Cancer vaccines: The next generation

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The field of cancer vaccines is as vibrant as ever. Despite pessimism, considerable advances are being made on a regular basis. Success stories continue to be published and newer, exciting and, perhaps, more potent strategies are being discovered frequently. Over the past two decades, this enormous effort has led to a shifting of how we think of vaccines. Although vaccines are not a standard of care, we have learned significant lessons that will continue to drive the field.

Introduction
In the USA, cancer is a leading cause of disease-related deaths, and in 2002 the death rate was about 193 deaths/100,000 individuals (http://www.Canques.Sear.Cancer.Gov). In the same year, the incidence rate was in excess of 450 cases per 100,000 individuals (http://www.Canques.Sear.Cancer.Gov). With a population of nearly 300,000,000 people, the economic and quality-of-life impact of cancer in the USA is enormous. For many cancers, conventional therapies render patients free of disease but relapse and death remains high, particularly in advanced cancers. Thus, there is great interest in developing novel therapies that can completely remove residual disease and prolong life. Although many novel approaches have been advanced in recent years, interest in cancer vaccines has been exceptionally strong. Over the past two decades, the revolution in biotechnology has led to many capabilities that we did not have before and which have begun to explain the successes and failures of cancer vaccines providing new direction. In this review, several crucial aspects of cancer vaccines are discussed, which includes assessing the effects of tumor burden on immunological and clinical efficacy, testing the different vaccine strategies and finding ways of combining vaccines with other novel biologics to enhance the antitumor response.

Therapy with vaccines: are all clinical settings equal?
In infectious diseases, vaccines are designed as prophylactic agents to protect individuals from becoming infected and developing disease [1]. Cancer vaccines, however, continue to be used as a therapeutic modality to directly destroy malignant cells. However, what has become clearer in recent years is that the most effective approach for the use of vaccines is also prevention. However, rather than protecting against malignancy, vaccines would be used to prevent relapse in minimal disease or no-evidence-of-disease settings (Fig. 1). The reason that this clinical setting seems better than the bulky cancer setting is that tumors alter many immunological parameters that directly interfere with the augmentation of immunity in the vaccine draining lymph nodes. As tumor burden increases, the impact of vaccines can decrease. The impact of tumor burden on dendritic cell populations (DC) has been examined extensively. DC have an important role in presenting vaccine antigens to T cells in the vaccine-draining lymph node and in the tumor bed, and are important for maintaining activation of immune effectors. Several investigations have documented that tumors increase levels of circulating and tumor-localized immature DC (iDC), a cell that cannot induce antitumor immunity but rather induces peripheral T cell tolerance [2]. Closely associated with the iDC are immature myeloid cells (iMC), which consist of a heterogeneous population of myeloid cells including immature macrophages and DC [3]. Like iDC, iMC also suppress T cell function and together both can...
ultimately suppress vaccine efficacy. Defective DC maturation reduces numbers of functionally competent DC that are available to elicit immunity during vaccination. The numbers of mature DC is proportional to the tumor burden and reduction in tumor burden leads to restoration of normal DC physiology and possibly vaccine efficacy [3].

Increasing tumor burden also leads to abnormalities in the peripheral lymphocyte populations as well. Several reports have emerged suggesting that tumor burden is associated with increased levels of peripheral regulatory T cells (Tregs), a subset of T cells that suppress the emergence of normal antigen-specific T cells [4]. What is not currently clear is whether tumors directly induce increased levels of Tregs and if reductions in tumor burden can decrease them. Tregs block T cell activation during vaccination (Fig. 2). In addition to peripheral increases, several studies have found that tumors accumulate Tregs in the tumor microenvironment where they directly block the actions of immune effectors entering the tumor tissue [5]. In addition to abnormal levels of Tregs, other deficits have been observed in the circulating T cell population in patients with cancer [6]. For example, in head and neck cancers a common finding is the down-modulation of T cell responsiveness leading to the reduced capacity of the T cells that respond to vaccine antigens.

