**Cancer Vaccines: Moving toward Prevention?**

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**Abstract**

After several decades of research, recent successful phase III controlled clinical trials have renewed enthusiasm for vaccine treatment of cancer. This perspective on the report by Berta and colleagues in this issue of the journal (beginning on page 994) discusses the potential prevention of oral cancer through vaccine strategies and, in the broader context, ideal characteristics of tumor antigens as candidates for vaccines for both treating and preventing cancer, potential primary and secondary prevention settings for vaccines, desirable types of immune effectors induced by vaccines, and safety. Cancer Prev Res; 4(7); 954–6. ©2011 AACR.

Often the development of a new class of cancer therapeutic agents is characterized by a wave of initial (naive) enthusiasm, followed by rejection associated with early failures, and ultimately real progress and renewed optimism as obstacles are more fully understood and overcome. This roller coaster of successes and failures was experienced by monoclonal antibody therapeutics prior to their incorporation into standard of care (1) and now, a decade later, by cancer vaccines.

The cancer vaccine hypothesis was first proposed in response to the success of childhood vaccines against infectious pathogens. Briefly, the idea is that like childhood vaccines (which contain parts of the bacteria or virus), there are proteins (antigens) that are either specifically expressed or overexpressed by tumor cells compared with normal cellular counterparts, and that these antigens can be identified, isolated, and packaged into appropriate delivery systems. If successful, the injected cancer vaccine activates the host immune system. Unlike most anti-cancer therapeutics, vaccines work indirectly by activating adaptive immunity (antibodies and T-cells), because they have no direct anti-cancer effect. Major theoretical advantages of this type of active immunotherapy, compared with passive immunotherapy with monoclonal antibodies, include that the immune response will be entirely host-derived, that is, containing no mouse or other xenogeneic component. For this reason, the immune responses may be sustained and not require frequent administrations, such as is required for chemotherapy or passive immunotherapy, aside from occasional boosters. Finally, the immune response will be polyclonal, that is, elicited against multiple determinant influences on the targeted antigen, thereby rendering the possibility of escape by alteration of a single determinant (e.g., mutation) much less likely.

Application of this simplistic concept soon gave way, however, to the reality of the complexity of suitable candidate cancer antigens, suboptimal vaccine delivery platforms, and the lack of available practical immune adjuvants for use in humans. Not the least obstacle was clinical application—cancer vaccines were administered in a therapeutic setting against advanced cancer burdens, distinguishing them from childhood vaccines, which are administered in a prevention setting absent established disease. Not surprisingly in view of these substantial obstacles, most early therapeutic cancer vaccines met with failure in large phase III controlled clinical trials. An in-depth analysis of how these obstacles have been overcome in recent years is beyond the scope of this perspective. However, one clear advance by the field has been to replace crude tumor-cell extracts with well-defined, highly purified cancer vaccine products. Tumor antigen candidates for current state-of-the-art cancer vaccine development have the following characteristics: (i) Specific expression or overexpression by tumor cells compared with normal cells, (ii) demonstrated immunogenicity (i.e., recognizable by the immune system) and oncogenicity (i.e., expression required for tumor cell survival), and (iii) cell-surface expression, either as an intact protein (required for the target of an antibody response) or as a peptide in the groove of a human leukocyte antigen (HLA) molecule (target of a T-cell response). Such technical and conceptual advances have catalyzed an upward trajectory of renewed enthusiasm for cancer vaccines and placed them directly back onto a path of accelerated development, underscored by recent reports of at least 3 positive phase III controlled clinical trials of cancer vaccines in diverse tumor types, including melanoma, lymphoma, and prostate cancer, for which the first-in-class regulatory approval of a cancer vaccine was granted by the U.S. Food and Drug Administration in May 2010 (Provenge; refs. 2–4). There is optimism that
these 3 recent successes herald the development of other such therapeutic vaccines for cancer.

One question is whether 'cancer' vaccines can ever be applied in the setting of primary cancer prevention (prevention of tumor development)? One can certainly point to commercially available vaccines against human papillomavirus and hepatitis B as examples of vaccines which prevent cervical and liver cancer, respectively, but strictly speaking, both are vaccines against viruses (albeit cancer-related) rather than against neoplastic cells. However, several studies in animal models now suggest that targeting antigens directly expressed by tumors with vaccines can prevent cancer development. For example, Jaini and colleagues (5) targeted the breast-cancer antigen alpha-lactalbumin with a vaccine containing the recombinant protein mixed with complete Freund’s adjuvant, which provided significant protection against development of autochthonous tumors in transgenic mouse models of breast cancer. Because this antigen is a breast-specific differentiation protein conditionally expressed only during lactation (and on human breast carcinoma cells), there was no collateral inflammation of normal, nonlactating breast tissue. Therefore, it was proposed for development as safe prophylaxis against breast cancer development in postchild-bearing women. Beatty and colleagues (6) targeted a true tumor antigen, human mucin 1 (MUC1), an epithelial mucin aberrantly expressed during chronic inflammation and colorectal carcinogenesis, with a long peptide vaccine corresponding to the extracellular region of MUC1. This vaccine in an adjuvant (a substance which provides nonspecific immune stimulation) prevented progression to colon cancer in a mouse model of inflammatory bowel disease that progresses to colitis-associated colon cancer. The vaccination was associated mechanistically with induction of MUC1-specific antibodies and cytotoxic T cells, which eliminated abnormal MUC1-bearing cells in colons with inflammatory bowel disease.

