Review
Harnessing the Immune System with Cancer Vaccines: From Prevention to Therapeutics

Ilene Le 1, Subramanian Dhandayuthapani 1,2,3, Jessica Chacon 1, Anna M. Eiring 1,2,4,* and Shrikanth S. Gadad 1,2,4,5,*

1 Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, TX 79905, USA; ilene.le@ttuhsc.edu (I.L.); s.dhandayuthapani@ttuhsc.edu (S.D.); jessica.chacon@ttuhsc.edu (J.C.)
2 L. Frederick Francis Graduate School of Biomedical Sciences, Texas Tech University Health Sciences Center El Paso, El Paso, TX 79905, USA
3 Center of Emphasis in Infectious Diseases, Department of Molecular and Translational Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, TX 79905, USA
4 Center of Emphasis in Cancer, Department of Molecular and Translational Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, TX 79905, USA
5 Mays Cancer Center, UT Health San Antonio MD Anderson Cancer Center, San Antonio, TX 78229, USA
* Correspondence: anna.eiring@ttuhsc.edu (A.M.E.); shrikanth.gadad@ttuhsc.edu (S.S.G.);
Tel.: +1-915-215-4812 (A.M.E.); +1-915-215-6431 (S.S.G.)

Abstract: Prophylactic vaccination against infectious diseases is one of the most successful public health measures of our lifetime. More recently, therapeutic vaccination against established diseases such as cancer has proven to be more challenging. In the host, cancer cells evade immunologic regulation by multiple means, including altering the antigens expressed on their cell surface or recruiting inflammatory cells that repress immune surveillance. Nevertheless, recent clinical data suggest that two classes of antigens show efficacy for the development of anticancer vaccines: tumor-associated antigens and neoantigens. In addition, many different vaccines derived from antigens based on cellular, peptide/protein, and genomic components are in development to establish their efficacy in cancer therapy. Some vaccines have shown promising results, which may lead to favorable outcomes when combined with standard therapeutic approaches. This review provides an overview of the innate and adaptive immune systems, their interactions with cancer cells, and the development of various different vaccines for use in anticancer therapeutics.

Keywords: cancer; cancer vaccines; antigens; immunotherapy

1. Introduction

Prior to the development of smallpox vaccination by Edward Jenner in the eighteenth century [1], immunization and protection methods against infectious diseases provided unpredictable results for patients [2]. Since its discovery, many scientific pioneers have fine-tuned the techniques necessary for vaccine development, which paved the way for modern vaccination protocols [2,3]. The protective nature of vaccines has resulted in the prevention of infections and the eradication of many different diseases. For example, some diseases that are now preventable through immunization include tetanus, diphtheria, tuberculosis, influenza, measles, mumps, rubella, hepatitis, and varicella-zoster, among others [2,4]. Interestingly, immunization against some viral infections, such as the human papillomavirus or hepatitis, can also prevent the development of cervical and liver cancer, respectively, by preventing infection with cancer-causing viruses [5,6]. In more recent years, studies have evaluated whether vaccines can also be used in cancer therapy [7,8]. With the success of vaccines in containing infections utilizing the host’s immune system, research is now focused on developing methods to harness this technology for cancer prevention and elimination [9]. However, progress has been slow due to the lack of validated biomarkers...
that predict vaccine efficacy, challenges relating to vaccine stability and delivery, and the costs associated with the production of personalized patient-specific vaccines [10]. As vaccines move from disease prevention to therapy, cancer vaccines are becoming an integral part of therapeutic strategies for tertiary and primary cancer prevention [11].

The current standard of care for cancer treatment consists of various options, including surgery, chemotherapy, radiotherapy, hormonal therapy, molecularly targeted therapy, and immunotherapy, which provide variable results due to several factors [12]. Immunotherapy focuses on harnessing the host immune system, both humoral and cellular, to attack malignant cells [13]. The immune system is a complex network of cells and proteins that provide innate (general) and adaptive (specific) defense mechanisms for the body (Figure 1A). Innate immunity includes anatomical barriers and physiological barriers (e.g., skin, mucous membranes), endocytic and phagocytic barriers (e.g., macrophages, neutrophils, natural killer cells), and inflammatory barriers (e.g., complement) [14,15]. The phagocytic macrophages of the innate immune system generally provide the first line of defense against many different microorganisms and are essential for controlling common bacterial infections. In addition to cellular immunity, the innate immune system also consists of proteins of the complement system, which can form pores directly in the bacterial cell surface, thereby killing the pathogen [16]. Notably, the innate immune response makes a crucial contribution to the activation of the adaptive immune system. Adaptive immunity functions to differentiate self-antigens from non-self-antigens, eliminate the pathogen or the infected cells, and produce immunologic memory in case there is a future infection with the same pathogen [15,17].

Adaptive immunity is also responsible for clearing the body of cancerous cells. Instead of bearing several different receptors such as the cells of the innate immune system, lymphocytes of the adaptive immune system bear antigen receptors of a single specificity. While each lymphocyte carries receptors targeting only one antigen, each is different, providing millions of diverse antigen receptor specificities. There are two branches of immunity within the adaptive immune system: antibody-mediated (humoral) immunity from B cells and cell-mediated (cellular) immunity from T cells [18]. While both components are essential, the cell-mediated mechanisms play a more prominent role in cancer clearance due to the killing capabilities of CD8\(^+\) cytotoxic T lymphocytes (CTLs) [18]. The methods employed by cell-mediated immunity include apoptosis of cells displaying foreign antigens, activation of macrophages and natural killer cells to destroy pathogens, and potentiating the immune response by stimulating cytokine production [15]. All the intricacies of the immune system work together to protect and remove any foreign material from the body [18].

Similarly, with the utilization of cancer vaccines, the host immune system can be redirected to target cancerous cells (Figure 1B) that find ways to evade the immune response [19]. Tumor antigens for the development of cancer vaccines can originate from genetic components such as DNA and mRNA, purified tumor proteins, long synthetic peptides, and tumor lysates [20]. Methods for antigen delivery include viral-based delivery, nanoparticles, and dendritic cell delivery [20–24]. The Food and Drug Administration (FDA) is now beginning to approve cancer vaccines as their development and efficacy are confirmed, such as the recently approved Sipuleucel-T (PROVENGE; Dendreon) for the treatment of recurrent prostate cancer [25]. The goal of cancer vaccination strategies is to induce antigen-specific, B cell-based humoral immunity and T cell-based cellular immunity that are capable of targeting and clearing the cancerous cells and inducing long-term immunological memory (Figure 1B). However, this becomes problematic when cancer cells evade the immune system, and strategies to overcome this problem are currently being employed in cancer therapeutics.
Figure 1. Innate versus adaptive immunity and the mechanisms by which cancer vaccines activate the immune system. (A) The schematic shows the hierarchy of hematopoietic lineage commitment, divided into innate versus adaptive immunity. Created using “Immune & Blood Cells”, by BioRender.com (accessed on 26 January 2022). Retrieved from https://app.biorender.com/categories/cell-types/ (accessed on 26 January 2022). LT-HSC, long-term hematopoietic stem cell; MPP, multipotent progenitor; NK cell, natural killer cell; ST-HSC, short-term hematopoietic stem cell. (B) The schematic shows multiple mechanisms by which cancer vaccines activate the immune system, both in the tumor site and within the lymphatic system, divided into cell-mediated versus humoral immunity. Adapted from “Cancer Vaccine Principle” by BioRender.com (accessed on 26 January 2022). Retrieved from https://app.biorender.com/biorender-templates (accessed on 26 January 2022). APC, antigen-presenting cell; CD, cluster of differentiation; IFN, interferon; IL, interleukin; MHC I, major histocompatibility complex I; MHC II, major histocompatibility complex II; T_{fh}, CD4+ T follicular helper cells; TNF, tumor necrosis factor.
Vaccines regulate or modulate anti-tumor immune responses; for example, administration of Sipuleucel-T leads to elevation of antigen-specific T cells, and activated lymphocytes are directed against tumors [26]. Notably, Sipuleucel-T stimulated a humoral immune response to other tumor antigens, triggering an anti-tumor cascade and improving clinical outcomes [27]. On the other hand, Talimogene laherparepvec (T-VEC), another oncolytic viral vaccine approved for melanoma therapy, selectively lysed the tumor cells to release tumor antigens [28,29] and also secreted granulocyte-macrophage colony-stimulating factor (GM-CSF), thereby recruiting dendritic cells (DC) to the tumor [30].