Although the presence of too much tumor is not generally beneficial to vaccination, in some respects, some residual small tumor burden could be important in developing and sustaining immunity. The presence of some antigen-positive tumor tissue during the immunization process permits both intra- and extramolecular epitope spreading to broaden the immune response [7]. Furthermore, the sustained presence of the antigen following immunization might prove useful for the generation and maintenance of immunologic memory [8].

**Immune complexity: how much focus is needed?**

Current understanding of immunity makes it possible to target specific epitopes and T cell subsets, but a central question that needs addressing is how much focus is needed in vaccine strategies? Studies with CD8 T cell-, CD4 T cell- and B-cell-targeted vaccines have all shown augmentation of immunity but the problem is identifying which strategy represents the best approach if indeed there is even one [9]. Many studies have focused exclusively on generating specifically CD8 (i.e. cytotoxic) T cell immunity with major histocompatibility complex (MHC) class I binding antigens. The major concern with this approach is that CD8 T cell targeted vaccines might not go on to generate immune memory, an ideal outcome of immunization [10]. Studies have suggested that concurrent augmentation of CD4 T cell immunity is necessary for a long-lived CD8 T cell response in both preclinical and clinical studies [11]. For example, Knutson et al. [10] has found that the simultaneous generation of a tumor antigen-specific CD4 and CD8 T cell response leads to a longer lived CD8 T cell
response compared to other CD8 T cell-targeted vaccine strategies [12].

The paradigm for immune augmentation in recent years has been to target a cell-mediated immune response (e.g. T helper 1 cells, T cytotoxic 1 cells). Given the successes of monoclonal antibody therapy [13], it is worthwhile to vaccinate with the intent of generating antibodies. Antibodies possess several different mechanisms against which they could control tumor, including antibody-dependent cytotoxicity, complement-mediated cytotoxicity and altered cellular signaling. Antibodies can be induced against several antigen subtypes including protein and carbohydrates [14].

In contrast to vaccines targeting specific cellular subsets, deoxyribonucleic acid (DNA)-, bacterial- or viral-based vaccines provide solutions for activating multiple effector arms. For example, Zhou et al. [15] recently reported preclinical findings that plasmid DNA vaccines encoding for tumor antigens and the natural killer cell activating receptor ligand, NKG2D, can elicit broad immunity including both the adaptive and innate immune systems. In another study, Brockstedt et al. [16] elicited both CD8 and CD4 therapeutic T cell immunity in mice using a vaccine platform based on killed but metabolically active Listeria monocytogenes. Because the various immune effectors are highly dependent on each other, it is probable that the most effective vaccine strategies are going to be those which elicit multiple immune effector arms including the innate immune system.

Vaccine strategies: is one better than another?  

