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Review Article

Cancer Vaccines: Another Aspect to Immunotherapy

Ismail Ibrahim Al-Janabi*

Retired Academic, Freelance Consultant Pharmacist and Science Writer, Epsom, Surrey, UK

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Abstract

Background: Therapeutic cancer vaccination is an important side of immunotherapy. For the vaccines to achieve their treatment aim, they must overcome barriers erected by a restrained immune system. ***Objective***: This simple review hopes to provide a foundation for the principles behind cancer vaccines. ***Methods***: Several literatures search engines were employed to collect peer-reviewed papers using the criteria outlined in the methods section. ***Main points***: In addition to the well-established "preventative" cancer vaccines, there are now a few therapeutic vaccines for the "treatment" of certain malignancies. Moreover, hundreds of ongoing clinical trials eagerly await their results due to the relative infancy of the field. The continued advancements in cancer immunotherapy can bring fruitful results to some of the clinical work in progress. ***Conclusions***: Therapeutic cancer vaccines are establishing themselves as another arm of immunotherapy in the fight against this complex disease.

Keywords: Cancer vaccines, Cancer immunotherapies, Tumour antigens.

لقاحات السرطان: جانب آخر للعلاج المناعي

الخلاصة

الخلفية: التطعيم ضد السرطان هو جانب مهم من العلاج المناعي، يجب على هذا العلاج التغلب على الحواجز التي يقيمها جهاز المناعة. **الهدف:** تأمل هذه المراجعة البسيطة في توفير أساس للمبادئ الكامنة وراء لقاحات السرطان. **الطرق:** تم استخدام العديد من البرامج الإلكترونية لجمع البحوث التي راجعها الخبراء باستعمال المعايير المعترف بها. **النقاط الرئيسية:** بالإضافة إلى لقاحات السرطان الوقائية، هناك الان عدد قليل من اللقاحات العلاجية لبعض الأورام الخبيثة. علاوة على ذلك، ونظراً لحداثة هذا المجال الدراسي نسبياً، هناك المئات من التجارب السريرية الجارية حالياً والتي يتم انتظار نتائجها بفارغ الصبر. ان التقدم المستمر في العلاج المناعي للسرطان يمكن ان يؤدي إلى نتائج مثمرة لبعض البحوث السريرية الجارية. **الاستنتاجات:** لقاحات السرطان العلاجية تثبت نفسها كذراع آخر للعلاج المناعي في مكافحة هذا المرض المعقد.

* ***Corresponding author***: Ismail I. Al-Janabi, Retired Academic, Freelance Consultant Pharmacist and Science Writer, Epsom, Surrey, UK; Email: ismail.janabi@gmail.com

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INTRODUCTION

Employing vaccines to treat and/or prevent infectious diseases dates to well before Edward Jenner was accredited with using the vaccines to protect against smallpox [1]. Vaccination to prevent infections is now considered the most successful health measure of all time [2]. Over the years, vaccines have prevented countless illnesses and saved numerous lives [3]. Their widespread use has eradicated some diseases (e.g., smallpox) and drastically reduced the incidence of others (e.g., polio) [4]. However, vaccinations intended for therapy rather than disease prevention, such as for chronic infections and cancer, have proven challenging because the vaccine must overcome the barriers of a restrained immune system. Treatment vaccines aim to help the immune system recognize and react to threats manifested as antigens. Only a minority of patients with cancer generate sufficient immune responses to eradicate their malignancy [5]. Patients frequently develop an immune response to their cancer that is typically insufficient to get rid of the disease. The main reason for this low-key response is because, unlike pathogens, cancer cells closely resemble normal, healthy cells. This makes the immune system unaware of the existence of a threat requiring its attention. Moreover, cancer cells often develop ways to evade immune defenses or erect barriers to protect themselves against immune attacks. Acknowledging this, scientists devised a variety of methods to boost current immune responses and initiate fresh immune reactions against cancer, with cancer vaccines serving as one such advancement in immunotherapy. Cancer immunotherapies aim to activate the host antitumor immunity, modify the suppressive microenvironment around the tumor, and ultimately result in tumor shrinkage and increased patient survival. This led to the hypothesis that using cancer antigens in vaccines would, due to their preferential targeting of cancer cells, enable effective

cancer treatment and be capable of inducing long-lasting immunity [2]. It took decades before the first cancer vaccine, based on a patient's tumor cells, was developed and tested for the treatment of colorectal cancer [6]. This was followed in 2010 by the successful licensing by the USA's Food and Drug Administration (FDA) of the Sipuleucel-T cell-based vaccine for the treatment of prostate cancer [7]. We must not overlook the other two prophylactic cancer vaccines that have already received approval: a) the human papillomavirus (HPV) vaccine, which prevents cervical cancer, and b) the hepatitis B virus vaccine, which prevents liver cancer [8]. The discovery of the first human melanoma-associated antigen and the advancement in sequencing technology have led to the emergence of new tumor antigens, propelling the field of cancer vaccines to the forefront of innovative cancer therapies [9,10].

