*Perspective*

# The Ultimate in Cancer Chemoprevention: Cancer Vaccines
*Perspective on Beatty et al., p. 438*

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## Abstract

This perspective on Beatty et al. (beginning on page 438 in this issue of the journal) discusses the role of the immune system as nature's ultimate chemoprevention agent. A successful immune response to vaccination results in immunologic memory. In the case of a successful cancer-related response, antigen-specific T cells will be poised to destroy an aberrantly expressed protein even if the host is not exposed until years after the end of immunizations. After the abnormal cell is eradicated, T cells will lie in wait for the next exposure. The ability to develop effective cancer vaccines for prevention is fast becoming a reality as immunogenic aberrant proteins that drive malignant transformation are identified. *Cancer Prev Res; 3(4); 406–9. ©2010 AACR.*

Vaccines that target pathogens are one of the most successful approaches for preventing disease in humans. Worldwide, vaccines prevent an estimated nearly 6 million annual deaths, and the U.S. incidence of infectious diseases commonly targeted by childhood vaccinations has decreased by 99% (1). Vaccines have eradicated smallpox and nearly eradicated polio (2), and numerous newer vaccines that were introduced in the last decade have had significant success in preventing both bacterial and viral infections. The successes of vaccines for preventing infections have led to the exploration of immune-targeting vaccine approaches for preventing and/or treating a variety of presumably noninfectious diseases including Alzheimer's disease, atherosclerosis, and even nicotine addiction, to name but a few (3–6).

Tumor-associated-antigen vaccines developed to treat cancer have been in clinical trials for decades and are, at last, showing some success in randomized phase III therapy studies, raising hope for their future use in clinical cancer prevention (7, 8). In this issue of the journal, Beatty et al. report that active immunization against MUC-1, a well-described tumor antigen, can prevent the development of cancer in a MUC-1–expressing transgenic mouse model of inflammatory bowel disease that progresses to malignancy (9). The study makes several important observations. First, tumor-associated antigens that are not related to a particular infection can induce protective antitumor immunity. Second, vaccination can elicit a protective response even when chronic inflammation, the initiator of malignancy, is prevalent in tissues. Last, immunization can modulate the tumor microenvironment toward enhancing a protective immune response.

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It is important to acknowledge that infection-related human cancers can be prevented by vaccination. Hepatitis B is a major risk factor for hepatocellular carcinoma, and a recent study of hepatitis B–vaccinated and unvaccinated individuals in Taiwan showed that the incidence of hepatocellular carcinoma was significantly lower in the vaccinated cohort (64 cases in 37,709,304 person years) compared with the nonvaccinated individuals (444 cases in 78,496,406 person years), for a vaccinated cohort relative risk of 0.31 ($P < 0.001$; ref. 10). Human papillomavirus (HPV) vaccines have shown efficacy in preventing HPV-associated cervical, vulval, and vaginal intraepithelial neoplasia (IEN) and malignancy by preventing HPV infection (11, 12). Cancers caused by chronic infection with any of a variety of viruses or other pathogens, however, account for less than 20% of all cancers worldwide (13).

The majority of immunogenic tumor-associated proteins that have shown some evidence of antitumor efficacy when targeted by immunotherapy are, for the most part, "self" antigens (14), or normal cellular proteins that became immunogenic during the malignant process. There are several potential mechanisms by which a normal cell regulatory protein becomes aberrant in cancer and, thus, immunogenic. For example, overexpression of cancer-associated proteins (e.g., HER-2/neu) can result in enhanced immunogenicity (15). Aberrantly glycosylated proteins, such as MUC-1, can undergo increased uptake by specific antigen-presenting cells (APC), thus increasing the potential for the initiation of an immune response (16). Frameshift mutations induced by microsatellite instability, which cause fine alterations in the amino acid sequence of proteins, also can cause a self protein to become immunogenic (17). These abnormal alterations, which result in immune self-recognition of the premalignant or malignant state, may also allow the immune response to have some specificity for preinvasive or invasive disease rather than for normal cells. The specificity of the immune response to abnormally expressed self proteins may limit concerns about the induction of generalized autoimmunity. In the mouse study of Beatty et al. (9), active immunization

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against MUC-1 certainly did not result in increased inflammation, either by symptoms or histology, and presumably no significant autoimmunity was observed. These data are encouraging for the translation of cancer vaccines targeting self proteins to the prevention setting in patients with no signs or symptoms, but with a high risk, of cancer.

