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Therapeutic Cancer Vaccines: Past, Present and Future

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Abstract

Therapeutic vaccines represent a viable option for active immunotherapy of cancers that aim to treat late stage disease by using a patient's own immune system. The promising results from clinical trials recently led to the approval of the first therapeutic cancer vaccine by the U.S. Food and Drug Administration. This major breakthrough not only provides a new treatment modality for cancer management, but also paves the way for rationally designing and optimizing future vaccines with improved anticancer efficacy. Numerous vaccine strategies are currently being evaluated both pre-clinically and clinically. This review discusses therapeutic cancer vaccines of diverse platforms or targets as well as the preclinical and clinical studies employing these therapeutic vaccines. We will also consider tumor-induced immune suppression that hinders the potency of therapeutic vaccines, and potential strategies to counteract these mechanisms for generating more robust and durable antitumor immune responses.

Keywords

cancer vaccine; immunotherapy; tumor-associated antigen; immune modulator; immunosuppression; tumor microenvironment

I. Introduction

Unlike prophylactic vaccines that are generally administered to healthy individuals, therapeutic cancer vaccines are administrated to cancer patients and designed to eradicate cancer cells through strengthening patient's own immune responses (Lollini et al., 2006). The various immune effector mechanisms mobilized by therapeutic vaccination specifically attack and destroy cancer cells and spare normal cells. Thus, therapeutic cancer vaccines, in principle, may be utilized to inhibit further growth of advanced cancers and/or relapsed

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tumors that are refractory to conventional therapies, such as surgery, radiation therapy and chemotherapy.

In 1891, Dr. William Coley made the first attempt to stimulate the immune system for improving a cancer patient's condition by intratumoral injections of inactivated *Streptococcus pyogenes* and *Serratia marcescens* (Coley's Toxin) (McCarthy, 2006). The idea came from the observation of spontaneous remissions of sarcomas in rare-cancer patients who had developed erysipelas. Despite his reported effective responses in patients, his work was viewed with skepticism by the scientific community. Todays, the field of immunology has developed into a highly sophisticated specialty, and the modern science of immunology has shown that Coley's principles were correct. Indeed, the bacillus camette-guerin (BCG) that is one similar example as the Coley's Toxin, is still being used intravesically to treat superficial bladder cancer (Lamm et al., 1991; Morales et al., 1976; van der Meijden et al., 2003).

Despite considerable efforts to develop cancer vaccines, the clinical translation of cancer vaccines into efficacious therapies has been challenging for decades. Nonetheless, the U.S. Food and Drug Administration (FDA) have approved two prophylactic vaccines, including one for hepatitis B virus that can cause liver cancer and another for human papillomavirus accounting for about 70% of cervical cancers. More encouragingly, recent advances in cancer immunology have achieved clinical proof-of-concept of therapeutic cancer vaccine. Sipuleucel-T, an immune cell based vaccine, for the first time, resulted in increased overall survival in hormone-refractory prostate cancer patients. This led to FDA approval of this vaccine with the brand name Provenge (Dendreon) in 2010 (Cheever and Higano, 2011).

Although the challenge of developing an effective cancer vaccine remains (Schreiber et al., 2011; Zhou and Levitsky, 2012), many diverse therapeutic vaccination strategies are under development or being evaluated in clinical trials. Based on their format/content, they may be classified into several major categories, which include cell vaccines (tumor or immune cell), protein/peptide vaccines, and genetic (DNA, RNA and viral) vaccines. In this review, we present a synopsis of the history of research in the field of therapeutic cancer vaccines as well as current state of vaccine therapeutics for treatment of human cancers. In addition, the obstacles for effective cancer vaccine therapy are also discussed in order to provide future directions for improvement and optimization of cancer vaccines.

II. Tumor cell vaccines

A. Autologous tumor cell vaccines

Autologous tumor vaccines prepared using patient-derived tumor cells represent one of the first types of cancer vaccines to be tested (Hanna and Peters, 1978). These tumor cells are typically irradiated, combined with an immunostimulatory adjuvant (e.g., BCG), and then administered to the individual from whom the tumor cells were isolated (Berger et al., 2007; Harris et al., 2000; Maver and McKneally, 1979; Schulof et al., 1988). Autologous tumor cell vaccines have been tested in various cancers, including lung cancer (Nemunaitis, 2003; Ruttinger et al., 2007; Schulof et al., 1988), colorectal cancer (de Weger et al., 2012; Hanna et al., 2001; Harris et al., 2000; Ockert et al., 1996), melanoma (Baars et al., 2002; Berd et al., 1990; Mendez et al., 2007), renal cell cancer (Antonia et al., 2002; Fishman et al., 2008; Kinoshita et al., 2001) and prostate cancer (Berger et al., 2007). One major advantage of whole tumor cell vaccines is its potential to present the entire spectrum of tumor-associated antigens to the patient's immune system. However, preparation of autologous tumor cell vaccines requires sufficient tumor specimen, which limits this technology to only certain tumor types or stages.

Autologous tumor cells may be modified to confer higher immunostimulatory characteristics. Newcastle disease virus (NDV)-infected autologous tumor cells were shown to induce tumor protective immunity in multiple animal tumor models, such as ESb lymphoma and B16 melanoma (Heicappell et al., 1986; Plaksin et al., 1994). Clinical trials demonstrated that these modified tumor cells were safe and had a positive effect on antitumor immune memory in cancer patients (Karcher et al., 2004; Ockert et al., 1996; Schirrmacher, 2005; Steiner et al., 2004). Immunization with tumor cells engineered to express IL-12, a key cytokine promoting Th1 immunity, also resulted in strong tumor suppression in mice accompanied by high IFN-γ production and increased activation of cytotoxic T lymphocyte (CTL) and natural killer (NK) cells (Asada et al., 2002). In a recent phase II trial, treatment with renal cell carcinoma transduced with co-stimulatory molecule B7-1 showed promising antitumor effect, as indicated by 3% pathologic complete response, 5% partial response, 64% stable disease and median survival of 21.8 months (Fishman et al., 2008).

GM-CSF-transduced autologous tumor cell vaccines (GVAX) have been extensively studied in preclinical and clinical studies (Armstrong et al., 1996; Dong et al., 1998; Dranoff et al., 1993a; Dranoff et al., 1997; Dunussi-Joannopoulos et al., 1998; Levitsky et al., 1996; Sampson et al., 1996; Soiffer et al., 2003; Soiffer et al., 1998; Wakimoto et al., 1996). Mechanistic studies showed that GVAX recruits dendritic cells (DCs) for presentation of tumor antigens and priming of $CD8^+$ T cells (Dranoff et al., 1993b; Mach et al., 2000). GVAX also stimulates the maturation of DCs by upregulating B7-1 expression (Dranoff, 2002; Mach et al., 2000). Immunization with GVAX, when combined with blockade of CTL-associated antigen 4 (CTLA-4), an immune checkpoint inhibitor (Leach et al., 1996), promotes the rejection of established murine melanoma by altering the balance of T effector cells (Teff) and T regulatory cells (Treg) (Quezada et al., 2006; van Elsas et al., 1999). Enhanced antitumor efficacy was evident when tumor cell vaccine engineered to express Flt3 ligand (FVAX) was combined with blockade of CTLA4 for the treatment of TRAMP prostate adenocarcinomas (Curran and Allison, 2009). In addition to CTLA-4, the programmed death-1 (PD-1) interaction with its ligand PD-L1/L2 or B7-1 also inhibits T cell activation and cytokine production (Butte et al., 2007). Interestingly, combination blockade of PD-1 and CTLA-4 synergized with FVAX, but not GVAX, in controlling the outgrowth of pre-established B16 tumors (Curran et al., 2010), suggesting that blockade of negative costimulatory pathways favors the expansion of tumor-specific T cells and maintenance of their effector functions, resulting in shifting the immunosuppressive tumor microenvironment to an inflammatory/immunostimulatory state. Other than targeting negative immunoregulatory pathways, GVAX has been formulated with lipopolysaccharide (LPS), a TLR4 agonist, for the treatment of several murine tumors (Davis et al., 2011). Intratumoral administration of LPS-absorbed GVAX markedly improved an antitumor response in comparison with GVAX alone. This enhanced anti-tumor effect correlated with increased tumor infiltration by activated DCs as well as $CD8^+$ and $CD4^+$ T cells.

B. Allogeneic tumor cell vaccines

Allogeneic whole tumor cell vaccines, which typically contain two or three established human tumor cell lines, may be used to overcome many limitations of autologous tumor cell vaccines. These include limitless sources of tumor antigens, standardized and large-scale vaccine production, reliable analysis of clinical outcomes, easy manipulation for expression of immunostimulatory molecules and cost-effectiveness.