METHODS

For this narrative review, a literature search was carried out for peer-reviewed articles using PubMed, Google Scholar, ResearchGate and Web of Science, covering the period between February 2004 and February 2024. The keywords and key phrases employed in the search were "cancer vaccines, "therapeutic cancer vaccines, "cancer antigens," and "cancer neoantigens." Chosen hits were selected and evaluated by the author, taking into consideration the citations of the article and the impact factor of the journal. Considering the wide scientific appeal of the field, many hits resulted from the initial search. However, studies deemed to be outside the scope of the basic narrative review intended for the present work were excluded. Publications before February 2004 were only considered if the initial reading of the article suggested that they represent a significant or historic contribution to the field of cancer vaccines.

Cancer Immunity Cycle

The goal of successful cancer immunotherapy is to amplify and enhance the body's delicately balanced immune response in a controlled manner, avoiding giving rise to unrestrained autoimmunity [11]. To do that, the therapy must target one or more steps in a cycle of individual processes, starting with the capture of cancer antigens by specialized cells generally known as antigen-presenting cells (APCs) and finishing with the killing of cancer cells and the resulting release of more antigens (refer to Figure 1).

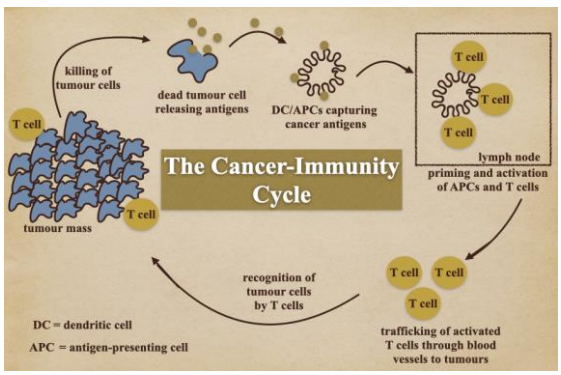

Figure 1: The cancer immunity cycle.

This cycle is called the "cancer immunity cycle," with each step possessing the potential to be rate-limiting in the overall generation of an optimal immune response to cancer [12]. Cancer antigens, produced and released by rogue cancer cells, are captured by antigen-presenting cells (APCs). The prime examples of APCs, particularly as far as cancer vaccination is concerned, are dendritic cells. In this review, we will continue to refer to dendritic cells as APCs. Following antigen uptake, protein-presenting machinery and costimulatory molecules of the APCs are upregulated [13]. Then, the APCs move to a lymph node and give T cells pieces (peptides) of the cancer antigens on HLA-1 or HLA-2 (human leukocyte antigen class I or II) complexes [14,15]. Major Histocompatibility Complexes (MHCs) are simply different general terms for the same proteins as HLAs, indicating their species independence. The presentation of cancer antigens, in the context of HLA complexes, to naive T cells will result in priming and activation of the T cells. Those T cells that are activated following the presentation of antigens in the context of HLA-I will be differentiated as cytotoxic T cells (Tc cells) and often referred to as $CD8^+$ T cells. However, those T cells that are activated following the presentation of antigens in the context of HLA-II will be differentiated into helper T cells (T_h) and are often referred to as $CD4^+$ T cells. The cytotoxic T cells will then travel towards the tumor site to infiltrate the tumor tissue and induce killing through cytotoxicity and the production of effector cytokines (16,17]. The recognition of cancer cells takes place through the interactions of the T cell receptors (TCRs) and their cognate antigens bound to HLA-I, which are ubiquitously expressed on all nucleated cells, and with the help of an array of immune checkpoint receptors to initiate the killing of cancer cells, as depicted in Figure 2 [18].

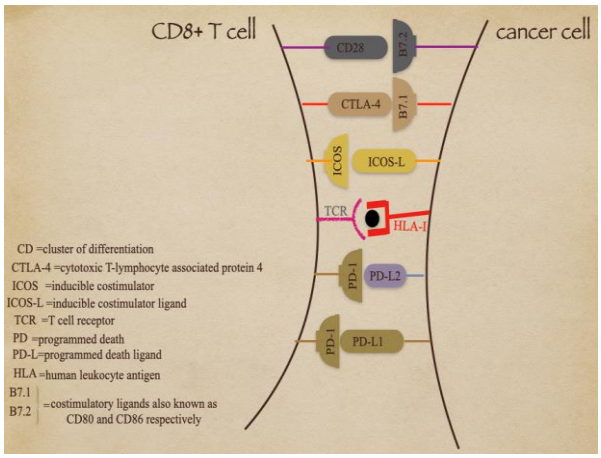

Figure 2: Recognition of cancer cells by cytotoxic $CD8^+$ T cell involves a multitude of costimulatory signals some of which are depicted in this figure in addition to the binding of TCR with HLA-I displaying its cognate antigen.

