REVIEW

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Cancer Vaccines: Mobilizing Immunity for Targeted Cancer Therapy

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Abstract

Objective: Cancer remains the leading cause of mortality in economically developed nations, presenting a major global health burden. Conventional anti-cancer therapies, such as chemotherapy and radiotherapy, often fall short of providing safe, targeted, and long-lasting treatments, particularly for aggressive and metastatic cancer types. **Method:** In recent years, cancer immunotherapy has emerged as a promising alternative that harnesses the patient's own immune system to recognize and eliminate malignant cells. Among the various immunotherapeutic strategies, cancer vaccines represent a dynamic and rapidly evolving field. These vaccines aim to stimulate or enhance tumor-specific immune responses and are tailored to target the diverse molecular and immunological hallmarks of cancer. **Result:** While several cancer vaccines have gained regulatory approval and entered clinical use, many others remain under investigation, requiring further optimization and evaluation through clinical trials. **Conclusion:** This review provides an overview of both clinically approved and emerging cancer vaccine strategies. Additionally, it examines the underlying factors that influence their clinical efficacy and translational potential, including immune evasion, delivery challenges, and patient-specific variables.

Keywords: Cancer- Immune system- Immunotherapy- Vaccines- Cancer Vaccines

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Introduction

About Cancer

Cancer is a fatal disease arising from a highly complex and diverse array of genetic and molecular factors, both intrinsic and extrinsic. Humanity has been waging one of its greatest battles in science and medicine over the past century to overcome this formidable challenge. As of 2022, approximately 20 million new cancer cases were diagnosed worldwide, with nearly 10 million cancer-related deaths. Cancer remains a leading cause of death globally, with its burden increasing in both high-income and low- to middle-income countries due to factors such as aging populations and lifestyle changes [1, 2]. Above all the problems associated with the treatment of cancer, metastasis, the spread of cancer cells from the primary tumour to seed (colonize) other distant tumours, is one of the greatest challenges that we are facing in cancer treatment today [3]. Although the conventional anti-cancer therapies are improving on effectively managing the primary tumours, more systemic, specific and targeted cancer treatments are needed to control the metastatic cancer cells [4].

Immunotherapy

Cancer immunotherapy, also called biological therapy of cancer, means the modulating and using of the patient's own immune system to target the cancer cells rather than using an extrinsic means of therapy. In that manner, cancer immunotherapy focuses on developing agents that activates or enhances the immune system's recognition and killing of the cancer cells [5].

The roots of cancer immunotherapy trace back to the late 18th century. In 1777, French physician Jean Godinot reportedly injected purulent material into a patient with advanced breast cancer, noting tumor regression as the patient developed a severe infection. This early observation laid the conceptual foundation for the link between immune activation and tumor control, which was later formalized by William Coley in the 1890s through his use of bacterial toxins (now known as "Coley's toxins") to treat sarcomas [6, 7].

Our knowledge about the molecular and cellular principles underlying the immune system's role on cancer has expanded considerably nowadays, leading to the development of diverse strategies ranging from immunostimulants to cancer vaccines (Table 1) to use the different aspects of the immune system as anti-cancer therapeutics. In this study, the mechanism of action of the newly developed and established cancer vaccine strategies will be reviewed and further, their progression in clinical trials for cancer treatments will be discussed.

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Table 1. General Overview of Cancer immunotherapy Strategies