In this review, we will discuss the common interactions between cancer cells and the immune system, harnessing the immune system for cancer therapy, and the current state of vaccines for use in cancer prevention and treatment.

2. Evasion of the Immune System by Cancerous Cells

For the adaptive immune system to mount an efficient anticancer response, a series of events must be initiated and allowed to proceed, known as the Cancer-Immunity Cycle [31]. The first step involves the production of cancer-specific antigens, known as neoantigens, that are released and captured by dendritic cells (DCs) for processing. To induce an anticancer response, the presentation of these antigens must be accompanied by signals (e.g., cytokines) that specify tumor immunity versus tolerance. In the next step, DCs present the captured antigens associated with major histocompatibility complex I (MHC class I) or II (MCH class II) on the surface of their cell. In the presence of the proper costimulatory molecules, engagement of the T cell receptor with MHC:antigen complexes on DC cells results in priming and activation of effector T cell responses. Finally, the activated T cells migrate and infiltrate the tumor, which presents the processed neoantigens in complex with MHC class I on the cell surface, resulting in cancer cell killing. Dying cancer cells release further tumor-associated antigens, thereby potentiating the process [31].

Each step of the Cancer-Immunity Cycle is coordinated by many different factors, including molecules that are either stimulatory or inhibitory. Stimulatory factors promote immunity, whereas inhibitory molecules keep the process in check to prevent autoimmunity [31]. Unfortunately, cancer cells can evade the immune response in several different ways. For example, tumor antigens may not be detected, DCs and T cells may develop tolerance to the antigen, treating it as self rather than foreign, or T cells may not properly home to the tumor site. Additionally, T cells can be prevented from infiltrating the tumor upon arrival, or factors present within the tumor microenvironment may suppress the effector T cell function [31,32].

The first mechanism used by cancer cells to suppress the immune response is by downregulating MHC class I, which is required for lymphocyte activation when complexed with a foreign antigen. Additionally, some tumor cells will downregulate the costimulatory molecules that are necessary for full T cell activation (see Figure 1B) [33]. Either mechanism results in a loss of the antigen presentation machinery, allowing the cancer cells/antigens to remain undetected by the immune system [34]. Cancer immune evasion can also be achieved through the binding of programmed death ligand-1 (PD-L1) or -2 (PD-L2) on the cancer cells to programmed cell death protein-1 (PD-1) on the surface of T cells, which inhibits T cell activation by inducing T cell exhaustion [35,36]. In a similar manner, CTL-associated antigen-4 (CTLA-4) on the surface of cancer cells can interact with CD80/CD86 costimulatory molecules on T cells, thereby blocking full T cell receptor activation by foreign antigen. Indeed, monoclonal antibodies that bind to PD-L1, PD-1, or CTLA-4, known as immune checkpoint inhibitors (ICIs), are now being used for the treatment of multiple different human malignancies, which ultimately turn on the patient’s immune system to target their specific type of cancer [36].

While the adaptive immune system can perform immunosurveillance to prevent cancer development, innate immunity and the process of inflammation can promote tumorigenesis [37]. Indeed, tumor-associated inflammation can, in some cases, lead to alterations that drive tumorigenesis and disease progression. Notably, the presence of intratumoral
cancer-associated fibroblasts (CAFs), macrophages, myeloid-derived suppressor cells (MD-SCs), and T regulatory cells (Tregs) can act as key sources of immune-inhibitory factors within the tumor microenvironment [31]. CAFs play a prominent role in supporting the growth of tumor cells, remodeling the extracellular matrix, promoting angiogenesis, and promoting inflammation [38]. In addition, CAFs regulate various cancer-related phenotypic outcomes such as extracellular matrix (ECM) remodeling, induction of pro-cancer growth molecules, and interaction with drug or other therapy-based regimens [20]. Recent studies have shown the role of CAFs in modulating the immune response, and efforts are currently exploring CAFs as a therapeutic target in cancer treatment. However, CAF-based therapeutic strategies may have significant challenges due to their involvement in pro- and anti-tumor responses [20].

Macrophages within the tumor microenvironment can exist in a pro-tumor phenotype (M2-like) or an anti-tumor phenotype (M1-like) [39]. The M2-like phenotype can promote tumorigenesis and metastasis by secreting cytokines and growth factors and promoting the expression of inhibitory molecules such as PD-1 [39,40]. A method to evade T cell-mediated killing includes upregulating immune checkpoints, which represses the activation of T cells [41,42]. Targeting those immunosuppressive cytokines can lead to T cell reactivation and tumor clearance [43]. Additionally, macrophages can help recruit Tregs and MDSCs to the tumor microenvironment, where they exhibit potent immunosuppressive activity [32,44]. Altogether, the ability of cancer cells to evade recognition by the immune system in part explains the reduced response to chemotherapy observed in certain cancers and cancer patients. All of these mechanisms of cancer immune evasion are currently being studied as novel targets in cancer therapy [32].

3. Cancer Immunotherapy

Cancerous cells can reside in the host body undetected through a variety of different regulatory processes, as described above [45]. Immunotherapy is a new form of cancer therapy focused on harnessing the host immune system to attack specific types of cancer cells [13]. Immunotherapy exists in both passive and active forms, such as adoptive cellular immunotherapy, natural killer cell therapy, chimeric antigen receptor T (CAR T) cell therapy, and the use of ICIs [46]. Adoptive T cell therapy allows for in vitro growth of patient-derived tumor antigen-specific T cells that are then reintroduced back into the patient [33]. Since Tregs are suppressive in the tumor microenvironment, lymphodepletion approaches are performed prior to re-infusing the T cell product back into the patient [43,47]. Adoptive cell therapy relies on the immune system to recognize tumor cells by modifying tumor-infiltrating lymphocytes, T cell receptors, or introducing chimeric antigen receptors [48]. When combined with cancer vaccines, adoptive cell therapy was shown to provide synergetic effects in solid skin tumors [49]. On the other hand, natural killer (NK) cell therapy focuses on the cells’ innate ability to recognize and eliminate cancerous cells without prior sensitization [50]. In metastatic solid tumors, clinical trials have demonstrated that activation of NK cells provides better immunotherapy outcomes when compared with T cells [51]. Immune checkpoint proteins, such as CTLA-4 and PD-1, prevent T cells from destroying cancer cells, as described above [41]. The PDI-Vaxx vaccine (Imugene Ltd., Sydney, Australia) produces polyclonal antibodies that inhibit PD-1 in breast and pancreatic cancer cells [52], resulting in a significant decrease in tumor growth in mice [52]. As a consequence, Imugene Ltd. has received FDA approval for clinical testing.