Cancer antigens released by lysed tumor cells can be captured again by APCs to induce polyclonal T cell responses, thus increasing the depth and breadth of the immune reaction [11,19-21]. The underperformance of the cancer immunity cycle can be attributed to three main reasons: a) unrecognized or undetected cancer

antigens; b) cancer antigens being treated as self rather than non-self, thereby eliciting regulatory T cell (Tregs) responses rather than effector T cell responses; and c) suppressive tumor microenvironment (TME) factors [22–24].

How do Cancer Vaccines Work?

The crucial three players in eliciting a good immune response to cancer vaccines are tumor antigens, antigen-presenting cells and T cells. Tumor antigens are central to the efficacy of cancer vaccines [25]. An ideal tumor antigen should be highly immunogenic, explicitly expressed by the tumor, and necessary for the survival of its cells [26,27]. Tumor antigens can be subdivided into a) tumor-associated antigens (TAAs), which are also known as shared antigens and b) tumor-specific antigens (TSAs), often referred to as neoantigens. Tumor-associated antigens include overexpressed antigens, differentiation antigens and cancer testicular antigens that are considered "self-proteins." They also encompass cancer antigens of viral origin, which are considered “non-self-proteins" [17]. Human epidermal growth factor receptor 2 (HER2) is a prominent example of overexpressed TAAs. Prostate-specific antigen (PSA) is an example of a differentiation antigen that is expressed by tumor cells as well as normal cells of the same tissue origin. These TAAs can be used with different patients and were the focus of the early cancer vaccines. However, the central immune tolerance of the thymus can recognize T cells carrying these “self-proteins” and eliminate them from the T cell repertoire, thus reducing the vaccine efficacy [28,29]. Subsequent clinical trials of cancer vaccines based on “self” TAAs had limited success in addition to the fact that the antigens they carry are also expressed in normal (non-malignant) tissues, increasing the vaccine-induced toxicity [13,30]. Nonetheless, clinical experience with Prostvac, a PSA-targeted vaccine and Sipuleucel-T (Provenge), which targets a chimeric GM-CSF-prostatic acid phosphatase (PAP) in prostate cancer, has shown that these TAA-based vaccines can generate an adequate antitumor response [31–34]. Tumor-specific antigens are a class of proteins specifically expressed in cancer cells and are often referred to as neoantigens [35]. This subgroup of cancer antigens has more potent immunogenicity, a stronger affinity for HLA binding and is unaffected by central immune tolerance [36,37]. Developments in next-generation sequencing technology and algorithms for binding prediction have greatly facilitated the discovery of new epitopes of this subgroup of cancer antigens [38, 39]. From a theoretical perspective, the higher the tumor mutational burden, the more nonsynonymous mutations and neoantigens will be available for HLA presentation [40]. An example of a cancer vaccine based on TSA is the mRNA neoantigen melanoma vaccine [38]. A neoantigen vaccine usually contains several antigens; for example, a personalized neoantigen DNA vaccine, named GNOS-PV02, encodes up to 40 antigens from hepatocellular carcinoma patients [41]. Cancer antigens of viral origin, which are “non-self-proteins” and are also a type of TSAs, can be highly immunogenic and have been successful in the prevention of certain virally induced cancers such as cervical cancer [26,42]. To expand the cancer antigen pool for vaccination, investigators have also combined neoantigens with shared antigens and combined vaccines with PD-1 and PD-L1 to increase antitumor activity [43–45]. Dendritic cells (DCs) represent the most important type of antigen-presenting cells [46–50]. Following the administration of the cancer vaccines and the uptake of antigens by dendritic cells, HLA-I, HLA-II and other co-stimulatory molecules on the surface of DCs will be upregulated [51]. Figures 3 and 4 illustrate the cross-communication between antigen-presenting cells and T cells and the steps involved in processing antigens [46–59]. To become fully activated, $CD8^+$ cells require two signals.

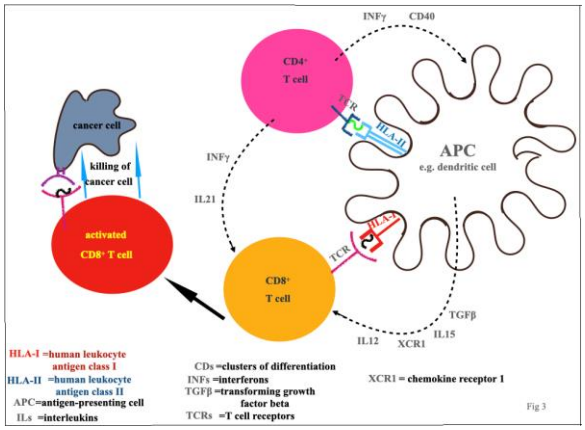

Figure 3: An illustration of the cross-communications between antigen-presenting cells and T cells leading up to the activation of the latter cells to eliminate cancer.