Canvaxin™ vaccine is an allogeneic whole-cell vaccine consisting of three melanoma lines combined with BCG as an adjuvant (Morton et al., 1992). In a phase II trial, the median overall survival (OS) and 5 year rate of survival were significantly higher in stage III melanoma patients receiving Canvaxin™ as postoperative adjuvant therapy compared to

control group (56.4 months and 49% versus 31.9 months and 37%; $p < 0.001$) (Morton et al., 2002). In another phase II trial in patients with completely resected disseminated stage IV melanoma, treatment with Canvaxin™ resulted in a 39% 5-year OS compared to the control arm (20%) (Hsueh et al., 2002). However, two multi-institutional randomized phase III trials in patients with stage III and IV melanoma failed to achieve a determination of vaccine efficacy, and therefore, these trials were discontinued (Sondak et al., 2006).

The clinical activity of allogeneic GVAX vaccine has been evaluated for treatment of recurrent prostate cancer (Simons et al., 2006; Small et al., 2007), breast cancer (Emens et al., 2009) and pancreatic cancer (Lutz et al., 2011). Although the phase II results of allogeneic GVAX prostate cancer vaccine trials were encouraging, phase III clinical trials that were designed to examine GVAX or GVAX in combination with chemotherapies for the treatment of metastatic castrate resistant prostate cancer (CRPC) failed to achieve a survival benefit and were terminated (Antonarakis and Drake, 2010; Lassi and Dawson, 2010). Despite these disappointing results, other combination strategies involving GVAX prostate cancer vaccine and anti-CTLA-4 antibodies (i.e., ipilimumab), an immunomodulating agent recently approved by the FDA for treatment of metastatic melanoma, are still being pursued (van den Eertwegh et al., 2012; Wang et al., 2011a).

Initial autologous tumor cell vaccines for non-small cell lung cancer (NSCLC) encountered manufacturing failures due to the availability of tumor specimens, although the results from pilot studies were positive (Hege and Carbone, 2003; Nemunaitis et al., 2004; Salgia et al., 2003). An allogeneic tumor cell vaccine (belagenpumatucel-L) consisting of four NSCLC lines engineered to secret antisense oligonucleotide to immunosuppressive cytokine TGF-β2 provides a promising strategy for the treatment of NSCLC. A dose-related survival difference was shown in a randomized phase II trial, in which stage II to IV NSCLC patients received intradermal injections of three dose levels of belagenpumatucel-L on a monthly or every-other-month schedule to a maximum of 16 injections (Nemunaitis et al., 2006; Nemunaitis et al., 2009). The ongoing phase III investigation (STOP trial) involves the use of belagenpumatucel-L as a maintenance therapy in patients with unresectable stage III/IV NSCLC who have responded to or have stable disease after first-line platinum-based chemotherapy. The objective is to compare the overall survival of subjects treated with belagenpumatucel-L versus those treated with placebo. The study commenced in July 2008 and is expected to enroll 506 patients by October 2012 (Kelly and Giaccone, 2011).

II. DC vaccines

A. The biology of DCs

DCs are the most potent professional antigen-presenting cells (APCs) (Banchereau and Steinman, 1998). They act as sentinels at peripheral tissues where they uptake, process and present pathogen- or host-derived antigenic peptides to naïve T lymphocytes at the lymphoid organs in the context of major histocompatibility (MHC) molecules (Banchereau et al., 2000; Timmerman and Levy, 1999). The significance of DCs in bridging innate and adaptive immunity is well established. Indeed, many cancer immunotherapeutic strategies target DCs directly or indirectly for the induction of antigen-specific immune responses. Earlier studies showed that different DC subsets direct development of distinct T cell populations and regulate different classes of immune responses *in vivo* (Maldonado-Lopez et al., 1999; Pulendran et al., 1999). An animal study showed that $CD8^+CD205^+$ DCs present antigens through both MHC class I and MHC class II molecules, whereas $CD8^-33D1^+$ DCs utilize the MHC class II presentation pathway (Dudziak et al., 2007). In addition, targeting antigens to DCs does not always result in immune activation, because engagement of certain receptor on DCs may induce immune suppression (Li et al., 2012). It appears that DC maturation signals are critical for avoiding the induction of T cell tolerance

or augmentation of effective antitumor immunity (Bonifaz et al., 2004; Hawiger et al., 2001; Idoyaga et al., 2008; Wang et al., 2012; Wei et al., 2009). Extensive studies on the biology of DCs demonstrate that three interactive signals are generally required for functional activation of DCs and subsequent innate and adaptive immunity against cancers, including adequate loading of MHC-peptide complexes to DCs for T cells priming, upregulation of co-stimulatory molecules such as CD40, CD80, and CD86, and production of cytokines capable of polarizing a Th1/Tc1 immune responses (Frankenberger and Schendel, 2012).

B. *Ex vivo* generated DCs as cancer vaccines

The pioneering work of Inaba, Steinman, and colleagues on culturing mouse DCs *ex vivo* from bone marrow precursors provided the basis of development of DC vaccines a decade ago (Inaba et al., 1992). In a similar manner, human DCs can be generated in culture from $CD34^+$ hematopoietic progenitors or from peripheral blood–derived monocytes (Banchereau and Palucka, 2005). Preparation of DC vaccines can be achieved by loading tumor-associated antigens to patients' autologous DCs that are simultaneously treated with adjuvants. These antigen-loaded, *ex vivo* matured DCs are administrated back into patients to induce anti-tumor immunity. Antigens utilized for this purpose include tumor-derived proteins or peptides (Banchereau et al., 2001; Murphy et al., 1996; Schuler-Thurner et al., 2002), whole tumor cells (Berard et al., 2000; Geiger et al., 2001; Palucka et al., 2006; Salcedo et al., 2006) DNA/RNA/virus (Nair et al., 2002; Steele et al., 2011; Su et al., 2005), or fusion of tumor cells and DCs (Rosenblatt et al., 2011).

One of the first trials testing the immunogenicity of DCs was conducted in metastatic prostate cancer, in which patients received autologous DCs pulsed with HLA-A0201-restricted peptides derived from prostate-specific membrane antigen (PSMA). Antigen-specific cellular responses and reduced PSA levels were observed in some patients supporting the potential use of this vaccine therapy (Murphy et al., 1996). DC vaccines have been tested in clinical trials for the treatment of prostate cancer (Kantoff et al., 2010a; Small et al., 2000; Small et al., 2006), melanoma (Lesterhuis et al., 2011; Nestle et al., 1998; Palucka et al., 2006; Romano et al., 2011; Thurner et al., 1999), renal cell carcinoma (Holtl et al., 1999), and glioma (Okada et al., 2011; Yu et al., 2001). However, this autologous vaccine regimen consists of leukaphereses to isolate peripheral blood mononuclear cells (PBMCs) from the patient and cell culture processing, which thus limits the number of vaccinations.

The Sipuleucel-T (Provenge™) was approved by the US FDA in 2010 for the treatment of asymptomatic metastatic castrate-resistant prostate cancer (mCRPC) (Longo, 2010). This autologous vaccine mainly consists of APCs from PBMCs that have been incubated with PA2024 that contains prostatic acid phosphatase (PAP, a prostate antigen) fused to GM-CSF. Although no difference in time to progression was observed, a survival advantage was achieved, with a statistically meaningful 4.1-month improvement in median survival in the active arm with respect to the placebo arm (25.8 vs. 21.7 months). In view of its favorable toxicity profile and manageable route of administration, the success of Sipuleucel-T as the first therapeutic cancer vaccine opens exciting new paradigms for prostate cancer and other cancers.

C. Modification of DCs to improve vaccine potency

Despite the clinical success of APC-based prostate cancer vaccine, the modest antitumor efficacy of Sipuleucel-T emphasizes the need for improvement and optimization of this approach. Considering that T cell activation is finely controlled by co-stimulatory molecules expressed on DCs, modification of the expression levels of activating or inhibitory molecules could enhance the DC vaccine potency. CD40 stimulation on DCs provided by

activated $CD4^+$ T cells is required for DC licensing and cross-priming of $CD8^+$ T cell responses (Quezada et al., 2004). CD40L overexpression in mouse DCs via virus transduction (Feder-Mengus et al., 2005; Kikuchi et al., 2000; Koya et al., 2003) or mRNA electroporation (Tcherepanova et al., 2008) led to elevated expression of B-7 molecules and enhanced production of IL-12p70, both of which are crucial for Th1-based antitumor immunity. Similarly, CD40L-expressing human DCs also resulted in increased activation of T cell reactivity with the poorly immunogenic tumor antigens, such as glycoprotein 100 (gp100) and Melan A (Bonehill et al., 2009; Knippertz et al., 2009). Modulation of other co-stimulatory molecules, such as CD70, GITRL, 4-1BBL (CD137L) and OX40L (Bonehill et al., 2008; Dannull et al., 2005; Grunebach et al., 2005; Tuyaerts et al., 2007), or pro-inflammatory factors, such as IL-12p70, IL-2, IL-18, CCR7 and CXCL10 also enhances DC functions by promoting its maturation/activation, migration and its capacity to stimulate antigen-specific Th1 and CTL responses (Iinuma et al., 2006; Kang et al., 2009; Minkis et al., 2008; Ogawa et al., 2004; Okada et al., 2005).

