIC. (2024). Accessed: May 17; 2024. Available from: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/imlygic.
94. Imlygic | European Medicines Agency (EMA); 2024. Accessed: May 17, 2024. Available from:https://www.ema.europa.eu/en/medicines/human/EPAR/imlygic.
95. COM (2012) 11 final - EUR-Lex - European Union. 2012. Accessed: May 17, 2024. Available from:http://ec.europa.eu/justice/data-protection/document/review2012/com. National consumer health privacy survey. (2005). Accessed: May 17; 2024. Available from:https://www.chcf.org/wp-content/uploads/2017/12/PDF-ConsumerPrivacy2005ExecSum.pdf.
96. National consumer health privacy survey. (2005). Accessed: May 17; 2024. Available from:https://www.chcf.org/wp-content/uploads/2017/12/PDF-ConsumerPrivacy2005ExecSum.pdf.
97. Joly Y, Knoppers BM, editors. Routledge handbook of medical law and ethics. Philpapers. Routledge; 2014 Sep 19.
98. Beauchamp T, Childress J. Principles of biomedical ethics: Marking its fortieth anniversary. Am J Bioeth. 2019;19(11):9-12. https://doi.org/10.1080/15265161.2019.1665402.
99. Juengst ET, Flatt MA, Settersten RA, Jr. Personalized genomic medicine and the rhetoric of empowerment. Hastings Cent Rep. 2012;42(5):34-40. https://doi.org/10.1002/hast.65.
100. Brothers KB, Rothstein MA. Ethical, legal and social implications of incorporating personalized medicine into healthcare. Per Med. 2015;12(1):43-51. https://doi.

org/10.2217/pme.14.65
101. Stanek EJ, Sanders CL, Taber KA, Khalid M, Patel A, Verbrugge RR, et al. Adoption of pharmacogenomic testing by us physicians: Results of a nationwide survey. Clin Pharmacol Ther. 2012;91(3):450-8. https://doi.org/10.1038/clpt.2011.306.
102. Hood L, Friend SH. Predictive, personalized, preventive, participatory (p4) cancer medicine. Nat Rev Clin Oncol. 2011;8(3):184-7. https://doi.org/10.1038/nrclinonc.2010.227
103. Khoury MJ. Dealing with the evidence dilemma in genomics and personalized medicine. Clin Pharmacol Ther. 2010;87(6):635-8. https://doi.org/10.1038/clpt.2010.4.