The first signal (signal 1) is antigen-specific and is provided by the interaction of TCR with the peptide-HLA-I complex and a second, antigen-non-specific signal (signal 2) is a co-stimulatory signal provided by co-stimulatory molecules present on the surface of dendritic cells and $CD8^+$ cells. The co-stimulatory signal (signal 2) is necessary for the proliferation, differentiation and survival of $CD8^+$ cells. Without signal 2, $CD8^+$ cells may become unresponsive (a state called anergy), undergo apoptosis or develop immune tolerance [13]. The opposite of co-stimulation is when co-inhibitory molecules interact with different signaling pathways to arrest T cell activation. The most known inhibitory molecules are CTLA4 and PD1 and their increased expression is linked to a state of T cell exhaustion [60]. Fully activated $CD8^+$ cells will then travel to the tumor site to exert their cytotoxic effects via ligation of their TCRs with antigens presented by HLA-I, assisted by several co-stimulatory interactions as illustrated in Figure 2. The number of activated $CD8^+$ cells in TME becomes a prognostic marker of cancer. These activated $CD8^+$ cells detect tumor cells presenting target antigens and attack them through various mechanisms involving the release of cytotoxic granules such as perforin and granzymes, the induction of apoptosis and the production of other cytotoxic factors such as IFN-γ and TNF-α [61,62]. Vaccine components alone are

seldom sufficient to induce a strong enough immune response to eradicate cancer [36]. A variety of other components are usually included, such as checkpoint inhibitors and cytokines [63–65]. Combining cancer vaccines with traditional treatments such as radiation, immunotherapy, hormone therapy and chemotherapy may lead to synergistic beneficial outcomes [36].

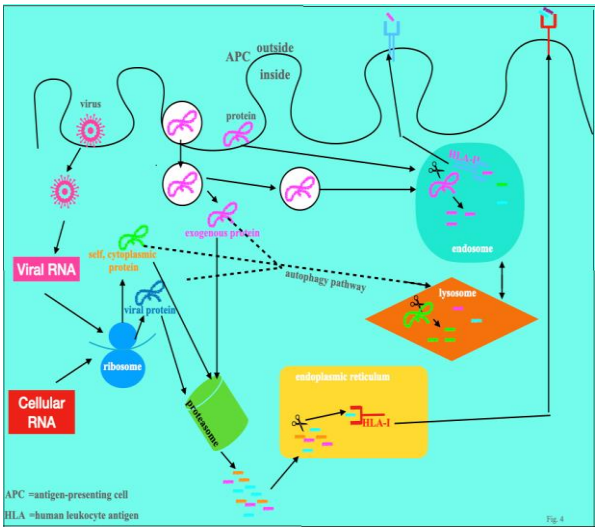

Figure 4: A simplified representation of the events following the uptake of proteins/viruses by antigen-presenting cells and leading up to the presentation of their fragments to T cells.

Resistance to Cancer Vaccines

Cancer vaccines must overcome several barriers before they can elicit immune protection against malignancies. These barriers could be put into two groups: a) tumor cell-driven (intrinsic) barriers and b) microenvironment-driven (extrinsic) barriers.

Tumour cell-driven barriers

These intrinsic barriers can include the following [13]: 1) Downregulation of cancer antigen expression, which may be a result of copy number loss at the genomic or epigenomic levels. Antigen loss could also be mediated by immune selection resulting from differences in immunogenicity among tumor cells, with the elimination of those exhibiting strong immunogenicity owing to an effective antitumor response [66]. 2) Downregulation of the expression of HLA-I molecules. These molecules are expressed by cancer cells (and almost all human nucleated cells) and their downregulation in cancer is often a strategy employed in the progression of malignancy [67–70]. The lack of costimulatory molecules in cancer cells, which leads to failure of T cell activation and T cell tolerance, also represents a reason for tumor immune escape [13,66]. 3) Altered antigen processing within the cancer could also lead to poor tumor cell recognition by CD8+ T cells [71]. 4) Mutations in signaling pathways supporting tumor immune control could also lead to the immune system's failure to recognize cancer. The signaling pathway WNT/β-catenin was linked to cancers that lack immune cell infiltration and are less likely to respond to immune checkpoint blockade [72,73].

Microenvironment-driven barriers

These extrinsic factors are primarily caused by the various immunosuppressive cells in TME, which can interfere with the activation and proliferation of T cells through the upregulation of immunosuppressive proteins and the inhibition of the function of dendritic cells [74,75]. The presence of immunosuppressive cells creates an inhibitory niche within TME that protects the tumor from immune attack. These immunosuppressive cells include: 1) Myeloid-derived suppressor cells (MDSCs), which are neutrophils and monocytes that follow a slightly different pathological activation route to become immunosuppressive [76]. The MDSCs are the cornerstone barriers protecting tumors from the onslaught of the immune system [77]. 2) Tumor-associated macrophages (TAMs) come in two main types: a) the antitumor M1 or b) the protumor M2 [78]. These macrophages are polarized into the M2 phenotype by cytokines such as IL4, IL10 and TGF-β released from T helper type 2 cells (Th2). Tumor-associated macrophages of the M2 type support tumor viability by promoting angiogenesis and TME remodeling [79]. 3) Cancer-associated fibroblasts (CAFs) prevent the migration and proliferation of DCs and T cells by remodeling the extracellular matrix through the construction of dense fibrous structures and the recruitment of MDSCs [80]. 4) T regulatory (Treg) cells, which inhibit the proliferation and activation of effector T cells. 5) Dendritic cells that are PD-L1-positive can suppress T cell function by presenting this inhibitory ligand to them. Strategies to counteract the suppressive effects of TME might lead to improvements in the efficacy of cancer vaccines.