While activating molecules expressed on DCs are involved in a pro-inflammatory or antitumor T cell response, certain suppressive molecules contribute to T tolerance or suppression. The ubiquitin-editing enzyme A20 negatively regulates both TLR and TNF receptor signaling-induced maturation of DCs and subsequent activation of $CD4^+$ T cells and CTLs in mouse models (Song et al., 2008). A20 silencing in human DCs also facilitates the development of IFN-γ producing Th1 cells and antigen specific $CD8^+$ T cells (Breckpot et al., 2009). Suppressor of cytokine signaling 1 (SOCS1), an immunosuppressive molecule induced by cytokines, such as IFN-γ, IL-12, IL-2, IL-7 and GM-CSF, has also been shown to inhibit DC functions through signal transducer and activator of transcription (STAT) signaling and impede antitumor immunity (Palmer and Restifo, 2009; Shen et al., 2004). Recently, our studies revealed that scavenger receptor SRA/CD204 represents a newly identified immune regulator. SRA/CD204 attenuates TLR4-engaged NF-κB-TRAF6 signaling pathways in DCs (Yu et al., 2011) and downregulates the immunogenicity of DCs and CTL-mediated antitumor immunity against several mouse tumors (Wang et al., 2007b; Yi et al., 2009; Yi et al., 2012). The absence or genetic silencing of SRA/CD204 profoundly enhances the immunostimulating, antigen-presenting functions of DCs and consequent antitumor immune responses involving IFN-γ and CTLs (Guo et al., 2012a; Guo et al., 2012b; Yi et al., 2011). These findings support the concept of targeting SRA/CD204 as a strategy to optimize the potency of current DC vaccines that may be used alone or in combination with conventional therapies, such as radiotherapy.

III. Protein/peptide-based cancer vaccines

A. Tumor-associated antigens as therapeutic targets

The availability of patient's samples or specimens and the complex procedure of preparing individualized vaccines greatly limit the broad use of autologous cancer vaccines, including whole tumor cells or DCs. Recombinant vaccines, which are based on peptides from defined tumor-associated antigens (TAAs), and usually administered together with an adjuvant or an immune modulator, clearly have advantages. MAGE-1 is the first gene that was reported to encode a human tumor antigen recognized by T cells (van der Bruggen et al., 1991). The identification of TAAs has provided opportunities for design of targeted therapeutic vaccines, and these antigens may be classified into several major categories. Cancer-testis antigens, such as MAGE, BAGE, NY-ESO-1 and SSX-2, are encoded by genes that are normally silenced in adult tissues but transcriptionally reactivated in tumor cells (De Smet et al., 1994; Gnjatic et al., 2010; Hofmann et al., 2008; Karbach et al., 2011). Tissue differentiation antigens are those of normal tissue origin and shared by both normal tissue and tumors, such as melanoma (gp100, Melan-A/Mart-1 and tyrosinase) (Bakker et al., 1994; Kawakami et al., 1994; Parkhurst et al., 1998), prostate cancer (PSA, PAP) (Correale

et al., 1997; Kantoff et al., 2010a) and breast carcinomas (mammaglobin-A) (Jaramillo et al., 2002). Similar to these differentiation-associated antigens, several other tumor antigens, such as CEA (Tsang et al., 1995), MUC-1(Finn et al., 2011; Kufe, 2009), HER2/Neu (Disis et al., 2009), tumor suppressor genes (p53) (Azuma et al., 2003), hTERT (Vonderheide et al., 1999) and certain anti-apoptotic proteins (i.e. livin and survivin) (Schmidt et al., 2003; Schmollinger et al., 2003) are also highly elevated in tumor tissues compared to normal counterparts. Unique tumor-specific antigens are often referred to mutated oncogenes (ras, B-raf) (Brichard and Lejeune, 2008; Parmiani et al., 2007). Targeting these tumor-specific antigens involved in driving the neoplastic process has the advantage of resistance to immunoselection with potential to be more effective. Clinical trials are underway to test vaccines that target relatively few *RAS* mutations found in colorectal and pancreatic cancers. However, the tremendous effort required for the identification of such candidate mutations may hamper their broad clinical use (Fox et al., 2009). It is also difficult to target a wide array of frame shift mutations and unique mutations that occur in individual tumors. Other antigens for potential vaccine targets include molecules (SOX-2, OCT-4) that are associated with cancer “stem cells” (Dhodapkar et al., 2010; Dhodapkar and Dhodapkar, 2011; Spisek et al., 2007) and/or the epithelial–mesenchymal transition (EMT) process (Polyak and Weinberg, 2009).

Protein/peptide-based vaccines are more cost effective than autologous or individualized vaccines. However, they also have a potential drawback because they target only one epitope or a few epitopes of the TAA. It is generally believed that induction of both antigen-specific CTLs and antigen-specific $CD4^+$ helper T cells is necessary for a cancer vaccine to be optimally efficacious. Some polypeptide vaccines (e.g., Stimuvax) potentially contain both CD4 and CD8 epitopes. Other approaches to enhance immunogenicity of a self-antigen are to alter the peptide sequence of TAAs to introduce enhancer agonist epitopes, which increase peptide binding to the MHC molecule or the T-cell receptor, resulting in higher levels of T-cell responses and/or higher avidity T cells (Dzutsev et al., 2007; Hodge et al., 2005; Hou et al., 2008; Jordan et al., 2010; Rosenberg et al., 1998).

Most peptide-based vaccines in clinical trials target cancer-testis antigens, differentiation-associated antigens, or certain oncofetal antigens (CEA, MUC-1). Although these vaccines were able to induce antigen-specific T cell responses, clinical outcomes have been disappointing (Buonaguro et al., 2011). In the Phase III study that led to the approval of ipilimumab (Hodi et al., 2010), no difference in overall survival was observed in patients with unresectable stage III or IV melanoma between the ipilimumab group and ipilimumab plus gp100 group. However, the encouraging results came from recent randomized Phase III trial involving patients with stage IV or locally advanced stage III cutaneous melanoma (Schwartzentruber et al., 2011). The group treated with the gp100 (210M) peptide in Montanide ISA-51 adjuvant plus IL-2 demonstrated a statistically significant improvement in overall clinical response (16% vs. 6%, $P = 0.03$) as well as longer progression-free survival (2.2 months vs. 1.6 months, $P = 0.008$) compared with the IL-2 group. The median overall survival was also longer in the gp100 peptide vaccination plus IL-2 group than in the IL-2 group (OS = 17.8 vs. 11.1 months; $P = 0.06$) (Schwartzentruber et al., 2011). Indeed, this was the first phase III trial to demonstrate a clinical benefit for a peptide vaccine in melanoma. The unique findings in this trial were not observed in three previous independent phase II clinical trials (Sosman et al., 2008).

B. Immunostimulatory adjuvants for protein/peptide-based vaccines

Given that TAAs are poorly immunogenic in nature, an immunostimulatory adjuvant is essential for generation of an effective immune response. Aluminum salts (alum) have been used as adjuvants with great success for almost a century and have been particularly effective at promoting protective humoral immunity. However, alum is not optimally

effective for diseases where cell-mediated immunity is required for protection. The recognition over the past two decades that activation of innate immunity is required to drive adaptive immune responses has radically altered theories as to how adjuvants promote adaptive immunity. In particular, the pioneering work of Charles Janeway demonstrated that adaptive immune responses are preceded by, and dependent on, innate immunity receptors triggered by microbial components (Janeway, 1992). Recognition of conserved moieties associated with pathogen or pathogen-associated molecular patterns (PAMPs) *via* pattern recognition receptors, e.g., toll-like receptors (TLRs), engages coordinated innate and adaptive immunity against microbial pathogen or infected cells (Kawai and Akira, 2011). TLR-mediated activation of antigen-presenting cells, e.g., DCs, is a crucial step in this process. Indeed, many established and experimental vaccines incorporate PAMPs, not only to protect against infectious diseases, but also as part of therapeutic immunizations against cancer (Wille-Reece et al., 2006). The use of these molecularly and functionally defined molecules as adjuvants greatly facilitates the rational design of vaccines.