The identification of tumor-associated antigens (e.g. HER-2/neu, tyrosinase, hTERT among others) has led to the testing of several tumor antigen-specific approaches that have provided definitive proof of principle that immunity to ‘self’ can be induced with immunization. Several types of vaccines that are able to generate antigen-specific immunity have been applied including peptide, DC, protein, DNA, carbohydrate and viral vaccines each with its own strengths and weaknesses [14,17–20]. Peptides are predicted or identified based on binding to specific human leukocyte antigen (HLA) class I or class II molecules that might limit the application to select subpopulations (e.g. HLA-A2). An advantage of targeting the class I molecule, HLA-A2, is that a high percentage (35–40%) of North Americans carry a copy of this gene. In general, however, the peptides that bind to HLA class I are largely nonoverlapping, increasing the numbers of peptides that would need to be included if the goal is to produce a vaccine with broader population coverage. Although individual HLA class II (e.g. HLA-DR) genotype frequencies are not as high as some HLA class I genotypes, recent investigations have revealed considerable promiscuity in that a single HLA-DR peptide might bind to several HLA-DR subtypes with considerable affinity [21]. Therefore, it might take fewer HLA class II peptides, compared to HLA class I, to prepare a broad-spectrum vaccine. Studies already performed with HLA class II (e.g. HLA-DR) genotype frequencies are not as high as some HLA class I genotypes, recent investigations have revealed considerable promiscuity in that a single HLA-DR peptide might bind to several HLA-DR subtypes with considerable affinity [21]. Therefore, it might take fewer HLA class II peptides, compared to HLA class I, to prepare a broad-spectrum vaccine. Studies already performed with HLA class II peptides suggest that immunity can be achieved in a high proportion of individuals without regard to HLA-DR genotype [7]. The major advantage of peptide-based vaccines is the ease of construction and delivery. By contrast, whole protein vaccines can be difficult to prepare and require sophisticated production facilities that increase costs and decrease feasibility but they can be used regardless of HLA genotype. Compared to peptides, proteins might lead to more effective and broad antibody responses that might be clinically relevant, particularly if the proteins are expressed on the cell surface of the tumors. However, recent studies indicate that if the right peptides are chosen, antibody responses can be achieved that are potentially therapeutic [22]. DNA-, bacterial- and virus-encoded antigens are also attractive approaches and can be used without regard to a patient’s HLA class I and class II genotype because, like proteinaceous vaccines, they depend on antigen processing and presentation by antigen presenting cells [23,24]. Like protein vaccines, these
approaches are complicated by production and purification issues.

Probably one of the more insidious problems associated with using antigen-specific vaccines is the emergence of antigen-loss variants, which are being reported more frequently, although there are so far still only a few mouse studies [25,26]. The data indicate that antigen-loss variants might occur in many different tumor types [27]. Multiantigen strategies are thus beginning to be used, which might not only reduce the risk of antigen loss variants but also increase the percentage of patients that would benefit from the vaccine [28]. Allogeneic whole cell vaccines are advantageous because they might overcome issues of antigen selection and antigen-loss variants [29].

Dosing and frequency are crucial issues that are becoming understood. Their importance is illustrated in infectious disease vaccination where it has been shown that high dose immunizations favor the rapid induction of short-term effectors whereas lower doses favor the induction of memory [1]. In a recent Phase I clinical trial of the effects of dose on the generation of immunity to the HER-2/neu tumor antigen, Disis et al. [30] confirmed that higher doses of antigen lead to a more rapid immune response suggesting that shorter vaccination schedules could be developed. However, they also found that the levels of HER-2/neu-specific T cells were equally persistent for all doses by in vitro analysis up to 12 months, suggesting that high- and low-dose strategies are both capable of eliciting memory [30]. Whether or not longer term memory immunity (i.e. >1 year) was elicited will only be borne out in studies boosting individuals in vivo after extended times following immunization or by examining dose-related clinical outcome differences.

Boosting also appears to be crucial in the magnitude of the vaccine-induced immune response. In the example above, the dose impacted the number of boosts that must be given to achieve the maximal vaccine response. But, it has also been found that boosting with a different vector system (i.e. heterologous prime boosting) leads to greater cell-mediated immunity than with homologous boosting strategies in an infectious disease setting and in animal models of cancer vaccination [31–34].

Improving immunogenicity can also be achieved by altering peptide sequences to enhance binding to MHC class I molecules [35]. Altered peptide strategies are applicable to most antigen-specific vaccine strategies including peptide, protein, DNA and viral vaccines, and recent studies have shed light on important MHC binding attributes of a peptide that improve its immunogenicity (Table 1). Lazarski et al. [36] found that immunogenicity is proportional to the kinetic stability of the peptide in the MHC class II cleft. Yu et al. [37] reported similar findings for MHC class I as well. Thus, increasing the half-life of the peptide:MHC complex might improve the immune response to vaccination.

The important question is whether altered peptides lead to immunity capable of recognizing naturally processed native antigen and whether this correlates into an effective antitumor response?