When vaccination is contemplated against tumor antigens in high-risk patients, it is not known whether the immunization will be prophylactic/preventive or therapeutic. These patients may already have IEN or occult invasive disease. The ability to image or assess occult lesions before vaccination often is limited in many sites. Beatty et al. showed a statistically significant decrease in disease development in immunized mice compared with controls, but the protective effect was not 100% (9). Was the failure of vaccine in some mice due to some characteristic of the induced immune response, to the vaccine targeting only a single antigen, or to the presence of occult IEN or invasive cancer at the time of immunization? There are few instances where vaccination after exposure to the infectious pathogen results in disease eradication. For example, HPV vaccines have efficacy in preventing the development of cervical IEN or cancer by preventing chronic infection but are of little efficacy in the treatment of cervical IEN (18). After host exposure to a viral or tumor antigen, the adaptive immune response requires time for T cells to clonally expand and achieve therapeutic levels.

Figure 1 depicts the theoretical outcomes of cancer-specific vaccination in relation to different states of disease burden. In the earliest prevention setting, individuals completely without IEN or invasive disease are vaccinated to a level of immunity considered to be protective (Fig. 1A). When IEN or cancer subsequently develops, immunologic memory induced via vaccination will result in the rapid immune recognition of the neoplasia and brisk proliferation of the adaptive immune response, eradicating the neoplasia before it gains a foothold. If vaccination begins after initiation of the malignant process, including IEN, a greater level of immunity may be required (versus immunity in the first setting; Fig. 1B). If the lesion is low volume and slow growing, sufficient therapeutic immunity may be reached to control the IEN progression to malignancy or even low-volume invasive disease. In some cases, the individual may have already developed an endogenous tumor-specific immune response simply by virtue of exposure to the lesion, as did the tumor-bearing mice in the MUC-1 antigen study (9). T-cell immune responses to a growing tumor are often nonfunctional, and the T cells may preferentially secrete type II cytokines, such as interleukin-10 and interleukin-4, and can enhance cancer growth by suppressing the development of CTLs (19–21). Last, vaccination in the face of established cancer with high tumor burden is often ineffective (Fig. 1C; ref. 22). Immunosuppressive cells in the tumor microenvironment limit the proliferation of T cells induced via immunization.

Immunization against MUC-1 in mice that were clinically free of cancer but had inflammatory bowel disease induced antigen-specific CTLs, implying that the character of the generated immune response was not completely immunosuppressive, that is, the T cells were not solely secreting type II cytokines (9). CTLs proliferate in a type I cytokine environment. Type I cytokines, which are secreted by antigen-specific T cells, elicit an IFN-γ–rich tumor microenvironment that is needed for APC activation. APC activation results in cross-priming (a mechanism by which tumor antigens are presented to T cells by APCs after taking up the antigens and processing them immunologically), which leads to the generation of tumor-specific CTLs capable of directly killing the tumor (as shown by Beatty et al.). Recent data on immunizing patients with vulval IEN support the notion that type I immune responses are critically needed for eradication of disease and can be elicited with immunization (23). Twenty grade 3 vulval IEN patients were immunized with peptides derived from HPV. At a postvaccination follow-up of 12 months, nearly 50% of these patients had complete resolution of disease. Complete response was associated with high levels of vaccine-induced IFN-γ–secreting cluster of differentiation 4 (CD4) and CD8 T cells.