Supporting this view, long-used BCG for the treatment of bladder carcinoma has been relatively effective and shown to activate TLR2 and TLR4 (Heldwein et al., 2003; Uehori et al., 2003). LPS, a natural ligand of TLR4, was reported to possess anticancer properties as early as the 1960s (Mizuno et al., 1968; Prigal, 1961). Monophosphoryl lipid A (MPL) is a chemically modified derivative of *S. minnesota* endotoxin that exhibits greatly reduced toxicity, but maintains most of the immunostimulatory properties of LPS (Mata-Haro et al., 2007). A plethora of studies have shown that MPL potently boosts a patient's immune response against viral and tumor-associated antigens (Schwarz, 2009). FDA approved the Cervarix vaccine formulated with MPL and aluminum salt as a prophylactic vaccine against human papillomavirus (Schiffman and Wacholder, 2012). Imiquimod (a TLR7 agonist) was approved by FDA in 2004 for use in humans against actinic keratosis and superficial basal cell carcinoma (Hoffman et al., 2005). These TLR agonists have strong potential in promoting the immunogenicity of weakly immunogenic TAAs. Indeed, several peptide/protein-based cancer vaccines combined with TLR agonists are being tested in clinical trials; these include Ampligen targeting TLR3 (NCT01355393), Histonol targeting TLR3 (NCT00773097, NCT01585350, NCT01437605), MELITAC 12.1 targeting TLR4 (NCT01585350) and Resiquimod targeting TLR9 (NCT00960752). The family of PRRs has greatly expanded in recent years, so there is tremendous effort being expended to investigate the role of innate immune pathways in defining the mechanisms of adjuvant action as well as roles of other PRRs (e.g., NLR, RLR) in adjuvant activity of therapeutic cancer vaccines.

In addition to sensing pathogen-associated signals, PRRs also recognize endogenous `alarmins', such as stress/heat shock proteins (HSPs) and HMGB-1(Bianchi, 2007; Lotze et al., 2007; Todryk et al., 2000). As intrinsic and highly conserved protein components of the cell, these damage-associated molecular patterns (DAMPs) also communicate the nature and magnitude of cellular injury to the host immune system. Although HSPs are known to act as molecular chaperones that participate in intracellular protein quality control (Calderwood et al., 2009; Lindquist and Craig, 1988; Mayer and Bukau, 2005), studies for the last two decades have established the concept that certain HSPs are capable of integrating both innate and adaptive immune responses, and can be utilized as immunostimulatory agents for cancer immunotherapy (Calderwood et al., 2005; Murshid et al., 2008; Srivastava, 2002a, b; Wang et al., 2006b).

Based on the early observations by Srivastava and his colleagues that HSPs isolated from cancer cells were able to induce tumor immunity (Srivastava et al., 1986; Udono et al., 1994), it was proposed that the immmunogenecity of HSPs was primarily attributed to their ability to bind antigenic peptides and transport these peptides to APCs for T cell priming (Srivastava, 2002a; Srivastava, 2005). This is consistent with the well-recognized capacity

of chaperones to bind polypeptide chains in response to physiological stress (Welch, 1993). To date, antitumor immunity elicited by HSPs, including the cytosolic heat shock proteins Hsp70, Hsp90, Hsp110, or the ER resident Grp94/gp96, Grp170 and calreticulin, has been shown against a variety of tumors of different histologic origins such as fibrosarcomas, lung carcinomas, melanomas, colon cancers, B cell lymphoma and prostate cancer (Graner et al., 2000; Janetzki et al., 2000; Srivastava et al., 1986; Tamura et al., 1997; Vanaja et al., 2000; Wang et al., 2001; Yedavelli et al., 1999). Interestingly, HSPs (e.g., Hsp70) prepared from DC-tumor fusion cells were shown to stimulate an enhanced T cell response and antitumor immunity compared to tumor-derived HSPs (Enomoto et al., 2006; Gong et al., 2010). Purification of chaperones from a cancer is believed to co-purify an antigenic peptide `fingerprint' of the cell of origin. Thus, vaccination with chaperone-peptide complexes derived from a tumor circumvents the need to identify CTL epitopes from individual cancers. This unique advantage extends the use of chaperone-based immunotherapy to cancers where specific tumor antigens have not yet been characterized.

The first autologous HSP vaccine, Oncophage (also known as HSP-peptide complex 96, HSPPC-96, Vitespen), has been examined in clinical trials of various types of malignancies, including metastatic colorectal carcinoma (Mazzaferro et al., 2003; Rivoltini et al., 2003), metastatic melanoma (Pilla et al., 2006; Testori et al., 2008), non-Hodgkin Lymphoma (Younes, 2003), RCC (Jonasch et al., 2008; Wood et al., 2008). Despite the positive results from early phase trials, the phase III trial conducted in Stage IV melanoma patients failed to demonstrate survival benefits (Testori et al., 2008). However, introspective analysis revealed overall survival benefit within the early stage IV melanoma patients (M1a, distant skin, subcutaneous or nodal metastasis; M1b, lung metastasis) (Testori et al., 2008). Similarly, no difference in recurrence-free survival between vaccination group and observation (control) group was observed in a separate phase III trial of RCC; although stage I and II patients seemed to benefit from vaccination (Wood et al., 2008). Further analysis of the data showed that patients with Stage I/II and T1/2/3a RCC had a recurrence-free survival of about 45% compared with the control group (Yang, 2008). As a result, Gp96 based vaccine (Oncophage/Vitespen) was approved in 2008 by the Russian Ministry of Health for adjuvant treatment of RCC (Carlson, 2008).

To overcome technical difficulties (tumor specimen requirement, time-consuming preparation, etc.) associated with the conventional autologous HSP vaccine approaches, we have developed a chaperoning technology to formulate recombinant HSP vaccines. This platform takes advantage of exceptional protein-holding capability of large HSPs (Hsp110, Grp170) (Easton et al., 2000; Oh et al., 1997; Park et al., 2003; Subjeck and Shyy, 1986), and generates chaperone complexes of the large HSP and clinically relevant tumor antigens (e.g., gp100, HER-2/Neu) *in vitro* (Manjili et al., 2002; Manjili et al., 2003; Park et al., 2006; Wang et al., 2007a; Wang et al., 2006a; Wang et al., 2003; Wang et al., 2010). The whole protein antigen employed in this approach contains a large reservoir of potential peptides that allow the individual's own MHC alleles to select the appropriate epitope for presentation, and increases the chance of polyepitope directed T and B cell responses. This synthetic approach can serve as a model to develop many different antigen targets, either alone or in combination vaccines (Wang et al., 2010). The promising preclinical results have led to a phase I clinical trial of recombinant chaperone vaccine targeting melanoma that is to be launched soon.

The immunological function of chaperones that has received the most attention thus far is the ability to shuttle peptides into the endogenous presentation pathway of professional APCs. Several receptors e.g., CD91, LOX1, SRA and SREC have been identified to be involved in the HSP-facilitated cross-priming event (Basu et al., 2001; Berwin et al., 2004; Berwin et al., 2003; Binder et al., 2000; Delneste et al., 2002; Facciponte et al., 2007; Gong

et al., 2009; Murshid et al., 2010; Theriault et al., 2006). Intriguingly, our recent work revealed that SRA absence markedly improved the therapeutic efficacy of the Hsp110/Grp170-gp100 vaccines in mice established with B16 melanoma (Qian et al., 2011; Wang et al., 2007b), suggesting the complex network of HSP-binding receptors and their potential distinct effects on HSP vaccine-induced immune responses.

IV. Genetic vaccines

Another strategy to deliver antigen or antigen fragments *in vivo* is to utilize viral or plasmid DNA vectors carrying the expression cassettes. Upon administration, they transfect somatic cells (myocytes, keratinocytes) or DCs that infiltrate muscle or skin as a part of the inflammatory response to vaccination, resulting in a subsequent cross-priming or direct antigen presentation. One major advantage of genetic vaccines is the easy delivery of multiple antigens in one immunization and activation of various arms of immunity (Aurisicchio and Ciliberto, 2012).

