Immunotherapy for Advanced Prostate Cancer

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The absence of curative therapies for advanced or recurrent forms of prostate cancer mandates continued development of novel, more effective treatment regimens. Due to recent advances in basic and translational research, therapeutic vaccines and monoclonal antibody-based therapies are steadily gaining ground as promising treatment modalities against prostate cancer. Several immunotherapeutic products have recently been investigated in later-phase trials and have reported evidence for clinical benefit while maintaining an excellent quality of life for participants. The cumulative clinical results available to date indicate that immune-based therapies will likely play a role in the treatment of patients with prostate and other malignancies. The objective of this article is to increase awareness of contemporary immunologic therapies and clinical trials of new biologic reagents against prostate cancer. We also seek to encourage urologists to actively participate in clinical trials and evaluate the potential of immunotherapeutic drugs for impacting standards of care.

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Prostate cancer will affect an estimated 1 in 5 males in the United States, and approximately one third of diagnosed men will present with locally advanced or metastatic disease.[1] Although primary and secondary hormonal manipulations effectively delay disease progression, toxicities are considerable and eventually hormone-refractory disease (HRPC) will develop, which is ultimately fatal. Aside from palliative options, the only Food and Drug

Administration (FDA)–approved systemic therapy for men with HPRC is docetaxel (Taxotere®; sanofi-aventis U.S. LLC, Bridgewater, NJ), which yields only a 2-month survival advantage at the expense of significant treatment-related toxicities, thus limiting this therapy mainly to patients with symptomatic disease.[2] Due to the lack of effective treatment options, intense efforts are under way to develop more specific, targeted therapies designed to improve the prognosis and quality of life of patients with advanced or recurrent prostate cancer, particularly those without cancer-related pain, many of whom elect not to pursue systemic chemotherapy. Immunotherapy is an investigational form of biological therapy that exploits the immune system to delay or halt malignant growth either by targeting tumor-associated antigens (TAAs) or by disrupting molecular pathways that promote tumor growth.

Among the many biological treatments that mediate immunologic antitumor responses, 2 general forms have advanced to the final phase of human testing, the last step before FDA approval is sought. These approaches revolve around therapeutic cancer vaccines designed to elicit antitumor T-cell responses, or monoclonal antibody drugs with intrinsic immunologic properties.

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Cancer vaccines are unusual from several points of view when compared with conventional drugs and even monoclonal antibodies. First, their mechanism of action is indirect and relies on an intact host immune system. Also, their efficacy in clinical settings is dependent on multiple and largely unknown factors that vary greatly depending on the specific immunologic approach. The objective of this review is to inform the urologic community of both contemporary immunologic therapies and ongoing clinical trials of new biologic agents against prostate cancer. We also seek to encourage urologists to actively participate in clinical trials and evaluate the potential of immunotherapeutic drugs to impact standards of care.

Cancer Vaccines

Vaccines have been part of the therapeutic arsenal against infectious diseases since they were first introduced to prevent smallpox more than 200 years ago. The underlying mechanism making vaccines so successful is the stimulation of protective immune responses directed against target antigens that are expressed by the infectious agent but not by the host's own cells. In cancer settings, this prophylactic approach has proven highly effective for a few malignancies known to be caused by infectious agents. For example, vaccination with classical hepatitis B has shown to reduce the incidence of hepatocellular carcinoma.[3] Also, Gardasil® (Merck & Co, Inc., Kenilworth, NJ), a quadrivalent human recombinant vaccine against human papillomavirus (HPV) types 6, 11, 16, and 18, has shown to be highly effective in young female adults against strains of HPV that are responsible for about 70% of all cervical cancers and most vaginal and vulvar cancers.