This recent work was the first demonstration that vaccination may be effective in treating IEN. Many HPV vaccines designed to prevent infection focus on the generation of an antibody response requiring type II T cells. Vaccine strategies that elicit a predominant type I cellular immune response, which generates high levels of IFN-γ–secreting T cells and CTLs, most likely are a more effective approach for eradicating postexposure, preinvasive disease. It is not currently known whether such vaccines would be effective in the pre-exposure setting. A better understanding of the nature of the type I response needed for disease regression will lead to more effective vaccine approaches for protecting against and/or resolving occult IEN and potentially low-volume invasive disease in high-risk patients.

The immunosuppressive effects of the tumor microenvironment are significant (Fig. 1C; ref. 24), and the observation that active immunization beneficially modulated the tumor microenvironment supports the potential for vaccines to suppress preinvasive or occult invasive disease (9). The tumor-specific T cells induced by immunization may directly combat environmental immunosuppression by locally secreting type I cytokines. Systemic levels of myeloid-derived suppressor cells (MDSC) were decreased in mice that received the MUC-1 vaccine versus in controls. MDSCs can inhibit adaptive immunity (25). Evidence suggests that increased expression of IFN regulatory factor 8, a member of the IFN-γ regulatory factor family, can block the immunosuppressive functions of MDSCs, further supporting the rationale for using prophylactic vaccines to generate type I immunity (26, 27). A recent study of active immunization in advanced-stage breast cancer patients also showed a link between active modulation of the tumor microenvironment and type I T cells. Peptide pools, or fragments of the HER-2/neu protein, were used to immunize patients against the overexpressed self tumor antigen HER-2/neu and generated high levels of both antigen-specific CD4 and CD8 IFN-γ–producing T cells (28). The magnitude of the elicited type I immune response
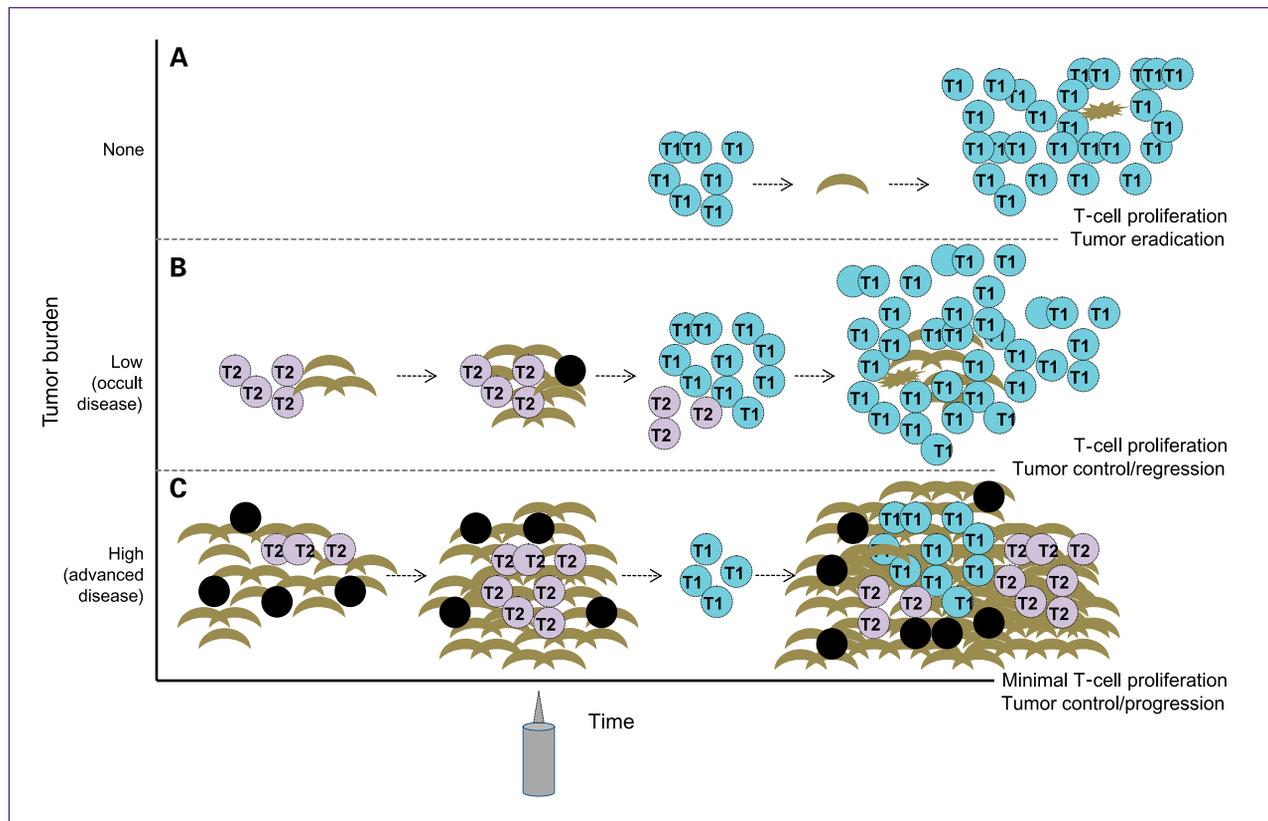
**Fig. 1.** Vaccine efficacy in relation to tumor burden. The syringe below the horizontal axis (time) indicates vaccination. A, when individuals have no disease, the elicited immune response is primarily type I (T1) T cells induced by vaccination (blue circles). On exposure to IEN or cancer (brown crescent), the T cells proliferate and eradicate disease (far right). B, when patients have occult IEN or low-burden invasive disease, a preexisting type II (T2) response (violet circles) may exist. Type II cytokines may depress immunity and recruit additional immunosuppressive cells, such as MDSCs or T regulatory cells (both represented by black circles). Vaccination may elicit a predominant type I response (blue circles), and type I T cells will proliferate to control or even potentially eradicate the neoplasia (far right). However, the type II T cells may prevent complete eradication of the neoplastic cells. C, in patients with advanced-stage disease, immunosuppressive factors in the tumor microenvironment can be overwhelming. Proliferating cancer further recruits suppressive cells. Active immunization at this stage generates low levels of immunity. T-cell proliferation is inhibited at the site of the tumor, resulting in minimal control and eventual progression of disease.