A. DNA vaccines

DNA vaccines are bacterial plasmids that are constructed to function as shuttle system to deliver and express tumor antigen (full-length, short peptides) for generating targeted cellular and humoral immunity (Liu, 2011). The transgene is usually driven by the cytomegalovirus immediate early promoter and its adjacent intron A sequence to ensure transcription efficiency. Elevated expression of encoded antigen can be achieved by optimization of codon-usage, such as substitution of codons for rare tRNA (Stratford et al., 2000). The backbone of bacterial DNA itself acts as PAMPs to stimulate the activation of immune cells through TLRs or other innate pattern recognition molecules (Barber, 2011; Beutler et al., 2006; Spies et al., 2003).

The ability to incorporate multiple genes into the vector creates opportunities to modulate intracellular routing and modification of antigens as well as subsequent immune outcome. Addition of a leader sequence targeting antigens to the endoplasmic reticulum (ER) induced a humoral response (Walter and Johnson, 1994), and also facilitated generation of $CD8^+$ T-cell responses, probably due to retrograde transfer of antigen from the ER to cytosol and direct delivery of DNA to APC at the immunization site (Rice et al., 2008). Fusing the single chain Fv of idiotypic immunoglobulin to fragment C derived from tetanus toxin in DNA vaccines results in the activation of fragment C-specific $CD4^+$ T helper cells, which facilitate anti-Id B cells to produce high levels of anti-Id antibodies for immune protection against lymphoma (King et al., 1998; Spellerberg et al., 1997).

In addition, DNA vaccines can be rationally combined with other immunostimulatory agents, such as TLR agonists, to optimize antibody responses. DNA cancer vaccine targeting HER-2/Neu or CEA, when used in conjunction with a novel TLR9 agonist IMO (Aurisicchio et al., 2009), or a TLR7 agonist SM360320 (Dharmapuri et al., 2009), resulted in greater antibody titers and antibody-dependent cellular cytotoxicity activity, which led to improved control of HER2-positive mammary carcinoma or CEA-positive colon carcinoma in murine models. In a therapeutic setting, active immunization with HER-2/Neu DNA vaccine synergized with anti-HER-2/Neu monoclonal antibodies for enhanced inhibition of established mouse breast tumors (Orlandi et al., 2011).

Achieving an effective and durable CTL response remains the ultimate goal of cancer vaccines. Generation of $CD4^+$ T cell helps *via* a class II MHC-dependent pathway is important for amplification of $CD8^+$ T cell responses and maintenance of memory during DNA vaccination (Maecker et al., 1998). Given poor immunogenicity of self TAAs , fusion of the TAAs to non-self antigens or molecules, such as virus × coat protein (Savelyeva et al.,

2001), GFP (Wolkers et al., 2002), a modified fragment C of tetanus toxin (Rice et al., 2002; Rice et al., 2006; Rice et al., 2001) can provide T helper signals to CTLs, resulting in enhanced cross-presentation of TAAs and antitumor immunity against several murine tumors. DNA vaccines that were designed to target tumor antigens to costimulatory B7 molecules on APCs by fusing the extracellular domain of CTLA-4 to HER-2/Neu induced protective humoral and cellular immune responses, which delayed onset of HER-2/Neu-driven mammary carcinoma (Sloots et al., 2008).

DNA vaccines have also been tested for immune targeting of stable, proliferating endothelial cells in the tumor vasculature. A DNA vaccine with the expression cassette for vascular-endothelial growth factor receptor 2 (FLK-1) promoted CTL-mediated killing of endothelial cells, resulting in potent therapeutic efficacy against several murine tumors (melanoma, colon carcinoma and lung carcinoma) and reducing the dissemination of pulmonary metastases (Niethammer et al., 2002). Oral administration of a xenogenic DNA vaccine encoding human tumor endothelial marker 8 (TEM8) effectively suppressed tumor angiogenesis and protected mice from subsequent challenge with a lethal dose of tumor cells (Ruan et al., 2009). Mice immunized with a DNA vaccine encoding human papilloma virus type-16 (HPV-16) E7 fused with calreticulin (CRT) developed a strong tumor-specific $CD8^+$ T cell response and also showed a dramatic reduction in microvessel density in lung tumor nodules, suggesting the enhanced antitumor effect involves dual immune-mediated attack of both cancer cells and endothelial cells (Cheng et al., 2001). Other DNA vaccine approaches targeting the angiostatin receptor angiomotin also augmented immune-mediated blockade of angiogenesis and tumor inhibition. Interestingly, the increased tumor vessel permeability following DNA vaccination further enhanced the antitumor effect of a chemotherapeutic agent, doxorubicin (Arigoni et al., 2012; Holmgren et al., 2006).

Although DNA vaccine platforms have shown promise in preclinical studies (Xiang et al., 2008), they fail to translate from mice and rats to non-human primates and humans (Liu and Ulmer, 2005; Rice et al., 2008). DNA vaccines are facing the obstacle of translation into the clinic due to efficacy rather than toxicity. However, new constructs and methods of administration may enhance their utility. In addition to subcutaneous or intradermal injection, DNA vaccines can be injected directly into the lymph nodes to increase antigen uptake by APCs and promote local inflammatory signals. This is currently being tested in Phase I/II trials for melanoma and other cancers (Ribas et al., 2011; Weber et al., 2011). Other approaches or carrier modalities, including gene gun, electroporation, ultrasound, laser, liposome, microparticles and nanoparticles, have been used to enhance antigen expression and DNA vaccine efficacy (Bins et al., 2005; Buchan et al., 2005; Dupuis et al., 2000; Greenland and Letvin, 2007).

B. RNA vaccines

Messenger RNA (mRNA) from autologous tumor tissues can also be used to induce a specific CTL response (Carralot et al., 2005; Scheel et al., 2005; Wolff et al., 1990). Administration of total RNA as a vaccine potentially generates immune responses against various tumor antigens to reduce the possibility of tumor escape. Unlike DNA vaccines, RNA vaccines are less likely to cause side effects or autoimmune diseases due to their rapid degradation and clearance. RNA vaccination is usually carried out together with other agents for stabilization or adjuvant effects, such as liposomes or protamines (Espuelas et al., 2005; Fotin-Mleczek et al., 2012; Qiu et al., 1996; Scheel et al., 2005). Chemical modification of the phosphodiester backbone (phosphorothioate RNA) can also provide a `danger' signal for stimulating the DCs through the MyD88 pathway (Scheel et al., 2004). Other modifications of RNA vaccines by integrating an RNA replicase polyprotein derived from the Semliki forest virus to generate “self-replicating” RNA (Ying et al., 1999) or using β-globin UTR to stabilize the RNA vaccine (Carralot et al., 2004) also lead to enhanced antigen-specific

immune responses. RNA-based cancer vaccines have only been clinically tested in phase I/II trials with patients with melanoma (Weide et al., 2008; Weide et al., 2009) or RCC (Oshiumi et al., 2003).

C. Viral-based vaccines

The rationale for using viruses as immunization vehicles is based on the phenomenon that viral infection often results in the presentation of MHC class I/II restricted, virus-specific peptides on infected cells. The viral vectors with low disease-causing potential and low intrinsic immunogenicity are engineered to encode TAAs or TAAs combined with immunomodulating molecules.

The first and most extensively evaluated viral-based vectors in cancer vaccine trials are from the poxviridae family, such as vaccinia, modified vaccinia strain Ankara (MVA), and the avipoxviruses (fowlpox and canarypox; ALVAC) (Marshall et al., 1999; Marshall et al., 2000; Walsh and Dolin, 2011). Poxviruses have the ability to accommodate large or several transgene inserts (Moss, 1996). Poxvirus replication and transcription are restricted to the cytoplasm, which minimizes risk to the host of insertional mutagenesis. It is believed that induction of a local inflammatory response by the host TLRs and other properties of vaccinia or MVA contribute to the enhanced immune response reactive with inserted TAAs in preclinical studies.

One promising viral cancer vaccine is PROSTVAC developed by Bavarian Nordic. This “off-the-shelf” platform consists of a replication-competent vaccinia priming vector and a replication-incompetent fowlpox-boosting vector. Each vector contains transgenes for PSA and three costimulatory molecules (CD80, CD54 and CD58) that are collectively designated TRICOM (Hodge et al., 2005). In double-blinded, placebo-controlled phase II trial, PROSTVAC improved median overall survival relative to the control vector (25.1 vs. 16.6 months, $P = .006$) (Kantoff et al., 2010b). Similar improvement in the median overall survival was also observed in a second PROSTVAC single-arm phase II study (Gulley et al., 2010). The pivotal phase III trial following these encouraging data from phase II studies are ongoing (NCT01322490).