Combining for success

There is some agreement in the field of cancer vaccination that combining vaccines with other agents such as monoclonal antibody therapy could lead to synergism and greater efficacy. Several strategies have emerged, some of which are being tested clinically. In some cases (e.g. trastuzumab), the combination of antibody therapy with vaccines emerged partly out of necessity to test vaccine strategies in patients who were on long-term adjuvant therapy with monoclonal antibody and partly because the combination is conceivably more effective than either strategy alone. In one recent study, Zum Buschenfelde et al. [38] found that pretreatment of HER-2/neu+ tumor cells with trastuzumab enhanced the cytolytic activity of HER-2/neu-specific T cells against the HER-2/neu-overexpressing tumors in vitro. Although mechanism is unclear, it is possible that trastuzumab promotes the internalization and degradation of HER-2/neu, resulting in increased presentation of HER-2/neu MHC class I epitopes that might lead to greater activation and expansion of HER-2/neu-specific T cells. Clinical trials are currently underway to test for potentially improved efficacy using this combination.

As previously mentioned, circulating Tregs might block the generation of an immune response and there is interest in preconditioning the immune system to deplete or inhibit Tregs to augment immunity. Agents like cyclophosphamide, which augment immune-based therapies in both human and mouse studies are thought to involve Treg depletion. Other strategies that are being examined that inhibit the function of Tregs include anti-CTLA-4 monoclonal antibodies and CD25-targeted agents such as Denileukin Diftitox [5,39].

Alternatively, targeted therapeutics, such as small molecule inhibitors, could also potentially work in concert with vaccines. An example is transforming growth factor beta (TGF-β) inhibitors. TGF-β is a growth factor that plays multiple roles in cancer [40,41]. TGF-β promotes tumor progression, invasion and metastasis by inducing epithelial to mesenchymal transition (EMT), migration and release of vascular endothelial growth factor [42]. TGF-β also directly inhibits cytotoxic actions of tumor-infiltrating CD8 T cells [42]. Thus, an agent that simultaneously blocks local immunosuppression (Fig. 3) and tumor progression might be better by providing sufficient time for the immune system to expand and destroy residual tumor burden. Many combinatorial strategies are currently being tested and time will tell whether such mixing will be therapeutically effective.
### Table 1. Vaccine strategies