correlated with the magnitude of decline in serum levels of transforming growth factor-β in these advanced-stage patients. Transforming growth factor-β is secreted by immunosuppressive CD4 T cells (T regulatory cells) and APCs (29). These subtypes of immune system cells are naturally trying to limit the immune responses against "self" and provide a protective inhibitory response against the development of autoimmunity. Because most tumor antigens are self-proteins, generating cancer-destructive immunity is a battle against regulatory mechanisms inhibiting self destruction. In the immunization study involving advanced breast cancer, a decrease of transforming growth factor-β in the tumor microenvironment resulted in the benefit of enhanced cross-priming, as evidenced by the development of epitope spreading after immunization in the majority of patients (28).

Work of the last several years has generated knowledge that will allow the clinical translation of cancer vaccines into the cancer prevention setting. A multitude of tumor antigens comprising almost every malignancy has been identified, and clinical trials of vaccines targeting self antigens in patients who have or had cancer have produced little toxicity. Furthermore, immune responses elicited with cancer vaccines administered over a few months have persisted over time, which would allow occasional booster immunizations to maintain protective immunity, in contrast to cancer-preventive agents that require years-long daily dosing. Cancer vaccines have shown evidence of efficacy in controlled trials, and the type of immune response to a cancer vaccine that will be needed for cancer prevention is becoming increasingly known. It is time to focus on cancer vaccines as cancer chemoprevention agents with a high likelihood of success.

## Disclosure of Potential Conflicts of Interest

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