Type of Immunotherapy	Agents or Strategies	Description
Immunostimulants	Interleukin-2 (IL-2)	A potent growth factor for T-cells
	Alpha-Interferon (IFN-α)	Activates T and B cells and has apoptotic, antiangiogenic and antiproliferative properties
Immunomodulators	Ipilimumab	Antibody to CTLA-4
	Tremelimumab	Antibody to CTLA-4
	MDX-1106	Antibody to PD-1
	PF-3512676	TLR-9 Agonist
Monoclonal Antibodies	Rituximab	Against the CD-20
	Trastuzumab	Against the HER-2
	Bevacizumab	Against the VEGF
	Cetuximab	Against the HER1/EGFR
Radioimmunotherapy	90Y-ibritumomab- tiuxetan	CD-20 Antibody conjugated to radioactive isotope yttrium-90
		CD-20 Antibody conjugated to radioactive isotope iodine-131
	131I-tositumomab	
Autograph or Allograph Transfer of Lymphocytes	Adoptive Cell Therapy (ACT)	Infusion of ex vivo grown tumour infiltrating or peripheral lymphocytes
	ACT + Genetically modified T-cells	Genetic modification of the lymphocytes before infusion
Cancer Vaccines	Sipuleucel-T	Infusion of autograph mononuclear cells with a tumour antigen and GM-CSF
	Vitespen	Peptide-based vaccine using heat shock proteins from patient's tumour
	BiovaxID	Anti-idiotype vaccine targeting B cell lymphomas
	DCVax	Dendritic cells pulsed with tumour lysates or antigens

CTLA-4, Cytotoxic T-lymphocyte antigen-4; PD-1, Programmed death-1; CD-20, B-lymphocyte antigen; HER1 and 2, Human epithermal growth factor-1 or 2; VEGF, Vascular endothelial growth factor; EGFR, Epidermal growth factor receptor; GM-CSF, Granulocyte-macrophage colony-stimulating factor.

Cancer Vaccines

Cancer vaccines probably create one of the most diverse classes in the immunotherapeutic approaches where it is also the case for the use of monoclonal antibodies. The development of cancer vaccines can be divided into two groups; preventative, also called prophylactic, and therapeutic. These groups are also further sub-grouped and some examples of each are briefly discussed here (Table 2).

Preventive cancer vaccines have been employed with considerable success for over three decades to reduce the risk of virus-associated tumorigenesis. Currently, seven human viruses are classified as carcinogenic by the International Agency for Research on Cancer (IARC): human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein–Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV), human T-cell lymphotropic virus type 1 (HTLV-1), and human immunodeficiency virus type 1 (HIV-1) [8]. Among these, only prophylactic vaccines against HPV and HBV

Table 2. The Classification of Diverse Cancer Vaccines in Immunotherapy

Vaccine type	Name of the Agent	Against to
Preventative		
Virus-based	Hepatitis B virus vaccine	Hepatocellular Carcinoma
	Human Papilloma virus vaccines: Gardasil and Cervarix	Cervical Cancer
Therapeutic		
Peptide or Protein-based	Vitespen	Melanoma and locally advance renal cell carcinoma
	Gp100	Melanoma
Autologous or Allogeneic Whole-Tumour-Cell	GVAX	Prostate Cancer
Dendritic-Cell-based	Sipuleucel-T (Provenge)	Advance metastatic prostate cancer
	DCVAX-Prostate	Prostate Cancer
	DCVAX-Brain	Glioblastoma
Gene Therapy-based	ProstVac-VF	Prostate Cancer
Idiotype Immunoglobulin-based	BiovaxID	Non-Hodgkin's lymphoma

are approved and widely used in clinical practice. These vaccines have significantly reduced the incidence of cervical cancer and hepatocellular carcinoma in vaccinated populations, underscoring the potential of immunization in cancer prevention [8].

The very first such preventative cancer vaccine was the hepatitis B virus vaccine in which, it was approved by FDA in 1981 and since then it has been used as one of the standard agents in scheduled routine vaccinations for infants [9]. The common use of this HBV vaccine not only dramatically reduced the rates of HBV infections but also reduced the number of incidences of Hepatocellular Carcinoma (HCC) where the immunization provided by this vaccine continued well for vaccinated individuals even in later ages [10, 11]. The initial development of these HBV vaccines was involved with inactivated and purified hepatitis B surface antigen (HBsAg) particles from plasma of the asymptomatic carriers of HBV infection [12]. Later on, the improvements in genomics and biotechnology led to the production of second-generation HBV vaccines that are DNA recombinant which can be produced either in yeast cells (Saccharomyces cerevisiae) (Recombivax) or mammalian cells (GenHevac B) [12].