Platforms of Cancer Vaccines

There are four major platforms for the construction of cancer vaccines: 1) cell-based platforms; 2) peptide-based platforms; 3) viral-based platforms; and 4) nucleic acid-based platforms (see Table 1) [5,13,81]. A paramount feature of the success of any of these constructs is the efficient presentation of cancer antigens to T cells [53,82]. We discuss below the essential characteristics of each of these platforms and the role of their common denominator of success, which is their action through dendritic cells.

Cell-based cancer vaccines

These vaccines were the types that were initially employed despite being expensive to prepare and cumbersome to manufacture. They are usually prepared from whole cells or fragments of cells for a broader immune response. This category of cancer vaccines includes: a) cancer cell-based vaccines; b) dendritic cell-based vaccines; c) APC-based vaccines; d) bacteria-based vaccines; and e) yeast-based vaccines (see Table 1). Cancer cell-based vaccines usually include all the tumor-associated antigens encompassing the epitopes of $CD4^+$ cells and $CD8^+$ T cells [82]. Under normal circumstances, a cancer cell exhibits poor immunogenicity as it secretes soluble factors that could suppress the immune response [83].

For this reason, additional modifications are often needed to enhance tumor cell immunogenicity when included in a cancer vaccine platform. The use of tumor cell vaccines is usually accompanied by immune stimulants such as granulocyte macrophage colony stimulating factor (GM-CSF).

Table 1: Cancer vaccine platforms in approved products and in products being developed.

Platform	Representative antigen examples	Target cancer	References
Cell-based			
- Cancer cell	Cells/GM-CSF	Pancreatic cancer	[86,102]
- Dendritic cell	Cells/GAA	Glioma	[96]
- APC	Cells/PAP	Prostate cancer	[98]
- Bacteria	Mesothelin	Mesothelioma	[100]
- Yeast	CEA	Carcinomas	[101]
Peptide-based			
- Peptide	HER2	BC	[103]
- Protein	MAGE-3	Melanoma	[103,104]
- Antibody	Racotumomab	NSCLC	[105,106]
Viral-based	Poxviruses/PSA	Prostate cancer	[31]
Nucleic acid-based			
- DNA	PAP	Prostate cancer	[107]
- RNA	Multineoantigens	Pancreatic cancer	[108]

APC: antigen-presenting cell; DNA: deoxyribonucleic acid; RNA: ribonucleic acid; HER2: human epidermal growth factor receptor 2; MAGE-3: melanoma-associated antigen 3; CEA: carcinoembryonic antigen; GM-CSF: granulocyte-macrophage colony-stimulating factor; GAA: glioma-associated antigen; PAP: prostatic acid phosphatase; PSA: prostate-specific antigen; BC: breast cancer; NSCLC: non-small cell lung cancer.