Trovax is a MVA vector-based cancer vaccine targeting renal cell carcinoma antigen 5T4. Phase III clinical trials of Trovax in metastatic renal cancer patients failed to meet the primary endpoint of overall survival (Amato et al., 2010). Another MVA vector-based vaccine TG4010 consists of expression cassettes encoding MUC1 antigen and IL-2. In a phase II trial of renal cell carcinoma, TG4010 combined with interferon-α2a and IL-2 resulted in 22.4 months mean overall survival compared with 19.3 months for all patients. MUC-1-specific $CD8^+$ T cells were associated with the prolonged survival (Oudard et al., 2011). A separate phase II trial of TG4010 combined with first-line chemotherapy (cisplatin plus gemcitabine) in advanced NSCLC demonstrated a significant 6 months increase in median survival (17.1 months in the experimental arm *vs.*11.3 months in the control arm). Activated NK cells were identified as predictive biomarkers for positive clinical outcome (Quoix et al., 2011). A confirmatory phase IIb/III trial of TG4010 for treatment of advanced stage (IV) NSCLC is ongoing (NCT01383148).

Recombinant adenovirus is another system that can be used as carriers for genetic vaccination. Adenoviruses are easy to engineer and propagate to high yields for clinical use. They also have the advantage of transducing both dividing and non-dividing cells for high expression of transgenes. Indeed, adenoviruses are used extensively as cancer gene therapeutic agents (Das et al., 2012; Liu et al., 2008; Raty et al., 2008). Although clinical evaluations of adenovirus platforms have been hindered by preexisting antiviral immunity, adenovirus vectors expressing various TAAs (PSA, HER-2/Neu) are currently being tested

for their immunological and clinical efficacy (NCT00583024, NCT00197522). Newer less immunogenic variants of adenoviruses and local delivery of adenovirus-based vaccines may circumvent this issue.

Herpes simplex virus type 1 (HSV-1) is an enveloped dsDNA virus with the ability to infect a wide variety of cell types, and to incorporate single or multiple transgenes. An oncolytic HSV-1 encoding granulocyte macrophage colony-stimulating factor (GM-CSF; Oncovex$^{GM\text{-}CSF}$) for direct injection into accessible melanoma lesions resulted in a 28% objective response rate in a Phase II clinical trial (Senzer et al., 2009). Responding patients demonstrated regression of both injected and noninjected lesions highlighting a dual mechanism of action of Oncovex$^{GM\text{-}CSF}$ which includes both a direct oncolytic activity in injected tumors and a secondary immune-mediated antitumor effect. The Oncovex$^{GM\text{-}CSF}$ Pivotal Trial in Melanoma (OPTIM), randomized Phase III clinical trial, has been initiated to evaluate Oncovex$^{GM\text{-}CSF}$ in patients with unresectable, metastatic melanoma (Kaufman and Bines, 2010).

Like viral vectors, bacteria and yeasts have shown utility as vaccine vehicles in preclinical studies, and may also be modified for immunizing cancer patients. Attenuated recombinant *Listeria monocytogenes* has been shown to induce both innate and adaptive antitumor immune responses (Singh and Paterson, 2006, 2007). *Saccharomyces cerevisiae* is inherently nonpathogenic and can be easily engineered and propagated for preparation of a TAA-targeted vaccine (Remondo et al., 2009; Wansley et al., 2008).

VI. Cancer vaccine therapy combined with other treatment modalities

Given the existence of such diverse vaccine platforms that potentially engage the innate and adaptive immune components, it is feasible and attractive to use combinatorial cancer vaccine therapy. In addition to cancer vaccines, a wide range of other promising immunotherapeutic modalities is being tested or approved for cancer treatment. These include adoptive cell transfer of *ex vivo* expanded tumor infiltrating lymphocytes (Rosenberg et al., 1994), use of therapeutic antibodies (e.g., trastuzumab) for antagonizing oncogenic pathways and triggering antibody dependent cytotoxicity and phagocytosis (Disis et al., 2009; Zhou and Levitsky, 2012), and administration of immune modulating antibodies targeting both co-inhibitory and co-stimulatory receptors on activated T cells or the corresponding ligands on APCs as well as tumor cells to enhance antitumor immune responses (Peggs et al., 2007; Wolchok et al., 2010). Therefore, a consensus view in cancer immunotherapy is developing that applications of rational combinations of multiple modalities targeting distinct aspects of tumor and immune pathways will achieve durable antitumor effects and more effective therapeutic outcomes.

A recent study demonstrated that recombinant CEA vaccines based on different poxviral and yeast platforms activated different T-cell repertoire and cytokine profiles, resulting in enhanced antitumor activity in mice (Boehm et al., 2010). Preclinical studies also showed that cancer DNA vaccine targeting CEA in combination with multiple co-stimulatory molecules (B7-1, ICAM-1, LFA-3 and GM-CSF) amplified T cell response and greatly enhanced antitumor responses (Grosenbach et al., 2001). Cancer vaccines combined with the administration of cytokines, such as IL-7 (Pellegrini et al., 2009), IFN-α (Pace et al., 2010; Sikora et al., 2009), can synergize to induce immune stimulation of DCs and T cells as well as antagonize Treg-mediated immune suppression, which leads to optimized and improved antitumor immune efficacy.

The recent FDA approval of anti-CTLA-4 antibodies (ipilimumab) for metastatic melanoma undoubtedly supports the rational combination of this immune checkpoint inhibitor with other vaccine therapies (Hodi et al., 2010; Lipson and Drake, 2011; Wang et al., 2011a).

Although no significant difference in the OS was seen in the recent phase III trial between the ipilimumab alone group and the ipilimumab plus gp100 vaccine group (Hodi et al., 2010), ipilimumab has been shown in several preclinical and clinical studies to enhance the avidity of T cells and to enhance antitumor effects in combination with vaccines (Brahmer et al., 2010; Chakraborty et al., 2007; Hodi et al., 2003; van Elsas et al., 1999; Yuan et al., 2008). In addition, administration of ipilimumab after vaccination with GVAX generated clinically meaningful antitumor immunity in a majority of metastatic melanoma patients (Hodi et al., 2008). Clinical trials evaluating different combinations of ipilimumab with vaccines are planned or ongoing in the adjuvant and metastatic setting for treatment of different types of cancer (ClinicalTrials.gov Identifier: NCT01302496, NCT00124670, NCT00836407).

Other promising candidates for immune modulation to enhance clinical vaccine efficacy include antibodies against PD-1 or PD-1L1 (Brahmer et al., 2010; Curran et al., 2010; Sakuishi et al., 2010), lymphocyte-activation gene-3 (LAG-3), T cell immunoglobulin mucin-3 (Tim-3) (Fourcade et al., 2010; Sakuishi et al., 2010), CD40 (Advani et al., 2009; Beatty et al., 2011), and inhibitors of transforming growth factor β (TGF-β) (Bogdahn et al., 2011; Bueno et al., 2008). The combination of PD-1 blockade with GM-CSF-secreting tumor cell immunotherapy leads to significantly improved antitumor responses in preclinical models (Li et al., 2009).

Emerging evidence from preclinical or clinical studies also support the idea of combining cancer vaccines with conventional therapies (radiation, chemotherapy) to achieve additive or synergistic effects, even though the dose and scheduling of the combining agent require additional studies for optimization. Certain chemotherapeutic agents (e.g., doxorubicin) can induce immunogenic cancer cell death, resulting in enhanced cross-priming of TAA-specific T cells and subsequent antitumor immunity (Apetoh et al., 2007; Ghiringhelli et al., 2009; Kepp et al., 2011; Tesniere et al., 2010; Zitvogel et al., 2010). Low doses of cyclophosphamide and doxorubicin also enhance the therapeutic efficacy of GM-CSF secreting whole tumor cell vaccines in tumor bearing mice and cancer patients, probably due to their ability to diminish the number of Tregs (Emens et al., 2009; Machiels et al., 2001). Docetaxel has been reported to increase the expression of TAAs, peptide-MHC complexes, and the death receptors expressed on tumor cells, thus sensitizing tumors to vaccine-induced T cell killing (Garnett et al., 2008). In addition, certain small molecule targeted therapeutics, such as BCL-2 inhibitor (Farsaci et al., 2010), B-raf inhibitor (Boni et al., 2010) and the tyrosine kinase inhibitor sunitinib (Farsaci et al., 2012; Finke et al., 2008; Ko et al., 2009) demonstrate the ability to enhance T cell functions and antitumor efficacy in preclinical studies. Recent studies also showed that the mTOR inhibitor rapamycin promotes production of IL-12 and development of memory $CD8^+$ T cells, leading to enhanced vaccine potency (Araki et al., 2009; Ohtani et al., 2008; Wang et al., 2011b).