<table>
<thead>
<tr>
<th>Vaccines in minimal disease setting</th>
<th>Pros</th>
<th>Cons</th>
<th>Latest developments</th>
<th>Who</th>
<th>Refs</th>
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<tr>
<td>(1) Residual tumors still provide antigen for maintenance of memory and epitope spreading, (2) excellent safety profile, (3) immunosuppression minimal</td>
<td></td>
<td>(1) Rapid tumor growth, (2) difficulties in assessing clinical outcome, (3) competing strategies (e.g. adjuvant chemotherapy)</td>
<td>(1) Tumors orchestrate a broad immunosuppressive network to block vaccine-induced immunity, supporting use of vaccines in minimal disease settings, (2) protection against relapse</td>
<td>Examples include G. Peoples (Walter Reed Medical Center), Mary L. Disis (University of Washington, <a href="http://www.tumorvaccinegroup.org/">http://www.tumorvaccinegroup.org/</a>), K.L. Knutson (Mayo Clinic, <a href="http://www.mayo.edu/">http://www.mayo.edu/</a>), Glaxo SmithKline (<a href="http://www.gsk.com/">http://www.gsk.com/</a>), Dendreon Corporation (<a href="http://www.dendreon.com/">http://www.dendreon.com/</a>), Cerus Corporation (<a href="http://www.cerus.com/">http://www.cerus.com/</a>)</td>
<td>[2,5–7,43]</td>
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<th>Vaccines in bulky disease setting</th>
<th>Pros</th>
<th>Cons</th>
<th>Latest developments</th>
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<tr>
<td>(1) Rapid clinical outcome assessment, (2) tumor microenvironment can be source of antigen to enhance epitope spreading and that development of immune memory</td>
<td></td>
<td>(1) Immunosuppressive microenvironment, (2) systemic immunosuppression, (3) tumor grows faster than immune system can be augmented</td>
<td>(1) Combination with anti-CTLA-4 antibodies can cause tumor regression in some patients, (2) vaccination might prolong overall survival</td>
<td>Examples include NewLink Genetics Corporation (<a href="http://www.newlinkgenetics.com/">http://www.newlinkgenetics.com/</a>), M. Zalupski (University of Michigan Cancer Center, <a href="http://www.cancer.med.umich.edu/">http://www.cancer.med.umich.edu/</a>), H. Kaufman (Herbert Irving Comprehensive Cancer Center, Columbia University, <a href="http://www.ccc.columbia.edu/">http://www.ccc.columbia.edu/</a>), R. Dillman (Hoag Cancer Center at Hoag Memorial Hospital Presbyterian)</td>
<td>[17,39]</td>
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<th>Effector-focused vaccines (e.g. CD8 or CD4 T cell targeting peptides)</th>
<th>Pros</th>
<th>Cons</th>
<th>Latest developments</th>
<th>Who</th>
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<tr>
<td>(1) Prediction algorithms are maturing, (2) ease of monitoring immune responses, (3) good safety profile, (4) easily modifiable antigens, (5) can target-specific immune effectors</td>
<td></td>
<td>(1) Narrow nonintegrated immune response, (2) short-lived immune responses with CD8 T cell peptides</td>
<td>(1) MHC class II epitopes are promiscuous, (2) personalization to match antigen expression and HLA background is feasible, (3) multiantigen strategies might have some clinical benefit</td>
<td>See below in ‘Peptide vaccines’</td>
<td>[7,9,12,21,28]</td>
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<th>Effector-unfocused vaccines (e.g. protein, DNA, whole cell among others)</th>
<th>Pros</th>
<th>Cons</th>
<th>Latest developments</th>
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<td>(1) Simultaneous amplification of multiple immune effectors, (2) some platforms, such as naked DNA can be manipulated to incorporate immune co-stimulatory molecules, (3) can be antigen specific in some cases such as DNA and protein</td>
<td></td>
<td>(1) Immune monitoring is difficult and potentially expensive, (2) proteins and cell lines have production issues</td>
<td>(1) Majority of patients develop T cell responses to tumor antigens</td>
<td>See below in ‘Protein’, ‘DNA’ and ‘Microbial-based vaccines’</td>
<td>[23]</td>
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<th>Peptide vaccines</th>
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<th>Cons</th>
<th>Latest developments</th>
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<td>(1) Ease of construction, storage, reconstitution and distribution, (2) easily altered to improve immune response, (3) antigen-specific</td>
<td></td>
<td>(1) Focus on specific immune effectors might be nonoptimal, (2) restricted to select HLA backgrounds</td>
<td>(1) High immune response rate with CD4 T cell epitopes without regard to HLA genotype, (2) epitope spreading</td>
<td>Examples include NIH/NCI, Antigen Express (<a href="http://www.antigenexpress.com/">http://www.antigenexpress.com/</a>), Ludwig Cancer Institute, G. Peoples (Walter Reed Medical Center), M.L. Disis (University of Washington, <a href="http://www.tumorvaccinegroup.org/">http://www.tumorvaccinegroup.org/</a>), K.L. Knutson (Mayo Clinic, <a href="http://www.mayo.edu/">http://www.mayo.edu/</a>)</td>
<td>[7,9,28]</td>
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<td>Table 1 (Continued)</td>
<td>Pros</td>
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<td><strong>Protein vaccines</strong></td>
<td>(1) Elicit multiple immune effectors including CD8 and CD4 T cells and B cells, (2) ability to control dose, (3) antigen-specific, (4) useful without regard to HLA genotype</td>
<td>(1) Production and consistency difficulties, (2) stability issues</td>
<td>(1) Higher doses lead to maximal immunity faster, (2) broad immune responses generated, (3) improved survival suggested</td>
<td>Examples include GlaxoSmithKline (<a href="http://www.gsk.com/">http://www.gsk.com/</a>), Ludwig Cancer Institute (<a href="http://www.liehr.org/">http://www.liehr.org/</a>)</td>
<td>[30,43]</td>
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<td><strong>DNA vaccines</strong> (naked plasmid)</td>