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The application of therapeutic cancer vaccines differs fundamentally from these preventative approaches because they are applied in patients with existing disease, predominantly advanced or metastatic carcinomas. A second distinction relates to the immunogenicity of the antigen targeted by the vaccine. Whereas viral antigens are exclusively expressed by the infectious agent, most TAAs are not cancer specific, but rather represent self-antigens that are overexpressed or reactivated in the cancer cell relative to the noncancerous cell of origin.[4] Because the immune system has already been exposed during ontogeny to these self-proteins, they are not readily recognized as a foreign protein, a process called tolerance. Multiple mechanisms confer immunological tolerance to host proteins, so that aberrant or exaggerated autoimmune responses can be prevented. Tolerance occurs both centrally by deleting T cell precursors in the thymus and peripherally due to intrinsic or tissue-specific factors. Moreover, recent studies demonstrate that tumor or surrounding stromal cells secrete soluble proteins like granulocyte-macrophage–colony-stimulating factor

(GM-CSF), interleukin-10 (IL-10), or transforming growth factor β (TGF-β) that cause local or systemic immunosuppression. These proteins mediate infiltration of tumors by regulatory T cells and myeloid suppressor cells which, in turn, suppress immune responsiveness through secretion of nitric oxide or reactive oxygen species.[5]

Despite many obstacles, several observations provide a compelling rationale to support continued development of biologic therapies, particularly in prostate cancer patients. First, due to its intrinsic low proliferative index, most prostate cancers are resistant to many cytotoxic drugs.

Cumulatively, tumor-derived factors mediate conditions that foster the proliferation, survival, and metastatic potential of tumor cells. Without a doubt, the induction of therapeutic immune responses against established tumors is more challenging than preventing cancers. Therefore, potent strategies are required to produce immune responses with a therapeutic impact in the cancer patient.

Rationale for the Development of Prostate Cancer Vaccines

Despite these obstacles, several observations provide a compelling rationale to support continued development of biologic therapies, particularly in prostate cancer patients. First, due to its intrinsic low proliferative index, most prostate cancers are resistant to many cytotoxic drugs. Active or passive immunotherapy does not rely on high cell proliferation, and can be directed against any gene product expressed by prostate cells and prostate cancer cells. Second, there is ample evidence from multiple clinical trials demonstrating that the majority of prostate cancer patients can, in fact, mount a vigorous antitumor response despite their advanced age and disease status.[6,7] Because prostate cancer is commonly a slowly progressing disease, multiple vaccinations or boosting is possible, thereby allowing sufficient time to develop a potent antitumor response. Moreover, highly relevant prostate TAAs have been identified that can serve as authentic targets even at metastatic sites.[8] Third, recent data suggest that there is considerable synergy between cancer vaccination and hormonal ablative therapy, which, in combination, boosts the expansion of vaccine-induced effector cells. Therefore, active immunotherapy against prostate cancer could be most efficacious when administered after androgen ablation.[9] Further supporting evidence for this new concept was provided by the demonstration that sex steroids such as testosterone or estrogens can be immunosuppressive by stimulating tumors to secrete TGF-β, a cytokine that promotes the expansion of immunosuppressive regulatory T cells.[10,11]

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The discussion above suggests that the patient pool for clinical prostate cancer immunotherapy trials must be carefully selected, as therapeutic vaccines are only suitable for patients who have an intact immune system capable of responding to the vaccine and who carry slowly progressing disease. A vaccine administered to a patient with fast-progressing metastatic disease is unlikely to be effective because induction of an immune response takes time and the patient may be immunocompromised as a result of his or her condition. Therefore, the recent investigational focus has shifted toward subjects with minimal tumor burden and to the treatment of patients in the adjuvant setting, with the expectation that lower tumor burden and improved immunocompetence may positively alter the clinical response to therapeutic vaccination.

A major obstacle hindering the clinical development of novel therapeutics is the fact that advanced prostate cancer is a particularly troublesome disease when it comes to classification and assessment of clinical benefit. Prostate-specific antigen (PSA), widely used as a clinical indicator and marker of response, has long been the focus to serve as a potential marker to demonstrate drug effectiveness. However, due to its lack of specificity, especially in HRPC, the FDA has not accepted PSA as a surrogate marker for clinical benefit, and prolongation of overall survival remains the legal standard for drug approval in the United States. Due to slow disease progression often observed in prostate cancer, it can literally require a decade or more to determine whether one treatment has prolonged overall survival when compared with another regimen. The lack of appropriate biomarkers with which to more rapidly predict treatment benefit is unequivocally accepted as a major hurdle that hinders accelerated development and investigation of novel prostate cancer therapies.