The second preventative cancer vaccine is the human papilloma virus vaccine. In the 1980s, it was demonstrated (by Harald zur Hausen) that certain HPV types, HPV16 and HPV18, were present in most cervical cancer biopsies and also in cervical cancer-derived cell lines [13]. Nowadays, HPV is known to be responsible for virtually all cases of cervical cancer in which the HPV16 and HPV18 are the high-risk HPVs that comprise almost 80% of the cervical cancer [8]. Currently, two major HPV vaccines, Gardasil (Merck) and Cervarix (GlaxoSmithKline), have been developed to target high-risk HPV types, particularly HPV16 and HPV18, which are responsible for approximately 70% of cervical cancer cases. Gardasil also provides protection against HPV6 and HPV11, which are responsible for about 90% of genital warts. Large phase III clinical trials have demonstrated that both vaccines are highly effective in preventing persistent HPV infection and high-grade cervical intraepithelial neoplasia (CIN 2/3), which are precursors to cervical cancer. Based on this evidence, the World Health Organization (WHO) recommended the inclusion of HPV vaccination in national immunization programs in 2009 as a primary preventive strategy against cervical cancer [14-16].

Apart from preventative vaccines, the therapeutic cancer vaccines aim to raise an immune response to an existing cancer rather than trying to prevent it from forming. This approach has been developed due to realization that the cancer patients can indeed produce both cytotoxic and helper T cells specific to antigens expressed in their tumours [17]. Therapeutic cancer vaccines intent to trigger or enhance these pre-existing T cell responses against the tumour cells and there are several different approaches in the making of these vaccines (Table 2) [18].

Peptide or Protein-Based Vaccines

This type of cancer vaccines uses a whole protein or short peptide derived from the tumour cells as a tumour cell-specific antigen for the immunization. A vaccine belongs to this type, called Vitespen, is a peptide-based vaccine which uses an autologous tumour-derived heat shock (chaperone) protein; glycoprotein (gp) 96–peptide complex (HSPPC-96) as an antigen [19]. In phase III clinical trials conducted in patients with melanoma and locally advanced renal cell carcinoma, Vitespen (HSPPC-96) did not demonstrate a statistically significant improvement in overall survival or recurrence-free survival when compared to standard treatment controls [20, 21]. However, subgroup analyses suggested that patients in earlier stages of disease, as well as those who received higher doses of the vaccine, may have derived modest clinical benefit. These findings have prompted further investigation into patient stratification and optimization of dosing strategies to enhance the therapeutic potential of peptide-based vaccines [22].

Another peptide-based therapeutic cancer vaccine is called Gp100 (or Gp100-based) that uses peptides from this glycoprotein 100 as a melanoma associated antigen for the vaccination [22]. Even though this vaccine has succeeded to demonstrate its ability to establish an immune response against the tumour cells, no reduction in tumour size was observed [23]. However, a recent study, where Gp100 was co-administrated with the Immunostimulant IL-2, showed an anti-cancer immune response with a prolonged progression-free survival rate in patients with advanced melanoma [24]. Even though there is some potential in the future of peptide or protein-Based cancer vaccines, these primary studies clearly indicate the difficulties associated with the use of them. These difficulties may arise from the fact that short and free peptides are likely to be discarded rather quickly from the body without having the chance to associate with a dendritic cell to cause an immune response. Following up from the same problem, another issue can be the lack of effective dendritic-cell-activating adjuvant that is supposed to assist the peptides to be loaded to dendritic cells and promote their activation and maturation [25]. Circumventing these issues can indeed improve the therapeutic benefits provided by these cancer vaccines.