<td>(1) Ease of construction, storage, reconstitution and distribution, (2) easy to dose, (3) antigen easily modified, (4) co-stimulatory molecules can be encoded to enhance immunity, (5) broad T cell and B cell responses, (6) can be used across multiple HLA backgrounds</td>
<td>(1) Lack of control of in vivo expression of construct, (2) persistent antigen expression in off target cells (e.g. skin and muscle), (3) integration into genomic DNA</td>
<td>(1) DNA encoding tumor antigen and natural killer activating ligands elicits a broad integrated antitumor response, (2) intranodal DNA elicits immunity and might provide protection</td>
<td>Examples include M.L. Disis (University of Washington, <a href="http://www.tumorvaccinegroup.org/">http://www.tumorvaccinegroup.org/</a>), C.L. Trimble (Sidney Kimmel Cancer Center, <a href="http://www.hopkinskimmelcancercenter.org/">http://www.hopkinskimmelcancercenter.org/</a>), NIH/NCI (<a href="http://www.nih.gov/">http://www.nih.gov/</a>), M.A. Perales, J.D. Wolchok and S. Slovin (Memorial Sloan Kettering Cancer Center, <a href="http://www.mskcc.org/">http://www.mskcc.org/</a>)</td>
<td>[15,24,44]</td>
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<td><strong>Microbial-based vaccines</strong> (e.g. bacterial or viral)</td>
<td>(1) Broad T and B cell responses, (2) strong foreign antigen help, (3) targetable to antigen presenting cells, (4) co-stimulatory molecules can be encoded</td>
<td>(1) Immunity to foreign antigens might swamp tumor-specific immunity, (2) difficulties in production and standardization, (3) integration of genes into DNA</td>
<td>(1) Metabolically active Listeria is a novel bacterial platform for tumor vaccines, (2) viral vaccine vectors generate tumor antigen-specific immunity and might provide disease protection</td>
<td>Examples include M. Morse (Duke Comprehensive Cancer Center, <a href="http://www.cancer.duke.edu/">http://www.cancer.duke.edu/</a>), NIH/NCI (<a href="http://www.nih.gov/">http://www.nih.gov/</a>), S. Antonia (H. Lee Moffitt Cancer Center and Research Institute, <a href="http://www.moffitt.usf.edu/">http://www.moffitt.usf.edu/</a>), M. Adamina (University Hospital Basel, <a href="http://www.unispital-basel.ch/">http://www.unispital-basel.ch/</a>), J.P. Eder (Dana Farber Harvard Cancer Center, <a href="http://www.dfhcc.harvard.edu/">http://www.dfhcc.harvard.edu/</a>), Cerus Corporation (<a href="http://www.cerus.com/">http://www.cerus.com/</a>)</td>
<td>[16,23]</td>
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<td><strong>Combinatorial vaccine therapy</strong> (e.g. vaccines with monoclonal antibodies, immune regulatory compounds or small molecule inhibitors)</td>
<td>(1) Eliminate antigen-loss variants, (2) block suppression by regulatory immune cells, (3) boost immune responses, (4) synergistic antitumor responses, (5) block immunosuppressive substances such as TGF-β^a</td>
<td>(1) Autoimmune toxicity, (2) unknown dosing problems such as frequency and timing of combinations, (3) proprietary issues</td>
<td>(1) Anti-CTLA-4 antibodies in combination with vaccines generates superior antitumor responses, (2) Trastuzumab sensitizes HER-2/neu-overexpressing tumors to tumor-specific T cells</td>
<td>Examples include M.L. Disis (University of Washington, <a href="http://www.tumorvaccinegroup.org/">http://www.tumorvaccinegroup.org/</a>), NIH/NCI (<a href="http://www.nih.gov/">http://www.nih.gov/</a>), M. Morse (Duke Comprehensive Cancer Center, <a href="http://www.cancer.duke.edu/">http://www.cancer.duke.edu/</a>), G. Schuler (Dermatologische Klinik MIT Poliklinik-Universitaetsklinikum Erlangen)</td>
<td>[5,38,39,45]</td>
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*a CTLA-4, cytotoxic T lymphocyte antigen 4.
*b CD, cluster of differentiation.
*c MHC, major histocompatibility complex.
*d HLA, human leukocyte antigen.
*e TGF-β, transforming growth factor beta.
Conclusions
Despite the fact that the successes of cancer vaccines have been limited, much has been learned in the past two decades providing many new testable hypotheses. We have moved from a generation that questioned whether tumors were in fact immunogenic to a new generation that aims to understand the best vaccines approaches and clinical settings in which to test them. Currently, however, there are many potential solutions to perplexing problems and new potentially effective vaccine platforms continue to emerge on a regular basis [15,16]. The testing of cancer vaccines has been largely confined to the advanced stage patient with active disease, but now it is apparent that this is not the best clinical setting owing to tumor-induced immunosuppression. Like infectious disease vaccines, perhaps the most appropriate setting is the prophylactic-like setting to prevent disease recurrence. In this clinical setting, it is probable that the immune system can dominate the tumor rather than the tumor dominating the immune system. In addition to defining the appropriate clinical setting, our vastly improved understanding of the general principles of immunology will change the types of vaccine strategies being tested from predominantly CD8 T cell-focused strategies to those that elicit a broad integrated antitumor response consisting of both adaptive (e.g. CD8 T cells, B cells, CD4 T cells) and innate immune effectors (e.g. NK cells). Concurrent modulation of the immune microenvironment with any of the variety of new approaches (e.g. antibodies and immunotoxins) will allow us to break down barriers that dampen or inhibit the function of immune effectors tipping the balance from suppressive to augmentative. It is also being increasingly recognized that tumors can readily adapt to new inflammatory environments such as through decreasing antigen expression or upregulating immunosuppression. Understanding mechanisms of escape and tumor adaptation will lead to the development of novel therapeutics (e.g. TGF-β small molecule inhibitors) that could be used in combination to maintain the tumor phenotype whereas the immune system does its job of