Autologous cancer cell vaccines have the advantage of presenting the patient with a unique set of antigens [84]. In one cancer cell-based vaccine, DCs and autologous cancer cells were fused to produce the finished product, thus combining the unique and desired characteristics of these two types of cells [85]. The logistical drawback of using autologous cancer cells has driven the development of allogenic cancer cell vaccines, which typically contain 2-3 tumor cell lines of a given neoplasia. The vaccine known as GVAX is one example that contains allogenic pancreatic, prostate or breast tumor cells [86–88]. The inclusion of interleukin-7 (IL-7) and interleukin-21 (IL-21) could synergistically strengthen the immune response against a cancer cell-based vaccine. Also, combining such vaccines with immune checkpoint inhibitors is quite commonly used [89,90]. In dendritic cell-based cancer vaccines, the constructs can exploit the presence of DCs *in vivo* in a non-targeted way or by coupling the antigen to antibodies specific to DC surface receptors [91–93]. Alternatively, the DCs are loaded *ex vivo* with the required cancer antigens before administration [53]. Given the importance of DCs for the initiation of $CD4^+$ and $CD8^+$ T cell responses, the design of dendritic cell-based vaccines must aim at achieving concentrated antigen delivery to DCs to drive their activation [94]. Dendritic cell activation will, in turn, drive both $CD4^+$ cells and $CD8^+$ T cells to be stimulated. $CD4^+$ cells are needed for optimal and sustained effector $CD8^+$ T cell responses as well as the induction and maintenance of $CD8^+$ T cell memory [55,57,58]. In addition to $CD8^+$ T cell supporting roles, $CD4^+$ T cells have intrinsic effector functions of their own [95]. Okada *et al*. used DCs loaded with synthetic peptides from glioma-associated antigen (GAA) and their data supported the immunogenicity and clinical activity of the vaccine [96]. Morse et al. employed a vaccine containing DCs mixed with poxviruses encoding cardioembryonic antigen (CEA) and Mucin1 (MUC1) as the cancer antigens to obtain antigen-specific T cell responses in colorectal cancer [97]. Cancer vaccines based on antigen-presenting cells (APCs) are usually made from blood following leukapheresis to separate and collect the required type of APCs. An approved candidate for this platform of vaccines is Sipuleucel-T, which consists of $CD54^+$ cells (APCs exhibiting the $CD54^+$ surface marker) that have been incubated with the PAP (prostate acid phosphatase)/GM-CSF (granulocyte-macrophage colony-stimulating factor) fusion construct as the cancer antigen for the treatment of prostate cancer [98]. An example of a bacteria-based cancer vaccine is the recombinant *Listeria monocytogenes* vaccine that expresses mesothelin to elicit specific T-cell responses against this antigen for the treatment of mesothelioma [99]. This bacterium is actively taken by APCs through phagocytosis and thus represents an ideal vector for the delivery of antigens [100]. Mesothelin is a cell-surface protein that is overexpressed in mesothelioma as well as ovarian cancer and functions as an adhesion protein. One bacteria-based cancer product does not even deliver defined tumor antigens to generate an antitumor response for example, the intravesical administration of the mycobacterium bacillus Calmette-Guerin (in the BCG vaccine), which is approved for the treatment of certain types of bladder cancer [5]. The brewer's yeast *Saccharomyces cerevisiae* is stable, non-pathogenic, easily engineered, propagated and purified to become a further addition to the arsenal of cancer vaccine platforms. Recombinant yeasts have been shown to activate DCs to present antigens on both classes of HLA molecules [101].

Peptide-based cancer vaccines

This category of cancer vaccines comprises three subclasses: a) short peptide-based vaccines; b) protein-based vaccines; and c) antibody-based vaccines. They are relatively easy to manufacture but require the inclusion of potent immune adjuvants

and/or immunomodulators to boost their immunogenicity, which would otherwise be weak and might lead to immune tolerance [5,13,82]. The early vaccines in this category used short peptides of less than 15 amino acids in length with minimal epitopes needed to target $CD8^+$ T cells but not $CD4^+$ cells, although for effective cancer vaccines both types of cells are needed to maintain cytotoxic T cell function [2,109]. The length of the peptide in these cancer vaccines dictates their performance. Short peptides do not require processing by APCs or other nucleated cells and can be directly loaded onto HLA-I molecules, in contrast to long peptides, which must be processed by APCs first before loading [110]. Parts of long peptides and proteins are degraded by the endosomal pathway and loaded on HLA-II molecules before being recognized by $CD4^+$ cells, while the other parts enter the cytoplasmic pathway, are processed by the proteasome and then presented by HLA-I to $CD8^+$ T cells [111]. Short peptides are usually produced by chemical synthesis, while long peptides are frequently made by protein expression systems such as mammalian cells, which closely resemble the natural tumor antigens. The immunogenicity of small antigens can be further enhanced by fusing with carrier proteins such as the heat shock protein [13]. Sipuleucel-T (Provenge) is a licensed product for the treatment of prostate cancer that is made up of a peptide/protein construct (PEP/GM-CSF) as the antigen presented by APCs, which are collected from the individual patient. Antibody-based cancer vaccines are those that are directed against specific antibodies but act as antigens, found on the surface of B-lymphoma cells [105,106]. They have the advantage of targeting a unique tumor-specific antigen but to date, they suffer from the drawbacks of being labor-intensive to produce and having to be patient-specific. The antibody racotumomab for the treatment of NSCLC is a prime example of this category of cancer vaccines.