Adoptive T cell transfer, ICIs, and bispecific antibodies are the most prevalent types of immunotherapies [53]. Although ICI-based immunotherapy has shown remarkable progress in cancer treatment, many cancers relapse over time [54]. However, due to this relapse, research is now focused on developing combinatorial therapies, including ICIs and cancer vaccines [55]. Cancer vaccines, as compared with ICIs, have the advantage of utilizing the entirety of the host immune system, instead of just an individualized component, for cancer cell targeting [56]. As demonstrated in preclinical models, when
both are combined, treatment success is greatly improved [20,29]. This makes cancer vaccines an area of interest to pursue further.

4. Cancer Vaccines

Similar to the mechanism of action for immunotherapy, cancer vaccines also utilize the host immune system to treat cancer. Cancer vaccines can elicit a cancer-specific immune response and diminish tumor size in patients [56]. Current cancer vaccines employ the activation of either humoral or cellular adaptive immune responses. The humoral approach generates antibodies based on tumor antigens presented on intact cancer cells (Figure 1B) [57]. For example, Sipuleucel-T (Provenge), a dendritic cell vaccine (discussed below) that is approved for use in some men with metastatic prostate cancer, stimulates an immune response to prostatic acid phosphatase, an antigen present in most prostate cancers [58]. These vaccines increase the level of IgG antibodies targeting tumor-specific antigens, thereby promoting the priming of T cells and their ability to detect cancer [59].

In the cellular process, T cells directly mount an immune response against protein-based tumor antigens (Figure 1B) [57]. The Sipuleucel-T vaccine showed a small but significant increase in survival of prostate cancer patients by about four months [60]. The cellular approach allows a broader immunologic effect, and most cancer vaccines aim to induce T cell activation [61]. Sipuleucel-T is recommended to treat men with metastatic prostate cancer, both asymptomatic and castration-resistant. Currently, numerous cancer vaccines are undergoing different phases of clinical trials to assess their therapeutic utility (Figure 2).

Figure 2. Cancer vaccines in clinical trials. The bar graph shows the frequency of therapeutic cancer vaccines in the USA, divided by phase of the clinical trial. Data were extracted from www.clinicaltrials.gov (accessed on 14 June 2021). Created with https://BioRender.com (accessed on 26 January 2022).

4.1. Cancer Antigens

When discussing tumor antigens, they can be classified into two general categories: tumor-associated and tumor-specific. Tumor-associated antigens (TAAs) can be found in tumor tissue, but they can also be present in normal tissue [62,63]. Because of their natural expression in the host, these antigens are involved in central and peripheral tolerance, leading to a weaker response due to depletion of high-affinity TAA-specific T cell receptors [64,65]. One of the first TAAs studied was carcinoembryonic antigen, which was found to be overexpressed in colorectal cancer [66]. Investigations demonstrated that the inadequate immune response was due to TAA expression on both cancerous and normal epithelial cells [66]. However, because of the decreased immune response due to
tolerance and lack of specificity for the tumor, there are concerns about potential toxicity from increased dosing to provide a more potent effect [65,67].

Tumor-specific antigens, or neoantigens, are tumor antigens that are solely expressed by cancer cells and not in normal tissue. Because the neoantigens are generally not present on normal host cells such as TAAs, neoantigens do not generate central and peripheral tolerance, making them a better target for therapy [64]. It was previously shown that tumor antigens have a more robust individual specificity engaged in stronger rejection of the tumor [62]. This indicates that neoantigens, compared with TAAs, can elicit a stronger immune response [62]. Furthermore, mutations in tumor cells can alter the amino acid sequence of peptides, leading to the formation of neoantigens that can be used for cancer vaccine development.

For this reason, neoantigens are highly cancer-specific when compared with TAAs [67]. Neoantigens, such as Neu-glycolyl-GM3 ganglioside, are overexpressed in multiple solid tumors. The Racotumomab vaccine has been shown to mimic ganglioside and have fair outcomes in patients with non-small-cell lung cancer [68]. Greater specificity leads to the generation of more robust immune responses. Therefore, neoantigens could provide a better target for developing vaccines for cancer therapy [69]. However, limitations to this approach include the necessity of sufficient sequencing data to determine the neoantigens present in individual patients and the high cost of production [70].

4.2. Types of Cancer Vaccines

The antigens used for cancer vaccines are divided into three major types: cellular, peptide/protein, and genetic (Table 1) [64,71]. Cellular vaccines can be further divided into whole tumor cell vaccines and dendritic cell vaccines. Whole tumor cell vaccines employ cancer cells that have been killed [67]. The target does not have to be identified beforehand, and there is non-specificity in the targeting of cancer [55,64,67]. Dendritic cell vaccines, in contrast, use autologous patient-derived dendritic cells that are loaded with peptide antigens or transfected with antigen genes [67]. Previous studies indicated a small but significant increase in the survival of patients with acute myeloid leukemia utilizing this approach [67,72]. While this vaccination method provides essential findings, the complexity and production costs have prevented frequent use [67].

| Vaccine                              | Type of Vector | Type of Antigen                        | Cancer Type               | References |
|--------------------------------------|----------------|----------------------------------------|---------------------------|------------|
| Sipuleucel-T (Provenge)              | Dendritic cell | Tumor-associated: Prostatic acid phosphatase | Prostate cancer          | [73,74]    |
| Bacille Calmette-Guérin (BCG)        | Bacteria       | Tumor-associated: Thomsen–Friedenreich (T) and sialyl-T (sT) | Bladder Cancer           | [75,76]    |
| Talimogene laherparepvec (T-VEC)     | Viral          | Tumor-associated: US12                 | Melanoma                 | [77,78]    |
| PSA-TRICOM (Prostvac-VF)             | Viral          | Tumor-associated: Prostate-specific antigen | Prostate cancer          | [73,79]    |
| MAGE-A3                              | Peptide        | Neoantigen                            | Lung cancer, Melanoma    | [73,80]    |
| NY-ESO1                              | Peptide        | Cancer-Testis antigen                  | Esophageal squamous cell carcinoma | [73,81] |
| Algenpantuecel-L (HyperAcute Pancreas) | Whole-cell    | Tumor-associated: αGal                 | Pancreatic adenocarcinoma | [73,82] |

Peptide/protein vaccines can be composed of tumor-associated antigens, cancer germline antigens, virus-associated antigens, or tumor-specific antigens [83]. The mechanism behind peptide vaccines is to generate T cells that are TAA-specific to mount an
immune response [84]. These vaccines are relatively stable and safe, but suffer from the limitation of epitopes for potential vaccine targets, weaker immunogenicity of tumor antigens, and immune evasion [64]. While peptide vaccines have the advantage of using synthetic peptides, the disadvantage is that the appropriate selection and modification of immunogens are necessary to elicit the desired immune response [84]. However, evidence has also shown that CD8\(^+\) T cells generated from protein-based vaccines are less effective than other vaccines [85].

Gene-based cancer vaccines utilize DNA and RNA to produce cancer-specific antigens from peptides and proteins to induce an immunologic response [64]. These vaccines act by delivering tumor antigen-encoding genes, thereby enhancing the immune response towards cells expressing those antigens [86]. Advantages of DNA vaccines include generating a systemic response and creating memory [86]. These vaccines can also deliver multiple genes simultaneously via the same delivery method [86]. An advantage of RNA vaccines over DNA vaccines is that transcription is unnecessary [20]. For this reason, they are further along in the process of antigen expression and MHC presentation. When using viral vectors or nucleic acids, the response of CD8\(^+\) T cells was shown to be effective and sustained [85]. However, there are still limitations to this vaccination method, including resistance due to tumor evolution, antigen tolerance, and an influx of inflammatory cells [86]. This vaccination method is also limited by the delivery method and the uptake efficiency into cells.