Autologous or Allogeneic Whole-Tumour-Cell Vaccines

Whole-tumour-cell cancer vaccines are prepared from either autologous tumour cells or allogeneic tumour cell lines. Even though the use of autologous tumour cells eliminates the antigen selection problem by providing the advantage of targeting the individual's own tumour associated antigens, this approached has been abandoned due to the motion that this kind of vaccine would not raise an effective anti-cancer immune response since it was not pre-existing in the first place [19]. Furthermore, the high complexity of the vaccine preparation for each individual patient additionally instigated the abandoning of this approach [26]. On the other hand, the use of allogeneic tumour cell lines for the whole-tumour-cell vaccination was favoured because of its ability to introduce multiple antigens and therefore to stimulate a better immune response [22]. An example to this class of cancer vaccines is called GVAX. It is a therapeutic cancer vaccine composed of genetically modified,

irradiated allogeneic prostate cancer cells engineered to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF), showed initial promise in early-phase clinical trials. However, its efficacy was later questioned in two large Phase III clinical studies. The VITAL-1 trial, which compared GVAX to standard docetaxel/prednisone therapy in asymptomatic castration-resistant prostate cancer (CRPC) patients, was terminated early due to a futility analysis indicating a low probability of meeting its survival endpoint. The VITAL-2 trial, testing GVAX in combination with docetaxel versus docetaxel alone in symptomatic CRPC patients, was also halted prematurely due to an unexpected increase in mortality in the GVAX arm. Despite these setbacks, exploratory analyses suggested that specific patient subgroups might benefit from GVAX, prompting ongoing interest in optimizing vaccine-based immunotherapy through improved patient selection and combination strategies [27, 28].

Gene Therapy-Based Vaccines

Gene therapy-based vaccines are also called vector or viral-vector vaccines since they use viruses to insert the vaccine [19]. In this approach, these viral vectors are engineered to encode for specific tumour antigens for the purpose of stimulating and enhancing the immune responses against cancer cells that carry the particular antigens. While advantages of using viruses as a delivery vehicle includes the ease of gene insertion, low cost and ability to induce persistent immune response, the viruses belonging to the poxvirus family create an attractive candidate for this treatment due to their safe applications since the 1960s [29]. The recombinant poxvirus vaccine, belonging to this class of cancer vaccines, is called ProstVac-VF that encodes for a prostate-specific antigen (PSA) and the adhesion molecules B7-1, ICAM-1 and LFA-3 to boost the T cell activation by resembling a specialized dendritic cell [26]. Additionally, GM-CSF is administrated along with the vector to further stimulate the immune response. In a phase II clinical trial against minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC), ProstVac-VF failed to improve progression-free survival but succeeded to demonstrate a significant increase in overall survival rates and more than 40% of decrease in death rates, leading to its schedule to be used in a large phase III clinical trial [30].

Idiotype Immunoglobulin-Based Vaccines

This type of cancer vaccines is prepared by fusing patient's malignant B lymphoma cells with a myeloma cell line in which the resulting heterohybridoma expresses antibodies that consist of patient's tumour-specific antigens called idiotypes [31]. Then the idiotypes are isolated from the produced antibodies from these heterohybridoma B cells, purified and are coupled to keyhole limpet hemocyanin (KLH) to enhance their immunogenic properties by providing specific T-cell responses [31]. The vaccine called BiovaxID was developed in such way as a cancer vaccine against the B-cell lymphomas. Three phase III clinical trials were performed with this vaccine in which one of them was for patients with follicular non-Hodgkin's lymphoma that the BiovaxID showed increased progression-free survival rates when administrated with GM-CSF [32]. Unfortunately, in the other two-phase III clinical studies, BiovaxID failed to provide a significant clinical benefit which may be due to the differences between the populations of patients or due to the time and labour-intensive manufacturing method of the BiovaxID [32].