Viral-based cancer vaccines

Viruses are naturally immunogenic and can make the innate and adaptive arms of the immune system work together to achieve a long-lasting response to cancer [13]. The virus's genetic components can be engineered to have sequences encoding tumor antigens of interest. They can be divided into three forms. 1) inactivated viruses; 2) attenuated viruses; and 3) viral subunits. The most common human cancer-related viruses are Epstein-Barr virus, HCV, HBV and HPV, with the latter two types of viruses being used in vaccines for the prevention of liver and cervical cancers, respectively [112]. These preventative cancer vaccines can be very effective in reducing the risk of viral infections, which are often the root cause of certain malignancies. Cervarix, Gardasil and Hepatitis B vaccines have been produced and marketed to guard against cancer as well as to prevent infections caused by viruses [113]. Cervarix prevents infections with types 16 and 18 HPV, while Gardasil is licensed for infections caused by types 6,11,16 and 18 HPV. A further version of Gardasil called Gardasil 9 is based on even more types of HPV, namely 6,11,16,18, 31, 33, 45, 52, and 58. For therapeutic cancer vaccines, the most evaluated viral vectors are the poxviruses, which can accept large inserts of foreign DNA, and their expression inside cells allows for the processing of any antigens they carry [114]. Replication and transcription of poxviruses are restricted to the cytoplasm of the cell, reducing the risk of insertional mutagenesis in the host. However, as with other viruses, their neutralization by the host immune response limits their use unless genetically engineered to overcome this problem [115–117]. Several clinical trials have been conducted on two therapeutic viral-based vaccine platforms named PROSTVAC (expressing PSA) and PANVAC (expressing CEA and MUC-1) with encouraging initial results [118]. The use of oncolytic viruses represents another strategy to deliver viruses intratumorally to treat cancer. These viruses can be modified to express GM-CSF to attract DCs and lymphocytes to the lysed tumor site [119]. T-VEC (talimogene laherparepvec) is an oncolytic herpes virus engineered to produce GM-CSF for enhanced immunogenicity and approved by the FDA and EMA in 2015 for the treatment of melanoma [36,120]. The mechanism of action of oncolytic virus vaccines is the *in-situ* killing of cancer cells and the release of antigens to prime and amplify the host antitumor response [121]. Other oncolytic viruses include adenovirus, measles virus, vaccinia virus and reovirus [122]. Various strategies are commonly used to optimize the effects of viral-based cancer vaccines, including the inclusion of PD-1 inhibitors and the engineering of immune molecule expression to disrupt the TME [13]. Other means that have been investigated to enhance the effects of viral vaccines for cancer include the use of chemotherapy, radiotherapy and adoptive T cell therapy. Heterogeneous viral vectors have also been employed to enhance the immune response, as in the case of PROSTVAC-V/F, which employs PSA-encoded vaccinia virus as the primary immunization agent and PSA avian poxvirus encoded for the follow-on booster effect [123].

Nucleic acid-based cancer vaccines

These vaccines can either be DNA-based or mRNA-based, which can simultaneously deliver multiple antigens, allowing the APCs to present various epitopes of several antigens. Nucleic acid-based vaccines can be simple, rapid and suitable for the development of personalized cancer therapies [13]. Compared to mRNA vaccines, DNA-based cancer vaccines exhibit superior stability, and early vaccines were of this type. A single DNA molecule, once it enters the nucleus of a cell, can produce multiple copies of mRNA molecules. However, the DNA has the potential to give rise to insertional mutagenesis [124]. DNA-based cancer vaccines can produce their action in one of several ways. The DNA molecule, once delivered in a suitable format, can go either directly to a somatic cell to be translated into antigens, which will be presented by HLA-I to $CD8^+$ T cells or the antigens released by that cell, through secretion or apoptosis, can be picked up by APCs to be presented

to T cells. Alternatively, the DNA molecules could be directly transfected into APCs and then the endogenous antigens, following their transcription and translation, are processed and presented to T cells [125]. Adjuvants are often used to boost the immunogenicity of DNA-based cancer vaccines. McNeel *et al*. found that a DNA vaccine encoding PAP can elicit an antigen-specific immune response in patients with prostate cancer [126]. Also, PTVC-HP (NCT03600350), an experimental DNA vaccine, uses plasmid DNA that codes for human PAP along with Nivolumab to treat people with prostate cancer. The COVID-19 pandemic has increased the prominence of mRNA-based cancer vaccines, which represent a new and promising platform. Here, exogenous synthetic mRNAs are introduced into cells to provide the cells with templates for making antigens [127,128]. The mRNA-based vaccines are conveniently divided into three types. 1) conventional (non-replicating) mRNA vaccines; 2) self-amplifying mRNA vaccines (SAMs); and 3) trans-amplifying mRNA vaccines (TAMs). There is a cap (7-methylguanisine 5 cap), 5′-UTR (5′-untranslated region), ORF (open reading frame), 3′-UTR (3′-untranslated region), and 3′poly(A) tail in a normal mRNA vaccine. Unlike conventional mRNA vaccines, there are two ORFs in SAMs, one encoding the cancer antigen of interest and the other encoding a viral replication component, enabling long-lasting mRNA amplification to allow the production of large amounts of antigens from low doses of vaccines [128,129]. The trans-amplifying mRNA vaccines use two different transcripts to achieve a similar effect to SAM. Making an mRNA vaccine can be simple, fast and safe, as the molecules do not tend to integrate into the host genome. However, the limited stability is one of its drawbacks, despite the fact that lipid nanotechnology and other delivery methods have greatly improved mRNA stability and translation efficiency [130–132]. To treat people with pancreatic ductal adenocarcinomas [108], Rojas et al. created a personalized mRNA vaccine called "autogene cevumeran" that had a mix of antigens (at least 20 for each patient). The authors found that the vaccine induced substantial T cell activity that may correlate with delayed pancreatic cancer recurrence.

Clinical Status of Cancer Vaccines

Apart from the “preventative” cancer vaccines mentioned earlier, there have been a total of 10 commercially approved “treatment” cancer vaccines in the world and these are listed in Table 2 [133,134].