4.3. Approved Cancer Vaccines

While cancer vaccines are still being widely studied, many vaccines have been approved for cancer therapy (Table 1). After the FDA approval of Sipuleucel-T (Provenge) in 2010, exponential advances have been made in cancer vaccine development [57]. Sipuleucel-T is a dendritic cell vaccine used to treat prostate cancer based on modifying dendritic cells from the patient [27]. However, there is controversy as to whether this vaccination provides enough benefit to outweigh the costs [87]. Still, clinical studies have shown that this vaccine is safe and effective, at least to some degree [25,58,73]. In contrast, PSA-TRICOM (Prostvac-VF) is a recombinant viral vaccine used to treat prostate cancer [88], which was shown to improve survival rates by as much as eight months [73].

Some peptide-based vaccines are made from cancer-testis antigens, such as MAGE-A3 and NY-ESO1 [89,90]. These proteins are widely studied and can induce a humoral and cellular immune response in cancer patients. While further use of the vaccine was halted due to limited benefit to the patients, other studies were conducted to explore combination therapies, adjuvant selection, and patient selection criteria to improve efficacy [73,91,92]. Algenpantucel-L (HypeAcute Pancreas) is a whole-cell vaccine developed from human tumor cell lines [93]. This vaccine strategy covers human tumor cell lines with antigens that are lethally irradiated before being injected back into the host to induce an immune response [73].

Some vaccines are bacterial-based, for example, Bacille Calmette–Guérin (BCG), approved for use in the treatment of bladder cancer (1990). BCG is one of the most widely used vaccines globally, which can treat certain bladder infections and eliminate residual bladder cancer cells after surgical resection [94]. The mechanism of action for this vaccine likely employs a combination of its direct effect on tumor cells through internalization of BCG and activation of the innate immune system. BCG ultimately leads to bladder cancer cell death through intracellular signal pathway activation and the release of cytokines by the immune system [95–97].

Talimogene laherparepvec (T-VEC) is another example approved in 2015 by the FDA to treat lesions in recurrent melanoma [98]. T-VEC is derived from herpes simplex virus type 1, designed to replicate inside the tumors and release GM-CSF, resulting in tumor-specific immune responses. The GM-CSF gene in T-VEC was engineered to replace viral genes such as ICP34.5 and ICP47 [99]. T-VEC has been shown to improve durable response rates and overall survival (OS) in patients >18 years of age [98]. This genetic modification
allows for an increased response from neutrophils while refocusing the target on malignant cells [98,100].

The current FDA-approved vaccines on the market for cancer therapy are the BCG vaccine, Sipuleucel-T vaccine, and Talimogene vaccine [101]. However, the most recent antigen-based cancer vaccine, PROSTVAC, with promising data in a phase II study [102], did not show any improvement in OS of castration-resistant prostate cancer (CRPC) in men aged 18 years or older [88]. The authors of the study suggest that the lack of an immune response or the inhibitory tumor microenvironment explains the failure of PROSTVAC in clinical trials. To enhance the efficacy of PROSTVAC, combination therapy involving ICIs is now being explored. There is a continual effort toward developing cancer vaccines that are safe and effective, which will be instrumental in the field of precision medicine.

4.4. Combination Therapies

While advances in cancer vaccine treatment have gained ground, cancer vaccines alone have not provided a strong enough response to eradicate cancer independently [57,103]. As cancer cells continue to evolve mechanisms avoiding immune system detection, it becomes necessary to invoke multiple methods for cancer eradication. Recent studies have shown that therapies combining previously studied drugs with cancer vaccines provide much more promising results [57,58]. Using combined techniques, the tumor’s initially impaired immune response could potentially be restored [104]. In addition, the efficacy of combination treatment has proven to be increased compared to that of monotherapy [104,105]. While vaccines can induce an immune reaction, solely using vaccines is not enough to elicit a sufficiently strong response to eradicate cancer [21]. Co-therapy of cancer vaccines with cytokines, radiotherapy, ICIs, small molecules, endocrine therapy, and/or chemotherapy have synergetic effects [57,86]. Combining previous methods of general cancer eradication with patient-specific treatments will provide better results and enhance overall survival [57,106–108]. While advances in cancer vaccines have made great strides, the direction for cancer eradication has moved towards combination therapies [29]. Previously, cancer vaccines were used as a last attempt. Still, the move to utilize them as part of the first-line treatment requires knowledge of when to administer for the appropriate immune response, the potential necessity for multiple doses, and the interaction between the therapies employed to provide the desired outcome [86,109].

5. Conclusions and Future Directions

Vaccinations have long protected humans from the devastating effects of infectious diseases and cancer. However, aspects of the innate and adaptive immune system are routinely utilized by cancer cells to evade immunologic responses in the host. The challenge is now to use vaccines as first-line cancer therapeutics. New vaccinations are being developed to target preexisting cancerous cells using the same techniques employed in cancer prevention. By targeting those mechanisms, cancer vaccines may also prevent cancer progression. Establishing and prioritizing immunogenic neoantigens will be critical to providing an optimal response during vaccine development. In addition, multiple different types of cancer vaccines can be employed to determine maximal effectiveness depending on the type of cancer. While research has shown promising results for cancer vaccines, additional studies have shown that the combination of cancer vaccines with previous standard therapies may provide the best results for cancer eradication.

There are still many challenges to overcome for vaccine-based anticancer therapeutics. Notably, the ability of T cells to respond to antigenic challenges is affected by numerous factors, including age, diet, gut microbiome, and the tumor microenvironment [110]. Potential areas of study for the future of cancer vaccines include tumors that are not responsive to immunotherapy [64]. Another issue is that a patient may express heterogeneity of tumor cells leading to inadequate treatment if the vaccine focuses on only one particular neoantigen [64]. This limitation could be mitigated by creating a vaccine targeting multiple neoantigens specific to the patient [111,112]. Indeed, BioNTech and Moderna are currently
exploring the combination of several different patient-specific neoantigens in mRNA-based vaccine clinical trials in an attempt to realize personalized medicine in cancer therapy. However, producing an individualized, patient-specific vaccine is very expensive due to analysis and production costs [68,113]. While still limited in some aspects, the continued advancement in cancer vaccination will provide better treatment outcomes for patients in the future.

**Author Contributions:** The authors confirm contributions to the paper as follows: Conceptualization: S.S.G., S.D. and I.L.; writing—original draft preparation: I.L. and S.S.G.; writing—review and editing: S.S.G., A.M.E., I.L., S.D. and J.C.; graphic design and tables: S.S.G. and A.M.E. All authors have read and agreed to the published version of the manuscript.