Local radiation not only debulks the tumor, but also generates an inflammatory microenvironment, thereby promoting presentation of dying tumor-released TAAs by DCs and subsequent T cell priming (Guo et al., 2012b; Hodge et al., 2008). In addition, radiation renders tumor cells more susceptible to attack by tumor-specific CTLs (Chakraborty et al., 2003; Garnett et al., 2004; Reits et al., 2006). Indeed, radiation therapy combined with a PSA-targeted vaccine displayed a favorable toxicity profile and generated significant T cell responses in prostate cancer patients (Gulley et al., 2005; Lechleider et al., 2008). Moreover, the preclinical and clinical evidence indicates potential benefits of hormonal therapy in combination with vaccine therapy (Arredouani et al., 2010; Mercader et al., 2001). Randomized clinical trials of PROSTVAC vaccine also suggest that vaccination combined with nilutamide hormone therapy potentially results in improved survival in patients with non-metastatic prostate cancer (Madan et al., 2008).

VII. Lessons learned from cancer vaccine trials

In contrast to other cytotoxic therapies, cancer vaccines have demonstrated minimal toxicity in all clinical trials that have been reported to date. Despite expression of many target TAAs in normal tissues, little evidence of autoimmunity has been observed, with the exception of vitiligo that is seen in patients receiving some melanoma vaccines (Banchereau et al., 2001; Luiten et al., 2005). Therapeutic cancer vaccines of different forms are being actively evaluated in the clinic. Ongoing Phase III trials are summarized in Table 1.

Clinical studies have now shown that patients who have received less prior chemotherapy are generally more responsive to vaccines (von Mehren et al., 2001). Thus, vaccine treatment of patients with a lower tumor burden may result in significantly improved outcomes (Gulley et al., 2011), highlighting the importance of selection of appropriate patient populations to be used in randomized vaccine trials. Strikingly, the mechanism of action and kinetics of clinical responses following vaccine therapy appear to differ significantly from that of chemotherapy (Stein et al., 2011). It may be explained by the time needed to establish the immune response, which is followed by continuing tumor cell destruction and cross-priming of T effector cells reactive with additional TAAs. Thus, antitumor activity of vaccine-induced immune activation over a long period results in a slower tumor growth rate and improved overall survival, even though patients fail to show substantial reductions in tumor burden and an improvement in relapse-free survival (Madan et al., 2010). Similar findings have been reported in the clinical trials evaluating ipilimumab treatment of metastatic melanoma, in which patients treated with ipilimumab showed a statistically significant advantage in overall survival without a statistically significant difference in time to progression (Hodi et al., 2010).

These findings indicate that traditional response criteria may not be adequate for evaluating clinical responses to vaccine therapy or immunotherapy. Classic Response Evaluation Criteria in Solid Tumors (RECIST criteria) were initially developed to monitor patients treated with cytotoxic chemotherapies (Therasse et al., 2006). Indeed, new guidelines or “immune response criteria” for the evaluation of immunotherapeutic activity in solid tumors have been developed to better classify and evaluate clinical activity (Wolchok et al., 2009).

Numerous studies have demonstrated that analysis of the immune infiltrates in cancer biopsies and “immune signature” can serve as independent prognostic predictors for survival (Ascierto et al., 2011; Ascierto et al., 2012; Camus et al., 2009; Galon et al., 2006). Future efforts should be focused on the identification and validation of diagnostic biomarkers in response to vaccine treatment. Obtaining information on the biomarkers of immune and clinical responsiveness to effective treatment will greatly facilitate the clinical development of therapeutic cancer vaccines.

VIII. Tumor-induced immune suppression and tumor microenvironment

Tumor-induced immunosuppressive mechanisms in the tumor microenvironment (TME) are one of the major reasons for the limited current success of therapeutic cancer vaccines. The original immuosurveillance concept proposed to interpret the cross-talk between the immune system and the tumor (Burnet, 1970) has been elaborated on by Schreiber et al. proposing the cancer `immunoediting' theory (Dunn et al., 2002; Dunn et al., 2004). In this model, it is suggested that tumor cells that escape initial immunosurveillance may enter an equilibrium phase where they are kept in check by the immune system; as soon as the immune response is suppressed or epigenetic changes in the quiescent tumor cells result in antigen loss or HLA loss, tumor escape and recurrence will occur. It is also believed that tumor `immunoediting' also occurs during vaccination therapy of established tumors and contributes to tumor progression or relapse (Schreiber et al., 2011).

These immunosuppression mechanisms constitute the principle obstacles for the development of effective therapeutic cancer vaccines (Fig. 1). Tumor cells can change themselves by alterations in the antigen processing-presenting machinery, loss of antigen or induction of anti-apoptotic mechanisms (Dunn et al., 2002; Khong and Restifo, 2002; Racanelli et al., 2010; Respa et al., 2011; Seliger et al., 2010). The lack of T-cell co-stimulatory molecules on most solid tumors and chronic exposure to TAAs may enable activated T cells to become anergized during activation (Kim and Ahmed, 2010). The TME contains a range of immunosuppressive leukocyte populations, including myeloid derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs) and Tregs. Analysis of PBMCs from patients with different types of cancer has also shown increased levels of MDSCs and Tregs with increased suppressive functions (Cesana et al., 2006; Vergati et al., 2011). These suppressive cells, tumor cells, and TAMs residing in the TME also release a number of immunosuppressive soluble factors, including TGF-β, IL-10, indoleamine-pyrrole 2,3 dioxygenase (IDO), galectin, and vascular endothelial growth factor (VEGF), which promote and establish an immunosuppressive state at the tumor site (Vesely et al., 2011).

MDSCs are immature myeloid cells that express CD11b and Gr-1 markers in tumor-bearing mice (Peranzoni et al., 2010). These include monocytic MDSCs and polymorphonuclear MDSCs (granulocytic MDSCs). In cancer patients, MDSCs are characterized as $LIN^{-}HLA\text{-}DR^{-}CD33^{+}CD11b^{+}$ cells in blood. There is a positive correlation between the frequency of MDSCs and advanced-stage tumors (Diaz-Montero et al., 2009; Kusmartsev et al., 2008; Raychaudhuri et al., 2011). MDSCs inhibit T cell activation via arginase, inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS) or reactive nitrogen species (RNS) (Movahedi et al., 2008; Youn et al., 2008). Various mechanisms are involved in MDSC-mediated immune suppression, which include depletion of nutrients necessary for lymphocytes (Rodriguez et al., 2004; Srivastava et al., 2010), generation of oxidative stress to induce the loss of TCR ζ-chain expression on T cells (Schmielau and Finn, 2001) and disruption of IL-2 receptor signaling (Mazzoni et al., 2002), interference with lymphocyte trafficking (Hanson et al., 2009; Molon et al., 2011), or promoting activation of Tregs by CD40-CD40L ligation (Pan et al., 2010) and production of IL-10 or TGF-β (Huang et al., 2006). Contact-dependent mechanisms of T cell suppression have also been reported in a mouse tumor model (Morales et al., 2009).

Macrophages are derived from circulating monocytes and terminally differentiate in various tissues. They express various surface markers and function differently in response to the local environmental cues (Mosser and Edwards, 2008). It is well known that TAM facilitate tumor progression and is associated with poor clinical outcomes (Mantovani and Sica, 2010; Qian and Pollard, 2010). TAMs are M2-like or alternatively activated macrophages that facilitate tumor angiogenesis and promote tumor invasion or metastasis (Lin et al., 2006; Qian et al., 2009). TAMs also promote tumor growth by producing IL-10 to drive the development of IL-4-expressing Th2 cells, which provides a positive feedback for stimulating TAM expansion (DeNardo et al., 2009). CCL22 produced by TAMs recruits Tregs to suppress CTL function (Curiel et al., 2004). Expression of PD1 ligand (PD1L) on monocytes/macrophages can induce apoptosis of activated T cells (Kuang et al., 2009).

Tregs not only suppress physiological and pathological immune responses against self, non-self and quasi-self-tumor antigens, but also are able to attenuate antitumor functions of $CD4^{+}$ helper T cells, NK cells, NKT cells and $CD8^{+}$ T cells (Sakaguchi, 2004; Shevach, 2002). A large number of Tregs can be recruited into the TME of tumor bearing mice or cancer patients, due to the self antigens released by dying tumor cells and inflammatory TME (Nishikawa et al., 2005; Pardoll, 2003). An increased presence of $CD4^{+}CD25^{+}Foxp3^{+}$ Tregs over $CD8^{+}$ T cells at the tumor site correlates with poor prognosis and therapeutic

outcomes in cancer patients (Bates et al., 2006; Curiel et al., 2004; Sato et al., 2005). Although not clearly defined, expression of the inhibitory surface molecules CTLA-4 and PD-1, secretion of the immunosuppressive soluble factors TGF-β, IL-10 and IL-35 as well as certain cytolytic molecules may mediate immunosuppression by Tregs (Vignali et al., 2008).