The report by Berta and colleagues in this issue of the journal (7) takes this concept of prevention one step further. Here the authors show that a DNA vaccine against an archetypal oncoantigen, ERBB2, which is transiently overexpressed in Syrian hamsters during chemical carcinogenesis, can reduce the severity of intraepithelial and invasive oral lesions. There are some minor quibbles with the robustness of the results. For example, true protection was not observed as a result of vaccination and the magnitudes of differences observed between immunized and control hamsters in severity of intraepithelial and exophytic lesions seem small, although they are statistically significant. Since studies addressing the expression of ERBB2 in human intraepithelial oral lesions have yielded conflicting results, one could also question how well the model mimics the human condition. The finding of specific antibody responses which correlated inversely with pathological score in immunized animals, however, provides proof of principle that an immune response against an oncoantigen can impede progression of carcinogenesis. Unfortunately, the question of induction of antigen-specific T cells, which are felt to be even more relevant as effector cells recognizing and lysing human tumor cells (8, 9), is unanswered because of technical constraints of the model.

A recently reported clinical trial of a lymphoma vaccine also provides potentially relevant information, as it is an example of secondary cancer prevention (or the prevention of recurrence). Previous preclinical studies in animal models showed optimal antitumor effects of the identical vaccine in the setting of minimal residual disease rather than against advanced tumor burdens (10), and a phase II study validated this strategy in patients (11); based on these data, a randomized double-blind, controlled multicenter phase III clinical trial was conducted to formally determine the clinical efficacy of this vaccine, which consisted of the unique B-cell–receptor protein isolated from the surface of each patient’s tumor, coupled to a carrier protein, and mixed with an adjuvant. The investigators selected follicular lymphoma as the target disease, taking advantage of the frequent remissions followed by inevitable relapse after standard chemotherapy in this low-grade lymphoma. Therefore, patients with previously untreated follicular lymphoma were treated with uniform chemotherapy, and patients with a complete remission (CR) were then randomized to receive either active or a control vaccine (consisting of carrier protein and adjuvant). The primary endpoint was disease-free survival. Of 234 enrolled patients, 177 had a CR and were subsequently randomized to receive either active or control vaccine. Of these 177 patients, 117 maintained remission for a 6-month interval between the end of chemotherapy and beginning of vaccination (a rest period to allow for immune reconstitution) and thus were eligible to receive vaccine therapy. This prospective, modified intent-to-treat analysis included 76 patients on active vaccine and 41 patients on control vaccine. The two arms were balanced for International Prognostic Index and other relevant clinical factors. After a median follow-up of 56.6 months (range 12.6–89.3 months), median time to relapse after randomization was 44.2 months (active vaccine) versus 30.6 months (control vaccine arm; P = 0.045; HR = 1.6; ref. 2). Two other phase III trials of similar lymphoma vaccines subsequently reported negative results, but only the first of these 3 trials used an induction program associated with a high CR rate and then restricted vaccine treatment to CR patients. It is tempting to speculate that minimal residual disease, as exemplified by CR, is necessary for the clinical antitumor effect of this lymphoma vaccine.

Another recent example of an effective cancer vaccine in the secondary prevention setting is a glioblastoma multiforme vaccine tested in a phase II trial (12). This trial gave a vaccine consisting of an epidermal growth factor receptor variant III (EGFRvIII) peptide to 18 patients with newly diagnosed EGFRvIII-expressing glioblastoma multiforme who had minimal residual disease after surgical resection of more than 95% of tumor volume. The vaccine’s 6-month progression-free survival rate was 67% and median overall survival was 26 months. After adjustment for age and performance status, overall survival strongly favored vaccinated patients compared with a control group...
matched for eligibility criteria and prior temozolomide treatment (HR = 5.3,

\( P = 0.0013 \)).

Taken together, these recent developments suggest the time is ripe for extending cancer vaccines, arguably the ultimate targeted therapy, to the prevention setting. Well-recognized potential target diseases include indolent hematologic tumors such as chronic lymphocytic leukemia and Waldenstrom’s macroglobulinemia, which do not require cytotoxic treatment in an early, asymptomatic stage, and premalignant conditions such as monoclonal gammopathy of uncertain significance and, considering the work of Berta and colleagues, high-risk oral intraepithelial neoplasia. In the interest of safety including avoiding collateral damage to normal tissues, another high-priority area for investigation is suitable candidate tumor antigens to target with vaccines; target antigens could be absolutely tumor-specific (expression restricted to the tumor, never by any normal tissues), such as the one targeted by the customized lymphoma vaccine discussed earlier (2), or could be transiently expressed on normal tissues (e.g., alpha-lactalbumin, ref. 5), or could have a pattern of expression restricted to normal tissues which are relatively expendable for survival (e.g., prostate-specific antigen). Finally, it will be exciting to integrate vaccines for cancer therapy or prevention with emerging new agents designed to release immune suppression, a barrier normally associated with established tumors (13) but potentially operative in the setting of premalignant disease as well.

**Disclosure of Potential Conflicts of Interest**

The author reports the following potential conflicts of interest: Paid consultant of Biovest International; paid consultant of and holds equity in Antigenics; holds equity in Xeme BioPharma, Inc; and receives research funding from Celgene.

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