**Funding:** S.S.G. is a CPRIT scholar in cancer research and is supported by a First-time Faculty Recruitment Award from the Cancer Prevention and Research Institute of Texas (CPRIT; RR170020). S.S.G. is also supported by the Lizanell and Colbert Coldwell Foundation. A.M.E. is funded by the Elsa U. Pardee Foundation and the National Cancer Institute of the National Institutes of Health (NIH; K22CA216008). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

**Acknowledgments:** The authors would like to thank members of the Gadad lab for their careful review and helpful suggestions on this work.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Lakhani, S. Early clinical pathologists: Edward Jenner (1749–1823). *J. Clin. Pathol.* 1992, 45, 756–758. [CrossRef] [PubMed]
2. Hajj Hussein, I.; Chams, N.; Chams, S.; El Sayegh, S.; Badran, R.; Raad, M.; Gerges-Geagea, A.; Leone, A.; Jurjus, A. Vaccines through centuries: Major cornerstones of global health. *Front. Public Health* 2015, 3, 269. [CrossRef] [PubMed]
3. Plotkin, S. History of vaccination. *Proc. Natl. Acad. Sci. USA* 2014, 111, 12283–12287. [CrossRef] [PubMed]
4. Plotkin, S.A. Vaccines: Past, present and future. *Nat. Med.* 2005, 11, S5–S11. [CrossRef]
5. Lei, J.; Ploner, A.; Elfstrom, K.M.; Wang, J.; Roth, A.; Fang, F.; Sundstrom, K.; Dillner, J.; Sparen, P. HPV vaccination and the risk of invasive cervical cancer. *N. Engl. J. Med.* 2020, 383, 1340–1348. [CrossRef]
6. Harper, D.M.; Franco, E.L.; Wheeler, C.; Ferris, D.G.; Jenkins, D.; Schuind, A.; Zahaf, T.; Innis, B.; Naud, P.; De Carvalho, N.S.; et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: A randomised controlled trial. *Lancet* 2004, 364, 1757–1765. [CrossRef]
7. Apostolopoulos, V. Cancer vaccines: Research and applications. *Cancers* 2019, 11, 1041. [CrossRef]
8. Pyzer, A.R.; Avigan, D.E.; Rosenblatt, J. Clinical trials of dendritic cell-based cancer vaccines in hematologic malignancies. *Hum. Vaccines Immunother.* 2014, 10, 3125–3131. [CrossRef]
9. Guo, C.; Manjili, M.H.; Subjeck, J.R.; Sarkar, D.; Fisher, P.B.; Wang, X.Y. Therapeutic cancer vaccines: Past, present, and future. *Adv. Cancer Res.* 2013, 119, 421–475. [CrossRef]
10. Huff, A.L.; Jaffee, E.M.; Zaidi, N. Messenger RNA vaccines for cancer immunotherapy: Progress promotes promise. *J. Clin. Investig.* 2022, 132, e156211. [CrossRef]
11. Lollini, P.L.; Cavallo, F.; Nanni, P.; Quaglino, E. The promise of preventive cancer vaccines. *Vaccines* 2015, 3, 467–489. [CrossRef] [PubMed]
12. Butterfield, L.H. Cancer vaccines. *BMJ* 2015, 350, h988. [CrossRef] [PubMed]
13. Inthagard, J.; Edwards, J.; Roseweir, A.K. Immunotherapy: Enhancing the efficacy of this promising therapeutic in multiple cancers. *Clin. Sci.* 2019, 133, 181–193. [CrossRef] [PubMed]
14. Turvey, S.E.; Broide, D.H. Innate immunity. *J. Allergy Clin. Immunol.* 2010, 125, S24–S32. [CrossRef] [PubMed]
15. Marshall, J.S.; Warrington, R.; Watson, W.; Kim, H.L. An introduction to immunology and immunopathology. *Allergy Asthma Clin. Immunol.* 2018, 14, 49. [CrossRef]
16. Janeway, C.A.; Travers, P.; Walport, M.; Schlomchik, M.J. *Immunobiology: The Immune System in Health and Disease*, 5th ed.; Garland Science: New York, NY, USA, 2001.
17. Bonilla, F.A.; Oettgen, H.C. Adaptive immunity. *J. Allergy Clin. Immunol.* 2010, 125, S33–S40. [CrossRef]
18. Chaplin, D.D. Overview of the immune response. *J. Allergy Clin. Immunol.* 2010, 125, S3–S23. [CrossRef]
19. Pardoll, D.M. Cancer vaccines. *Nat. Med.* 1998, 4, 525–531. [CrossRef]
20. Saxena, M.; van der Burg, S.H.; Melief, C.J.M.; Bhardwaj, N. Therapeutic cancer vaccines. *Nat. Rev. Cancer* 2021, 21, 360–378. [CrossRef]
21. Gatti-Mays, M.E.; Redman, J.M.; Collins, J.M.; Blusic, M. Cancer vaccines: Enhanced immunogenic modulation through therapeutic combinations. *Hum. Vaccines Immunother.* 2017, 13, 2561–2574. [CrossRef]
22. Larocca, C.; Schlom, J. Viral vector-based therapeutic cancer vaccines. *Cancer J.* 2011, 17, 359–371. [CrossRef] [PubMed]
23. Toussaint, B.; Chauchet, X.; Wang, Y.; Polack, B.; Le Gouellec, A. Live-attenuated bacteria as a cancer vaccine vector. Expert Rev Vaccines 2013, 12, 1139–1154. [CrossRef] [PubMed]

24. Draper, S.J.; Heeney, J.L. Viruses as vaccine vectors for infectious diseases and cancer. Nat. Rev. Microbiol. 2010, 8, 62–73. [CrossRef] [PubMed]

25. Cheever, M.A.; Higano, C.S. PROVENGE (sipuleucel-T) in prostate cancer: The first FDA-approved therapeutic cancer vaccine. Clin. Cancer Res. 2011, 17, 3520–3526. [CrossRef]

26. Fong, L.; Carroll, P.; Weinberg, V.; Chan, S.; Lewis, J.; Corman, J.; Amling, C.L.; Stephenson, R.A.; Simko, J.; Sheikh, N.A.; et al. Activated lymphocyte recruitment into the tumor microenvironment following preoperative sipuleucel-T for localized prostate cancer. J. Natl. Cancer Inst. 2014, 106, dju268. [CrossRef]

27. GuhaThakurta, D.; Sheikh, N.A.; Fan, L.Q.; Kandadi, H.; Meagher, T.C.; Hall, S.J.; Kantoff, P.W.; Higano, C.S.; Small, E.J.; Gardner, T.A.; et al. Humoral immune response against nontargeted tumor antigens after treatment with Sipuleucel-T and its association with improved clinical outcome. Clin. Cancer Res. 2015, 21, 3619–3630. [CrossRef]

28. Kohlhapp, F.J.; Kaufman, H.L. Molecular pathways: Mechanism of action for Talimogene Laherparepvec, a new oncolytic virus immunotherapy. Clin. Cancer Res. 2016, 22, 1048–1054. [CrossRef]

29. Zhao, J.; Chen, Y.; Ding, Z.Y.; Liu, J.Y. Safety and efficacy of therapeutic cancer vaccines alone or in combination with immune checkpoint inhibitors in cancer treatment. Front. Pharmacol. 2019, 10, 1184. [CrossRef]

30. Toda, M.; Martuza, R.L.; Rabkin, S.D. Tumor growth inhibition by intratumoral inoculation of defective herpes simplex virus vectors expressing granulocyte-macrophage colony-stimulating factor. Mol. Ther. 2000, 2, 324–329. [CrossRef]

31. Chen, D.S.; Mellman, I. Oncology meets immunology: The cancer-immunity cycle. Immunity 2013, 39, 1–10. [CrossRef]

32. Motz, G.T.; Coukos, G. Deciphering and reversing tumor immune suppression. Nat. Rev. Cancer 2013, 13, 61–73. [CrossRef] [PubMed]

33. Liu, M.; Guo, F. Recent updates on cancer immunotherapy. Mol. Ther. 2018, 26, 592–600. [CrossRef]

34. de Charette, M.; Marabelle, A.; Houot, R. Turning tumour cells into antigen presenting cells: The next step to improve cancer immunotherapy? Eur. J. Cancer 2016, 68, 134–147. [CrossRef]