In addition to the immunosuppressive TME, the immune counteracting mechanisms engaged during cancer vaccine responses may also compromise antitumor responses and contribute to tumor escape. Tregs can be expanded in response to viral-based vaccination or multiple cycles of GVAX vaccines (LaCelle et al., 2009; Zhou et al., 2006; Zhou and Levitsky, 2007). Anti-CTLA-4 antibodies abrogate Treg-mediated suppression by decreasing Tregs in the TME, but expanding the overall Tregs (Kavanagh et al., 2008; Quezada et al., 2006). Widely used TLR agonists as vaccine adjuvants (Caramalho et al., 2003; Conroy et al., 2008; Crellin et al., 2005) and PD-1 blockade (Currie et al., 2009) also enhance the proliferation or amplify the suppressive function of Tregs. GM-CSF-based cancer vaccines could potentially attenuate antitumor responses by expanding MDSCs in animal models of cancer (Serafini et al., 2004) and in cancer patients (Filipazzi et al., 2007; Slingluff et al., 2009). Other factors induced following vaccination include IL-6, IL-17 and IL-1β, which drive the expansion of MDSCs due to their regulatory properties (Bunt et al., 2007; He et al., 2010; Rider et al., 2011). Therefore, innovative strategies are mandatory for overcoming these tumor-dependent and -independent immunoregulatory or immunosuppressive mechanisms or pathways to achieve beneficial clinical outcomes in cancer vaccine therapy.

VIV. Concluding remarks

Effective, safe and enduring cancer treatments constitute major challenges of medical sciences, with therapeutic cancer vaccines emerging as attractive approaches for provoking long-lasting protective antitumor immunity. Recent approval of the first therapeutic cancer vaccine will pave the way for developing innovative, next generation of vaccines with enahnced antitumor potency. Based on current data from clinical trials and the safety profiles of therapeutic vaccines, they will most probably be used in the adjuvant or neoadjuvant setting for the treatment of patients with minimal residual disease or more indolent metastatic disease, or those patients with a high risk of recurrence. Ultimate translation of cancer vaccines into clinically available medications with broad applications will require overcoming the immune tolerance/suppression pathways in the TME. A better understanding of host-tumor interactions and tumor immune escape mechanisms are required to develop effective cancer vaccines. Identification of unique tumor gene or protein products responsible for transformation of normal cells into tumor cells and promoting cancer progression will also uncover new potential targets for vaccine therapy. In addition, `immune signatures' will have to be established and exploited to define patient populations who will most likely respond to and benefit from vaccine therapies. Strategically combining vaccine strategies with other agents or approaches that synergistically enhance antitumor immunity and/or engage complementary antitumor responses should also lead to further improved clinical outcomes.

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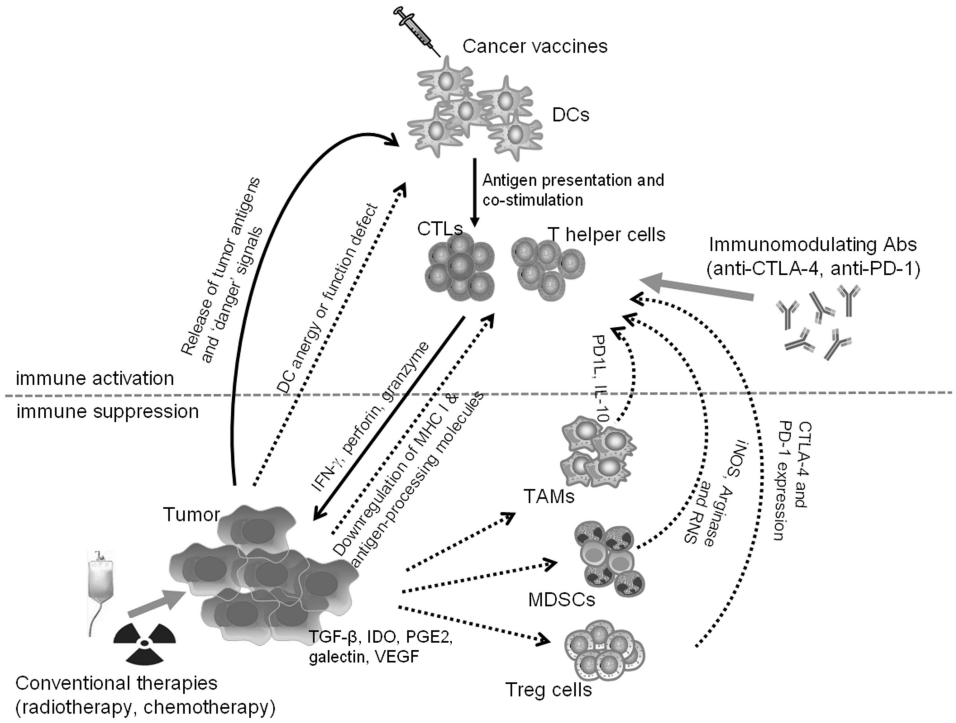

Figure 1. Counteracting tumor-induced immune suppression to achieve effective cancer vaccine therapy

Active immunization with therapeutic vaccines generally targets the host DCs for effective presentation of tumor-associated antigens and subsequent priming of $CD8^+$ CTLs and $CD4^+$ T helper cells. These tumor-specific T effector cells together with other innate immune cells can result in inhibition or destruction of cancer cells. In the tumor microenvironment, cancer cells produce immunosuppressive soluble factors (TGF-β, IL-10, IDO, galectin and VEGF) and expand or recruit immune regulatory cells (MDSCs, Tregs and TAMs), which establish an immunosuppressive state at the tumor site. This complex molecular and cellular network attenuates vaccine-induced antitumor immune responses and promotes tumor escape from immune attack. To overcome the immune suppressive mechanisms, novel immune modulators (anti-CTLA-4 and anti-PD1 antibodies) may be used to enhance vaccine potency and restore durable antitumor immunity. Cancer vaccines can also be combined with conventional cancer treatments, such as radiotherapy and chemotherapy, to engage multivalent antitumor effects for optimized therapeutic efficacy.

Table 1

Ongoing phase III trials of therapeutic cancer vaccines

Vaccines		Description	Cancer type	NCI ID
DC/APCs	AGS-003	autologous DCs transfected with tumor and CD40L RNAs	RCC	NCT01582672
	DCVax®-L	autologous DCs loaded with tumor lysate	GBM	NCT00045968
	Cvac	autologous DCs pulsed with MUC1-mannan fusion protein	EOC	NCT01521143
Peptides/proteins	GV1001	hTERT peptide	NSCLC	NCT01579188
	GV1001	hTERT peptide	Pancreatic Cancer	NCT00425360
	NeuVax™	HER2/neu peptide combined with GM-CSF	Breast Cancer	NCT01479244
	N/A	MAGE-A3 and NY-ESO-1 peptides combined with GM-CSF	Multiple Myeloma	NCT00090493
	Stimuvax	liposome-encapsulated synthetic peptide derived from MUC-1	NSCLC	NCT01015443
	Rindopepimut	hEGFR variant III specific peptide conjugated to KLH	GBM	NCT01480479
	POL-103A	protein antigens from 3 melanoma cell lines with alum adjuvant	Melanoma	NCT01546571
Virus vectors	PROSTVAC	recombinant fowlpox/vaccinia virus encoding hPSA and TRICOM	Metastatic Prostate Cancer	NCT01322490
	CG0070	oncolytic adenovirus encoding GM-CSF	Bladder Cancer	NCT01438112
	INGN 201	adenovirus encoding p53	SCCHN	NCT00041613
	INGN 201	adenovirus encoding p53 combined with cisplatin and fluorouracil	SCCHN	NCT00041626
	TG4010	modified vaccinia virus encoding human MUC1 and IL-2	NSCLC	NCT01383148

EGFR, epidermal growth factor receptor; EOC, epithelial ovarian cancer; GBM, glioblastoma; GM-CSF, granulocyte-macrophage colony-stimulating factor; hPSA, human prostate specific antigen; hTERT, human telomerase reverse transcriptase; KLH, keyhole limpet hemocyanin; MUC1, mucin 1; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCCHN, squamous cell cancer of the head and neck; TRICOM, recombinant vaccinia virus vaccine encoding three co-stimulatory molecule transgenes B7.1, ICAM-1, and LFA-3.