Dendritic-Cell-Based Vaccines

Among all the cancer vaccines discussed here, perhaps dendritic-dell-based vaccines hold of the highest potentials in the field of therapeutic vaccination that still needs to be explored. Considering the amount of information accumulated in the recent decades, the importance of dendritic cells is now known for a potent T-cell stimulation and therefore a persistent anti-cancer immune response [19, 26]. One of the dendritic-dell-based vaccines is called DCVax-Prostate which is an autologous dendritic cell vaccine however it does not use a whole protein as in peptide or protein-based vaccines and it does not include GM-CSF in its administration. Its manufacturing follows an incubation of the patient's dendritic cells with a prostate-specific membrane antigen (PSMA) before it is infused back in to the same patient [19, 26]. The phase I and II clinical trials in patients with prostate cancer, DCVax-prostate proved to be able to induce an anti-cancer immune response against the prostate cancer cells [33]. Another dendritic-dell-based vaccine is called DCVax-Brain -Brain which uses the exact same concept as in DCVax-prostate but instead of PSMA the autologous dendritic cells are loaded with the patient's tumour cell lysates [26]. DCVax-Brain, commonly referred to as DCVax-L, is a dendritic cell-based therapeutic vaccine developed for patients with glioblastoma multiforme (GBM), the most aggressive and prevalent malignant primary brain tumor in adults. Phase I and II clinical trials demonstrated that the vaccine was well tolerated, with minimal toxicity, and capable of eliciting tumor-specific immune responses [34, 35]. These early findings provided the rationale for the large-scale Phase III trial, which later reported prolonged survival in a subset of patients, particularly those with newly diagnosed GBM and low tumor burden [36].

Sipuleucel-T (Provenge)

The use of Sipuleucel-T for advance metastatic prostate cancer was approved by FDA in 2010, making Sipuleucel-T the first FDA approved therapeutic cancer vaccine [19, 26]. It is an autologous personalized vaccine that is prepared from the patient's own peripheral blood mononuclear cells (Figure 1). After discarding platelets, monocytes, low-density lymphocytes and erythrocytes by leukapheresis, the remaining dendritic cells, T cells, B cells, and natural killer cells are incubated from 36 to 44-hour ex vivo with a fusion protein PA2024 which is composed of a prostate cancer antigen, prostatic acid phosphatise (PAP) and GM-CSF [9, 19, 26]. After the ex vivo incubation, the cells are infused back into the same patient where the cells are thought to effectively present the antigen to host immune system and activate the cytotoxic T-cell responses against the tumour cells [37].