35. Ricklefs, F.L.; Alayo, Q.; Krenzlin, H.; Mahmoud, A.B.; Sperezana, M.C.; Nakashima, H.; Hayes, J.L.; Lee, K.; Balaj, L.; Passaro, C.; et al. Immune evasion mediated by PD-L1 on glioblastoma-derived extracellular vesicles. Sci. Adv. 2018, 4, eaar2766. [CrossRef] [PubMed]

36. Wojtukiewicz, M.Z.; Rek, M.M.; Karpowicz, K.; Górska, M.; Polityńska, B.; Wojtkiewicz, A.M.; Moniuszko, M.; Radziwon, P.; Tucker, S.C.; Honn, K.V. Inhibitors of immune checkpoints-PD-1, PD-L1, CTLA-4—new opportunities for cancer patients and a new challenge for internists and general practitioners. Cancer Metastasis Rev. 2021, 40, 949–982. [CrossRef]

37. Hou, J.; Karin, M.; Sun, B. Targeting cancer-promoting inflammation—have anti-inflammatory therapies come of age? Nat. Rev. Clin. Oncol. 2021, 18, 261–279. [CrossRef]

38. Monteran, L.; Erez, N. The dark side of fibroblasts: Cancer-associated fibroblasts as mediators of immunosuppression in the tumor microenvironment. Front. Immunol. 2019, 10, 1835. [CrossRef] [PubMed]

39. Mehta, A.K.; Cheney, E.M.; Hartl, C.A.; Pantelidou, C.; Oliwa, M.; Castrillon, J.A.; Lin, J.R.; Hurst, K.E.; de Oliveira Taveira, M.; Johnson, N.T.; et al. Targeting immunosuppressive macrophages overcomes PARP inhibitor resistance in BRCA1-associated triple-negative breast cancer. Nat. Cancer 2021, 2, 66–82. [CrossRef]

40. Oyarce, C.; Vizzaino-Castro, A.; Chen, S.; Boerma, A.; Daemen, T. Re-polarization of immunosuppressive macrophages to tumor-cytotoxic macrophages by repurposed metabolic drugs. Oncoimmunology 2021, 10, 1898753. [CrossRef]

41. Huang, Q.; Lei, Y.; Li, X.; Guo, F.; Liu, M. A highlight of the mechanisms of immune checkpoint blocker resistance. Front. Cell Dev. Biol. 2020, 8, 580140. [CrossRef]

42. Wei, S.C.; Duffy, C.R.; Allison, J.P. Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov. 2018, 8, 1069–1086. [CrossRef] [PubMed]

43. Vinay, D.S.; Ryan, E.P.; Pawelec, G.; Talib, W.H.; Stagg, J.; Lichtor, T.; Decker, W.K.; Whelan, R.L.; Kumara, H.; et al. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. Semin. Cancer Biol. 2015, 35, S185–S198. [CrossRef] [PubMed]

44. Veglia, F.; Sanseverino, E.; Gabrilovich, D.I. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. Nat. Rev. Immunol. 2021, 21, 485–498. [CrossRef]

45. Gonzalez, H.; Hagerling, C.; Werb, Z. Roles of the immune system in cancer: From tumor initiation to metastatic progression. Genes Dev. 2018, 32, 1267–1284. [CrossRef] [PubMed]

46. Tan, S.; Li, D.; Zhu, X. Cancer immunotherapy: Pros, cons and beyond. Biomed. Pharmacother. 2020, 124, 109821. [CrossRef] [PubMed]

47. Gasparoto, T.H.; de Souza Malaspina, T.S.; Benevides, L.; de Melo, E.J., Jr.; Costa, M.R.; Damante, J.H.; Ikoma, M.R.; Garlet, G.P.; Cavassani, K.A.; da Silva, J.S.; et al. Patients with oral squamous cell carcinoma are characterized by increased frequency of suppressive regulatory T cells in the blood and tumor microenvironment. Cancer Immunol. Immunother. 2010, 59, 819–828. [CrossRef]

48. Rohaan, M.W.; Wilgenhof, S.; Haenen, J. Adoptive cellular therapies: The current landscape. Virchows Arch. 2019, 474, 449–461. [CrossRef]