Figure 3. The tumor immune microenvironment is complex and immunosuppressive. The schematic diagram shows a simplified immune microenvironment that consists of major immune effectors which are attempting to destroy the aberrant tissue. In addition to producing factors with directly immunosuppressive effects as described in Fig. 1 (e.g. VEGF), tumors support tolerizing conditions by recruiting Tregs and iDC into the microenvironment. These suppressive cells block the functions of the anti-tumor immune cells which include CD4 T cells, CD8 T cells, the NK and mature DC. The plus (+) sign indicates a positive effect and an X indicates a negative or inhibitory effect. Studies and trials are aimed at boosting the anti-tumor immune effectors, blocking the suppressive molecule and cells or both. Effective anti-tumor immunity will require coordination among several cell types orchestrated by CD4 T cell responses which support B cell and CD8 T cells by secreting cytokines such as IL-2, IL-10 and IL-6. The antitumor immune effectors recognize tumor antigens (e.g. HER-2/neu and Globo H) in unique ways to cause tumor destruction.
destroying and removing malignant tissue. Perhaps the combination of approaches that target both the tumor cell and the immune system is the ultimate answer to improving clinical responses following vaccination. Only time will tell what approaches will work best. The only certainty in the field of cancer vaccines is that the old generation of cancer vaccine strategies is gone and the next generation is now.

References