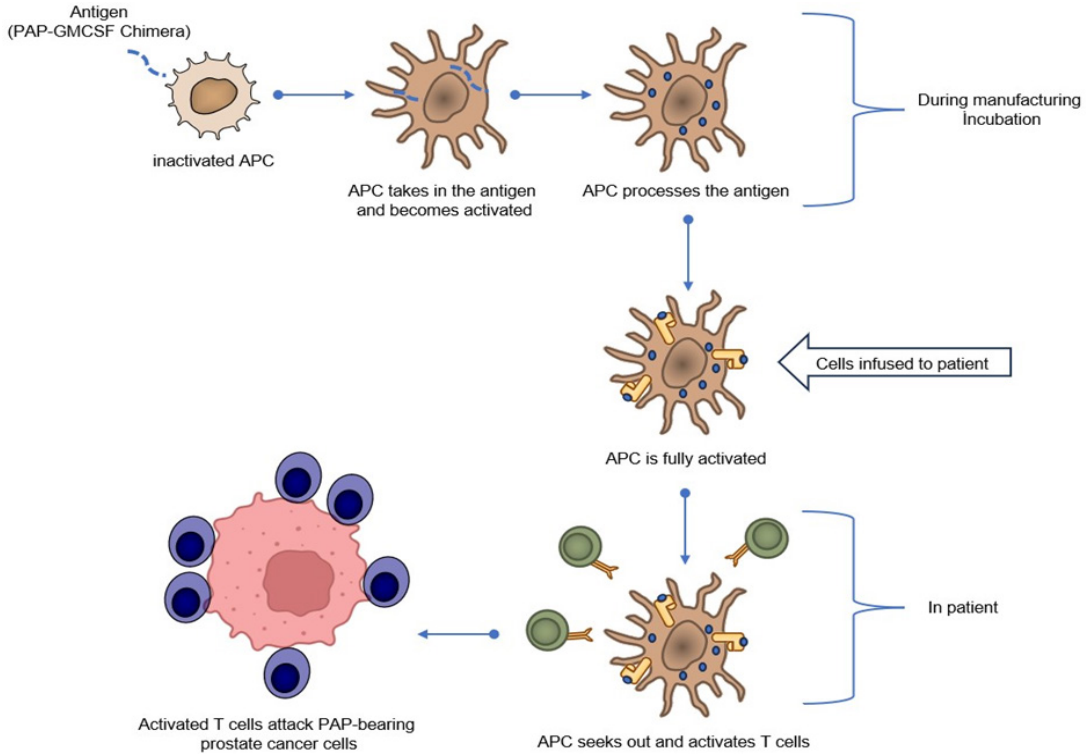

Figure 1. The Preparation and Proposed Mechanism of Action of Sipuleucel-T Cancer Vaccine. PAP, Prostatic acid phosphatise; GM-CSF, Granulocyte-macrophage colony-stimulating factor; APC, Antigen presenting cell.

Even though the Sipuleucel-T vaccine is considered as an autologous dendritic-cell-based vaccine, its mechanism of action is not fully comprehended since it has not been clearly demonstrated yet whether the complex mixture of the ex vivo incubated cells indeed contain the PAP-loaded dendritic cells or that the induction of PAP-specific T-cells by the infusion indeed exists [38]. Therefore, there is still a need for further characterization of the incubated cells to fully understand the mechanism of this vaccine. Although the phase III clinical studies of Sipuleucel-T did not show reduction in tumour size or reduction in disease progression rate, it succeeded to provide a significant increase in the median survival rates that led to its FDA approval [39]. This appearance of increase in overall survival provided by the Sipuleucel-T vaccine without demonstration of an observable anti-tumour effect has led to the discussion that the tumour response criteria in clinical trials might be in need of modification for this kind of immunotherapeutic approaches.

In the light of these developments, it is encouraging to see that cancer vaccines are finally emerging as an effective immunotherapy. However, there are several limitations that are associated with these developments. The selection of a suitable tumour antigen to target and work with still remains to be a problem for autologous cancer vaccines where the tumour cells can also have a diverse range of different antigens that can decrease the efficiency of a cancer vaccine that targets only one or two of them. The selected antigen can also be present in healthy cells or can be very similar to those in healthy cells therefore the vaccine can create undesired effects. Another limiting issue with cancer vaccines in that an appropriate adjuvant needs to be developed that can ensure the proper maturation of dendritic cells to facilitate an anti-tumour cytotoxic T-cell response. However, one of the most important points is the issue of immunosuppressive factors used by cancer cells that alters the effectiveness of the anti-tumour cytotoxic T-cell population that has been raised by these vaccines. This problem might be solved with the use of Immunomodulators that are mentioned but not discussed in this study such as anti-CTLA-4 mAb or anti-PD-1 mAb. This issue of immune checkpoints creating immunosuppressive factors for the immunotherapies is further discussed below.

Discussions and Perspectives

The development of cancer vaccines has opened new avenues in cancer treatment and prevention. While traditional therapies such as chemotherapy, radiation, and surgery remain central to the management of many cancers, they often lack specificity and can result in significant side effects. Cancer vaccines, in contrast, offer a targeted approach, training the immune system to recognize and eliminate cancer cells while sparing healthy tissues. Despite the promise, numerous challenges remain in translating these theoretical advantages into widespread clinical success.