49. Grenier, J.M.; Yeung, S.T.; Qiu, Z.; Jellison, E.R.; Khanna, K.M. Combining adoptive cell therapy with cytomegalovirus-based vaccine is protective against solid skin tumors. Front. Immunol. 2017, 8, 1993. [CrossRef]
50. Li, Y.; Yin, J.; Li, T.; Huang, S.; Yan, H.; Leavenworth, J.; Wang, X. NK cell-based cancer immunotherapy: From basic biology to clinical application. Sci. China Life Sci. 2015, 58, 1233–1245. [CrossRef]
51. Naivarani, S.R.; Lawson, C.; Tai, I.H. Treatment of metastatic disease through natural killer cell modulation by infected cell vaccines. Viruses 2019, 11, 434. [PubMed]
52. Guo, L.; Kaumaya, P.T.P. First prototype checkpoint inhibitor B-cell epitope vaccine (PD1-Vaxx) en route to human Phase 1 clinical trial in Australia and USA: Exploiting future novel syngeneic vaccine combinations. Br. J. Cancer 2021, 125, 152–154. [CrossRef] [PubMed]
53. Koury, J.; Lucero, M.; Cato, C.; Chang, L.; Geiger, J.; Henry, D.; Hernandez, J.; Hung, F.; Kaur, P.; Teskey, G.; et al. Immunotherapies: Exploiting the immune system for cancer treatment. J. Immunol. Res. 2018, 2018, 9585614. [CrossRef] [PubMed]
54. Davis, I.D. An overview of cancer immunotherapy. Immunol. Cell Biol. 2000, 78, 179–195. [CrossRef] [PubMed]
55. Keenan, B.P.; Jaffe, E.M. Whole cell vaccines—past progress and future strategies. Semin. Oncol. 2012, 39, 276–286. [CrossRef]
56. Maeng, H.M.; Berzofsky, J.A. Strategies for developing and optimizing cancer vaccines. F1000Research 2019, 8, 654. [CrossRef]
57. Maeng, H.; Terabe, M.; Berzofsky, J.A. Cancer vaccines: Translation from mice to human clinical trials. Curr. Opin. Immunol. 2018, 51, 111–122. [CrossRef]
58. Kantoff, P.W.; Higano, C.S.; Shore, N.D.; Berger, E.R.; Small, E.J.; Penson, D.F.; Redfern, C.H.; Ferrari, A.C.; Dreicer, R.; Sims, R.B.; et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N. Engl. J. Med. 2010, 363, 411–422. [CrossRef]
59. Crews, D.W.; Dombroski, J.A.; King, M.R. Prophylactic cancer vaccines engineered to elicit specific adaptive immune response. Front. Oncol. 2021, 11, 626463. [CrossRef]
60. Gould, P. Sipuleucel-T shows partial advantage in prostate cancer. Lancet Oncol. 2006, 7, 710. [CrossRef]
61. Ott, P.A.; Wu, C.J. Cancer vaccines: Steering T cells down the right path to eradicate tumors. Cancer Discov. 2019, 9, 476–481. [CrossRef]
62. Peng, M.; Mo, Y.; Wang, Y.; Wu, P.; Zhang, Y.; Xiong, F.; Guo, C.; Wu, X.; Li, Y.; Li, X.; et al. Neoadontigene vaccine: An emerging tumor immunotherapy. Mol. Cancer 2019, 18, 128. [CrossRef] [PubMed]
63. Ward, J.P.; Gubin, M.M.; Schreiber, R.D. The role of neoantigens in naturally occurring and therapeutically induced immune responses to cancer. Adv. Immunol. 2016, 130, 25–74. [CrossRef] [PubMed]
64. Pan, R.Y.; Chung, W.H.; Chu, M.T.; Chen, S.J.; Chen, H.C.; Zheng, L.; Hung, S.I. Recent development and clinical application of cancer vaccine: Targeting neoantigens. J. Immunol. Res. 2018, 2018, 4325874. [CrossRef] [PubMed]
65. Terbuch, A.; Lopez, J. Next generation cancer vaccines—Make it personal! Vaccines 2018, 6, 52. [CrossRef]
66. Wagner, S.; Mullins, C.S.; Linnebacher, M. Colorectal cancer vaccines: Tumor-associated antigens vs neoantigens. World J. Gastroenterol. 2018, 24, 5418–5432. [CrossRef]
67. Hollingsworth, R.E.; Jansen, K. Turning the corner on therapeutic cancer vaccines. NPJ Vaccines 2019, 4, 7. [CrossRef]
68. Hu, Z.; Ott, P.A.; Wu, C.J. Towards personalized, tumour-specific, therapeutic vaccines for cancer. Nat. Rev. Immunol. 2018, 18, 168–182. [CrossRef]
69. Ott, P.A.; Hu-Lieskovsk, S.; Chmielowski, B.; Govindan, R.; Naing, A.; Bhardwaj, N.; Margolin, K.; Awad, M.M.; Hellmann, M.D.; Lin, J.J.; et al. A phase Ib trial of personalized neoantigen therapy plus anti-PD-1 in patients with advanced melanoma, non-small cell lung cancer, or bladder cancer. Cell 2020, 183, 347–362 e324. [CrossRef]
70. Chu, Y.; Liu, Q.; Wei, J.; Liu, B. Personalized cancer neoantigen vaccines come of age. Theranostics 2018, 8, 4238–4246. [CrossRef]
71. Galluzzi, L.; Vaccheli, E.; Bravo-San Pedro, J.M.; Buque, A.; Senvollia, L.; Baracco, E.E.; Bloy, N.; Castoldi, F.; Abastado, J.P.; Agostinis, P.; et al. Classification of current anticancer immunotherapies. Oncotarget 2014, 5, 12472–12508. [CrossRef]
72. Van Tendeloo, V.F.; Van de Velde, A.; Van Driessche, A.; Cools, N.; Anguille, S.; Ladell, K.; Gostick, E.; Vermeulen, K.; Pieters, K.; Nijs, G.; et al. Induction of complete and molecular remissions in acute myeloid leukemia by Wilms’ tumor 1 antigen-targeted dendritic cell vaccination. Proc. Natl. Acad. Sci. USA 2010, 107, 13824–13829. [CrossRef] [PubMed]
73. Thomas, S.; Prendergast, G.C. Cancer vaccines: A brief overview. Methods Mol. Biol. 2016, 1403, 755–761. [CrossRef] [PubMed]
74. Handy, C.E.; Antonarakis, E.S. Sipuleucel-T for the treatment of prostate cancer: Novel insights and future directions. Future Oncol. 2018, 14, 907–917. [CrossRef]
75. Mustafa, A.S. BCG as a vector for novel recombinant vaccines against infectious diseases and cancers. Vaccines 2020, 8, 736. [CrossRef] [PubMed]
76. Severino, P.F.; Silva, M.; Carrascal, M.; Malagolini, N.; Chiricolo, M.; Venturi, G.; Barbaro Forleo, R.; Astolfi, A.; Catera, M.; Videira, P.A.; et al. Oxidative damage and response to Bacillus Calmette-Guerin in bladder cancer cells expressing sialytransferase ST3GAL1. BMC Cancer 2018, 18, 198. [CrossRef] [PubMed]
77. Haitz, K.; Khoshravi, H.; Lin, J.Y.; Menge, T.; Nambudiri, V.E. Review of talimogene laherparepvec: A first-in-class oncolytic viral treatment of advanced melanoma. J. Am. Acad. Dermatol. 2020, 83, 189–196. [CrossRef]
78. Raman, S.S.; Hecht, J.R.; Chan, E. Talimogene laherparepvec: Review of its mechanism of action and clinical efficacy and safety. Immunotherapy 2019, 11, 705–723. [CrossRef]
79. Gulley, J.L.; Madan, R.A.; Tsang, K.Y.; Jochems, C.; Marte, J.L.; Farsaci, B.; Tucker, J.A.; Hodge, J.W.; Liewehr, D.J.; Steinberg, S.M.; et al. Immune impact induced by PROSTVAC (PSA-TRICOM), a therapeutic vaccine for prostate cancer. Cancer Immunol. Res. 2014, 2, 133–141. [CrossRef]
80. Peled, N.; Oton, A.B.; Hirsch, F.R.; Bunn, P. MAGE A3 antigen-specific cancer immunotherapeutic. Immunotherapy 2009, 1, 19–25. [CrossRef]
81. Thomas, R.; Al-Khadairi, G.; Roelands, J.; Hendrickx, W.; Dermine, G.; Bedognetti, D.; Decock, J. NY-ESO-1 based immunotherapy of cancer: Current perspectives. Front. Immunol. 2018, 9, 947. [CrossRef] [PubMed]
82. McCormick, K.A.; Cowlert, A.L.; Rossi, G.R.; Vahanian, N.N.; Link, C.; Chiorean, E.G. Pancreatic cancer: Update on immunotherapies and algenpantucel-L. Hum. Vaccines Immunother. 2016, 12, 563–575. [CrossRef] [PubMed]
83. Obara, W.; Kehlhaier, M.; Katagiri, T.; Kato, R.; Kato, Y.; Takata, R. Present status and future perspective of peptide-based vaccine therapy for urological cancer. Cancer Sci. 2018, 109, 550–559. [CrossRef] [PubMed]
84. Kumai, T.; Kobayashi, H.; Harabuchi, Y.; Celis, E. Peptide vaccines in cancer-old concept revisited. Curr. Opin. Immunol. 2017, 45, 1–7. [CrossRef] [PubMed]
85. Beijnen, E.M.S.; van Haren, S.D. Vaccine-induced CD8(+) T cell responses in children: A review of age-specific molecular determinants contributing to antigen cross-presentation. Front. Immunol. 2020, 11, 607977. [CrossRef] [PubMed]
86. Lopes, A.; Vandermeulen, G.; Preat, V. Cancer DNA vaccines: Current preclinical and clinical developments and future perspectives. J. Exp. Clin. Cancer Res. 2018, 37, 104. [CrossRef] [PubMed]
87. Caram, M.E.V.; Ross, R.; Lin, P.; Mukherjee, B. Factors associated with use of Sipuleucel-T to treat patients with advanced prostate cancer. JAMA Netw. Open 2019, 2, e192589. [CrossRef] [PubMed]
88. Gulley, J.L.; Borre, M.; Vogelzang, N.J.; Ng, S.; Agarwal, N.; Parker, C.C.; Pook, D.W.; Rathenborg, P.; Flaig, T.W.; Carles, J.; et al. Phase III Trial of PROSTVAC in asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. J. Clin. Oncol. 2019, 37, 1051–1061. [CrossRef]
89. Chomez, P.; De Backer, O.; Bertrand, M.; De Plaen, E.; Boon, T.; Lucas, S. An overview of the MAGE gene family with the identification of all human members of the family. Cancer Res. 2001, 61, 5544–5551.
90. Gnajetic, S.; Nishikawa, H.; Jungbluth, A.A.; Gure, A.O.; Ritter, G.; Jager, E.; Knuth, A.; Chen, Y.T.; Old, L.J. NY-ESO-1: Review of an immunogenic tumor antigen. Adv. Cancer Res. 2006, 95, 1–30. [CrossRef]
91. Morgan, R.A.; Chinnasamy, N.; Abate-Daga, D.; Gros, A.; Robbins, P.F.; Zheng, Z.; Dudley, M.E.; Feldman, S.A.; Yang, J.C.; Sherry, R.M.; et al. Cancer regression and neurological toxicity following anti-MAGE-A3 TCR gene therapy. J. Immunother. 2013, 36, 133–151. [CrossRef]
92. Baumgaertner, P.; Costa Nunes, C.; Cachot, A.; Maby-El Hajjami, H.; Cagnon, L.; Braun, M.; Derre, L.; Rivals, J.P.; Rimoldi, D.; Gnajetic, S.; et al. Vaccination of stage III/IV melanoma patients with long NY-ESO-1 peptide and CpG-B elicits robust CD8(+) and CD4(+) T-cell responses with multiple specificities including a novel DR7-restricted epitope. Oncoimmunology 2016, 5, e1216290. [CrossRef]
93. Hardacre, J.M.; Mulcahy, M.; Small, W.; Link, C.; Chiorean, E.G. Addition of algenpantucel-L immunotherapy to standard adjuvant therapy for pancreatic cancer: A phase 2 study. J. Gastrointest. Surg. 2013, 17, 94–100; discussion pp. 100–101. [CrossRef] [PubMed]
94. Parmar, K.; Siddiqui, A.; Nugent, K. Bacillus Calmette-Guerin Vaccine and Nonspecific Immunity. Am. J. Med. Sci. 2021, 361, 683–689. [CrossRef] [PubMed]
95. Han, J.; Gu, X.; Li, Y.; Wu, Q. Mechanisms of BCG in the treatment of bladder cancer-current understanding and the prospect. Biomed. Pharmacother. 2020, 129, 110393. [CrossRef] [PubMed]
96. Lamm, D.L.; Blumenstein, B.A.; Crawford, E.D.; Montie, J.E.; Scardino, P.; Grossman, H.B.; Stanisic, T.H.; Smith, J.A., Jr.; Sullivan, J.; Sarosdy, M.F.; et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guerin for transitional-cell carcinoma of the bladder. N. Engl. J. Med. 1991, 325, 1205–1209. [CrossRef] [PubMed]
97. Sylvester, R.J.; van der, M.A.; Lamm, D.L. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomized clinical trials. J. Urol. 2002, 168, 1964–1970. [CrossRef]
98. Andtbacka, R.H.; Kaufman, H.L.; Collichio, F.; Amatrad, T.; Senzer, N.; Chesney, J.; Delman, K.A.; Spitzer, L.E.; Puzanov, I.; Agarvala, S.S.; et al. Talimogene Laherparepvec improves durable response rate in patients with advanced melanoma. J. Clin. Oncol. 2015, 33, 2780–2788. [CrossRef]
99. Liu, B.L.; Robinson, M.; Han, Z.Q.; Branston, R.H.; English, C.; Reay, P.; McGrath, Y.; Thomas, S.K.; Thornton, M.; Bullock, P.; et al. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties. Gene Ther. 2003, 10, 292–303. [CrossRef]
100. Grigg, C.; Blake, Z.; Gartrell, R.; Sacher, A.; Taback, B.; Saenger, Y. Talimogene laherparepvec (T-Vect) for the treatment of melanoma and other cancers. Semin. Oncol. 2016, 43, 638–646. [CrossRef] [PubMed]
101. DeMaria, P.J.; Bilusic, M. Cancer vaccines. Hematol. Oncol. Clin. N. Am. 2019, 33, 199–214. [CrossRef] [PubMed]
102. Kantoff, P.W.; Schuetz, T.J.; Blumenstein, B.A.; Glode, L.M.; Bilhartz, D.L.; Wyand, M.; Manson, K.; Panici, D.L.; Laus, R.; Schlam, J.; 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, 1099–1105. [CrossRef] [PubMed]
103. Melief, C.J.; van Hall, T.; Arens, R.; Ossendorp, F.; van der Burg, S.H. Therapeutic cancer vaccines. J. Clin. Investig. 2015, 125, 3401–3412. [CrossRef] [PubMed]
104. Bhatt, D.; Daemen, T. Therapeutic Vaccines and Cancer Immunotherapy. Vaccines 2020, 8, 596. [CrossRef] [PubMed]
105. Melero, I.; Berman, D.M.; Aznar, M.A.; Korman, A.J.; Perez Gracia, J.L.; Haanen, J. Evolving synergistic combinations of targeted immunotherapies to combat cancer. Nat. Rev. Cancer 2015, 15, 457–472. [CrossRef]
106. Madan, R.A.; Mohebtash, M.; Arlen, P.M.; Vergati, M.; Rauckhorst, M.; Steinberg, S.M.; Tsang, K.Y.; Poole, D.J.; Parnes, H.L.; Wright, J.J.; et al. Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: A phase 1 dose-escalation trial. *Lancet Oncol.* 2012, 13, 501–508. [CrossRef]