Table 2: Approved vaccines for the treatment of cancer in various countries

Product	Country of license	Cancer type(s)	Notes
Sipuleucel-T (Provenge)	USA	Prostate cancer	Autologous APCs containing PAP/GM-CSF fusion protein
Intravesical BCG (TheraCys)	USA	Urethelial carcinoma	Following supply shortages, a competing strain of BCG vaccine is available under the name TICE.
Talimogene laherparepvec (T-VEC Imlygic)	USA	Melanoma	Oncolytic genetically modified herpes simplex virus
Nadofaragene firadonevec (Adstiladrin)	USA	Bladder cancer	A non-replicating adenovirus containing INF-α2b
mRNA-4157/V940	USA	Melanoma	A single synthetic mRNA coding for up to 34 neoantigens and given with Pembrolizumab
Hybricell	Brazil	Kidney cancer and melanoma	Autologous monocytes treated with cytokines and converted to DCs and fused with patient’s cancer cells
CreaVaxRCC	South Korea	Renal carcinoma	Autologous DCs treated with tumour extracts and cytokines
Apceden	India	NSCLC, CRC, ovarian and prostate cancers	Personalised DC-based vaccine
OncoPhage	Russia	Renal cell carcinoma	Autologous heat shock protein vaccine
M-Vax	Switzerland	Melanoma	Autologous cancer cells mixed with BCG
DCVax-L	Switzerland	Glioblastoma	Autologous DCs and tumour cells mix
CimaVax-EGF	Cuba, Peru, Paraguay, Colombia and Bosnia	NSCLC	A recombinant EGF conjugated to a protein carrier
BioVaxID	Compassionate use in various countries	B-cell lymphoma	Clonal immunoglobulin idiotype

APCs: antigen-presenting cells; PAP: prostatic acid phosphatase; GM-CSF: granulocyte-macrophage colony-stimulating factor; BCG: Bacillus Calmette-Guerin; DCs: dendritic cells; NSCLC: non-small cell lung cancer; CRC: colorectal cancer; EGF: epidermal growth factor.

Furthermore, the US regulators (the FDA) have granted a breakthrough therapy designation for an mRNA vaccine manufactured by the pharmaceutical company MSD under the developmental name mRNA-4157/V940 for the treatment of melanoma in 2023. Clinical assessment of some of these global vaccines has been generally disappointing and, in some cases, incomplete, with reasons being attributed to TME immunosuppression, insufficient T cell response and choice of cancer antigens, among others [134,135]. Up to July 2022, there have been 360 clinical trials using cancer vaccines for treatment with 377 interventions (a few of the trials had more than one intervention) [134]. The highest number of clinical trials were using cell-based cancer vaccines (37.7%), followed closely by those using peptide-based vaccines (32.6%) (see Figure 5).

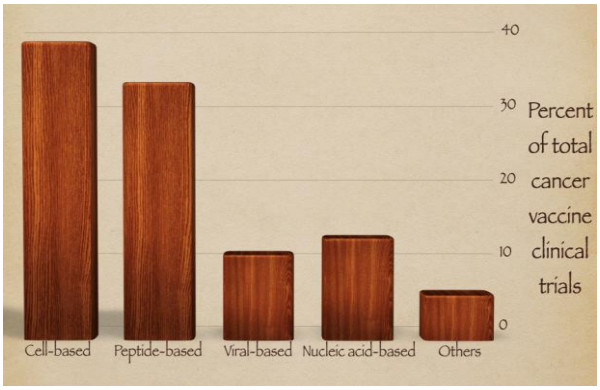

Figure 5: The contribution of different types of cancer vaccines to the total number of ongoing clinical trials.

Viral-based cancer vaccines made up 10.9% of the total number of trials. The remaining 5.8% of the clinical trials represented vaccines that could not be assigned to one of the other four categories due to the nature of the methodology employed. It appears that, although some of the cancer vaccines that have been approved globally for the treatment of malignancies have yet to show their potential, there is a great deal of interest and effort in improving and developing this therapy.

Conclusions and Prospects

The high number of clinical trials being conducted to test the safety and efficacy of cancer vaccines is a testimony to the continued interest in this arm of immunotherapy. This field has come a long way from the early empirical observations of the value of vaccination to a complicated scientific discipline reflecting advancements in immunology. In addition to well-established cancer "prevention" vaccines, there are now a few approved cancer vaccines for the "treatment`' of several types of malignancies, as well as hundreds of clinical trials. Future cancer vaccines might employ combinations of vaccine components and other forms of cancer therapies, such as immune checkpoint inhibitors, chemotherapy and radiotherapy, to further boost the immune response. Further developments in the identification and validation of cancer neoantigens can yield new targets for improved T cell responses. The question of what constitutes a potent antitumor response can be addressed by investigating the differences between the blood-immune response and the response to the disease as observed in the clinic. This could lead to a better design of clinical trials, such as targeting the cancer antigens to a specific subset of dendritic cells to obtain highly potent T cells.

Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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