One of the key hurdles in cancer vaccine development is the complexity and heterogeneity of tumors. Cancer is not a single disease but a collection of related conditions characterized by genetic mutations and molecular diversity. Each tumor can present unique antigens, making the design of a one-size-fits-all vaccine problematic. As such, researchers are increasingly turning toward personalized cancer vaccines that tailor antigens based on the individual patient's tumor profile. Neoantigen

vaccines, which target patient-specific tumor mutations, have shown considerable promise in early-stage clinical trials. However, the high costs and technical demands of developing personalized vaccines present barriers to widespread adoption.

Moreover, cancer cells are adept at immune evasion. They create an immunosuppressive tumor microenvironment (TME), which hampers the ability of vaccines to generate a robust and lasting immune response. Regulatory T cells, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs) within the TME actively inhibit immune activity, rendering vaccines less effective. Overcoming these immunosuppressive barriers remains a critical challenge. Researchers are exploring combination therapies that pair vaccines with immune checkpoint inhibitors, such as anti-PD-1/PD-L1 antibodies, to improve outcomes by reducing immune suppression. Clinical trials have shown promising synergies between cancer vaccines and checkpoint blockade therapies, indicating that multi-modality treatments may be the key to enhancing vaccine efficacy.

The timing and administration of cancer vaccines also warrant further investigation. Optimal timing of vaccination in relation to other therapies, such as chemotherapy or radiation, remains an open question. Some studies suggest that administering vaccines during periods of minimal residual disease, when the tumor burden is low, may enhance the likelihood of an immune response capable of preventing relapse. However, determining the ideal therapeutic window will likely depend on the specific cancer type, stage of disease, and the patient's overall immune status.

In addition to therapeutic cancer vaccines, preventive vaccines have the potential to dramatically reduce the incidence of virus-related cancers. The success of vaccines against human papillomavirus (HPV) and hepatitis B virus (HBV), both of which are known to cause cancers, illustrates the preventive power of vaccination. Widespread HPV vaccination, for instance, has led to a significant decline in the rates of cervical and other HPV-associated cancers. Expanding the development of preventive vaccines for other virus-linked cancers, such as those associated with Epstein-Barr virus (EBV) or human T-cell lymphotropic virus (HTLV), could further reduce cancer incidence globally.

Despite progress, the road to cancer vaccine approval is long, requiring extensive clinical trials to demonstrate safety and efficacy. Many cancer vaccines that show promise in preclinical models fail to achieve the same success in human trials. This is partly due to differences in the immune systems of humans and animal models, underscoring the need for more representative preclinical testing methods. Furthermore, the variability in immune responses among individuals can complicate vaccine development. Age, genetics, and previous treatments can all influence how a patient responds to immunization, necessitating a more personalized approach to vaccine design.

The field of cancer vaccines is also benefiting from advances in vaccine delivery technologies. Novel platforms such as mRNA vaccines, which gained worldwide attention during the COVID-19 pandemic, are now being applied in the cancer space. mRNA vaccines offer the advantage of rapid development and the ability to encode multiple antigens, making them an attractive option for personalized cancer treatment. Early-stage trials of mRNA cancer vaccines have demonstrated promising results, although much work remains to optimize this approach.

Looking ahead, the integration of cancer vaccines into the broader landscape of cancer immunotherapy will be critical. A deeper understanding of tumor immunology, improved biomarkers for patient selection, and enhanced delivery methods will all be essential for unlocking the full potential of cancer vaccines. Collaborative efforts between academia, industry, and regulatory agencies will play a crucial role in bringing these innovations from the lab to the clinic.

In conclusion, cancer vaccines represent a powerful tool in the fight against cancer, offering the potential for long-lasting, targeted immune responses. However, significant challenges remain, particularly in overcoming tumor heterogeneity, immune suppression, and variability in patient responses. Continued research, along with advancements in personalized medicine and combination therapies, will be pivotal in translating the promise of cancer vaccines into clinical success.

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Conflict of interest

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