107. Wilgenhof, S.; Corthals, J.; Heirman, C.; van Baren, N.; Lucas, S.; Kvistborg, P.; Thielemans, K.; Neyns, B. Phase II Study of Autologous Monocyte-Derived mRNA Electroporated Dendritic Cells (TriMixDC-MEL) Plus Ipilimumab in Patients With Pretreated Advanced Melanoma. *J. Clin. Oncol.* 2016, 34, 1330–1338. [CrossRef]

108. Tanyi, J.L.; Bobisse, S.; Ophir, E.; Tuyaerts, S.; Roberti, A.; Genolet, R.; Baumgartner, P.; Stevenson, B.J.; Iseli, C.; Dangaj, D.; et al. Personalized cancer vaccine effectively mobilizes antitumor T cell immunity in ovarian cancer. *Sci. Transl. Med.* 2018, 10, eaao5931. [CrossRef]

109. Rosenberg, S.A.; Yang, J.C.; Restifo, N.P. Cancer immunotherapy: Moving beyond current vaccines. *Nat. Med.* 2004, 10, 909–915. [CrossRef]

110. Smith, P.L.; Piadel, K.; Dalgleish, A.G. Directing T-cell immune responses for cancer vaccination and immunotherapy. *Vaccines* 2021, 9, 1392. [CrossRef]

111. Sahin, U.; Derhovanessian, E.; Miller, M.; Kloke, B.P.; Simon, P.; Lower, M.; Bukur, V.; Tadmor, A.D.; Luxemburger, U.; Schrors, B.; et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature* 2017, 547, 222–226. [CrossRef]

112. Ott, P.A.; Hu, Z.; Keskin, D.B.; Shukla, S.A.; Sun, J.; Bozym, D.J.; Zhang, W.; Luoma, A.; Giobbie-Hurder, A.; Peter, L.; et al. An immunogenic personal neoantigen vaccine for patients with melanoma. *Nature* 2017, 547, 217–221. [CrossRef] [PubMed]

113. Geynisman, D.M.; Chien, C.R.; Smieliauskas, F.; Shen, C.; Shih, Y.C. Economic evaluation of therapeutic cancer vaccines and immunotherapy: A systematic review. *Hum. Vaccines Immunother.* 2014, 10, 3415–3424. [CrossRef] [PubMed]