Monoclonal Antibody–based Strategies

Monoclonal antibody (MAb)–based approaches were the first form of immunotherapy to receive FDA approval for the treatment of patients with

solid or hematopoietic malignancies. MAbs such as rituximab (anti-CD20) and trastuzumab (anti-erbB2) represent a fast-growing class of cancer therapeutics in the rapidly expanding market for oncologic drugs.[12] For patients with metastatic prostate cancer, a variety of MAb-based approaches are currently being developed. These include unconjugated antibodies that target and kill cancer cells by enhancing complement fixation or by initiating antibody-dependent cell-mediated cytotoxicity. Unconjugated antibodies may also exert antitumor activity by modulating signaling pathways mediated by specific MAb binding to cell surface antigens or receptors. Antibodies can be conjugated with radioisotopes, cytotoxic agents, or immunotoxins, and thereby used as a carrier to deliver radioactive or cytotoxic compounds in a targeted manner directly to the cancer cell. Therapeutic antibodies currently being investigated for prostate cancer include those that target tumor-associated antigens (TAAs), such as PSA, mucin, prostate-specific membrane antigen (PSMA), and cell surface receptors such as the epidermal growth factor receptor (EGFR) and the human epidermal growth factor receptor 2 (HER2/neu).[13]

Aside from targeting prostate or prostate tumor–associated antigens, MAbs have also been used to directly activate T cell function by either inhibiting regulatory receptors or activating immunostimulatory receptors. For example, cytotoxic T lymphocyte–associated protein 4 (CTLA-4; CD152), a molecule expressed on activated T cells, has been identified as a major regulator of T cell function.[14] CTLA-4 competes with coactivating CD28 for binding of B7-1 and B7-2 on antigen-presenting cells (APCs), thus causing down-modulation of T cell activity. Conversely, abrogation of CTLA-4 using an antibody induces systemic, but unspecific, immune activation. Accordingly, it was shown that transient blockade of CTLA-4 function using an anti-CTLA-4 MAb can lead to enhanced antitumor immunity in mice both alone and when used in combination with a vaccine.[15] In a transgenic murine model of prostate cancer, the coadministration of CTLA-4 MAb and a vaccine consisting of autologous tumor cells genetically engineered to secrete GM-CSF reduced the incidence and histological severity of prostate cancer and led to autoimmune prostatitis in normal mice, suggesting an antigen-specific immune response against self-antigens involved in tumor rejection.[15] This autoimmunity is believed to result from an unmasking and/or activation of pre-existing T cells with reactivity to normal prostatic tissues. Subsequent studies corroborated the notion that CTLA-4 blockade could serve as a useful adjunct to antigen (Ag)-specific immunotherapy to potentiate the vaccine-induced antitumor responses.

In recent years, multiple antibodies blocking human CTLA-4 have been identified and entered clinical development. Two antibodies, CP-675,206 and MDX-010 (ipilimumab), have already advanced to registration trials conducted in patients with various solid malignancies. In prostate cancer settings, MDX-010 has been tested in several phase I/II studies either as monotherapy or in combination with chemotherapy, immunotherapy, and vaccines. All these studies revealed that intravenous administration of MDX-010 was safe and elicits clinical activity. Interestingly, clinical responses are typically associated with unique and characteristic inflammatory-type manifestations, termed immune breakthrough events (IBEs), that may include enterocolitis, dermatitis, and hypophysitis.[16] Most recently, CTLA-4 antibodies have been combined with vaccine- or peptide-based strategies in an attempt to direct the vaccine-induced immune responses toward targeting tumor antigens.[17]

In contrast to CTLA-4, 4-1BB (CD137) is an immunostimulatory cell surface receptor expressed by activated CD4+ and CD8+ T cells.[18] Engagement of the 4-1BB receptor has shown to relay strong costimulatory signals within activated T cells resulting in their enhanced proliferation and cytokine secretion, preferentially within the CD8+ T cell subpopulation.[19] BMS-66513 (Bristol-Myers Squibb, New York, NY), a fully human antibody with specificity for CD137, is currently being investigated in various tumor models, including HRPC, and clinical trial results are expected to be announced in late 2007. Preliminary experience from ongoing clinical trials suggests clinical activity as well as autoimmune manifestations that are distinct from those observed after CTLA-4 MAb administration.

In summary, CTLA-4 or 4-1BB targeted therapy carries considerable promise in the treatment of human cancer, albeit at the cost of inducing autoimmune manifestations. The challenge will be how to control these toxicities as we have learned to deal with the toxicities of currently employed conventional regimens.

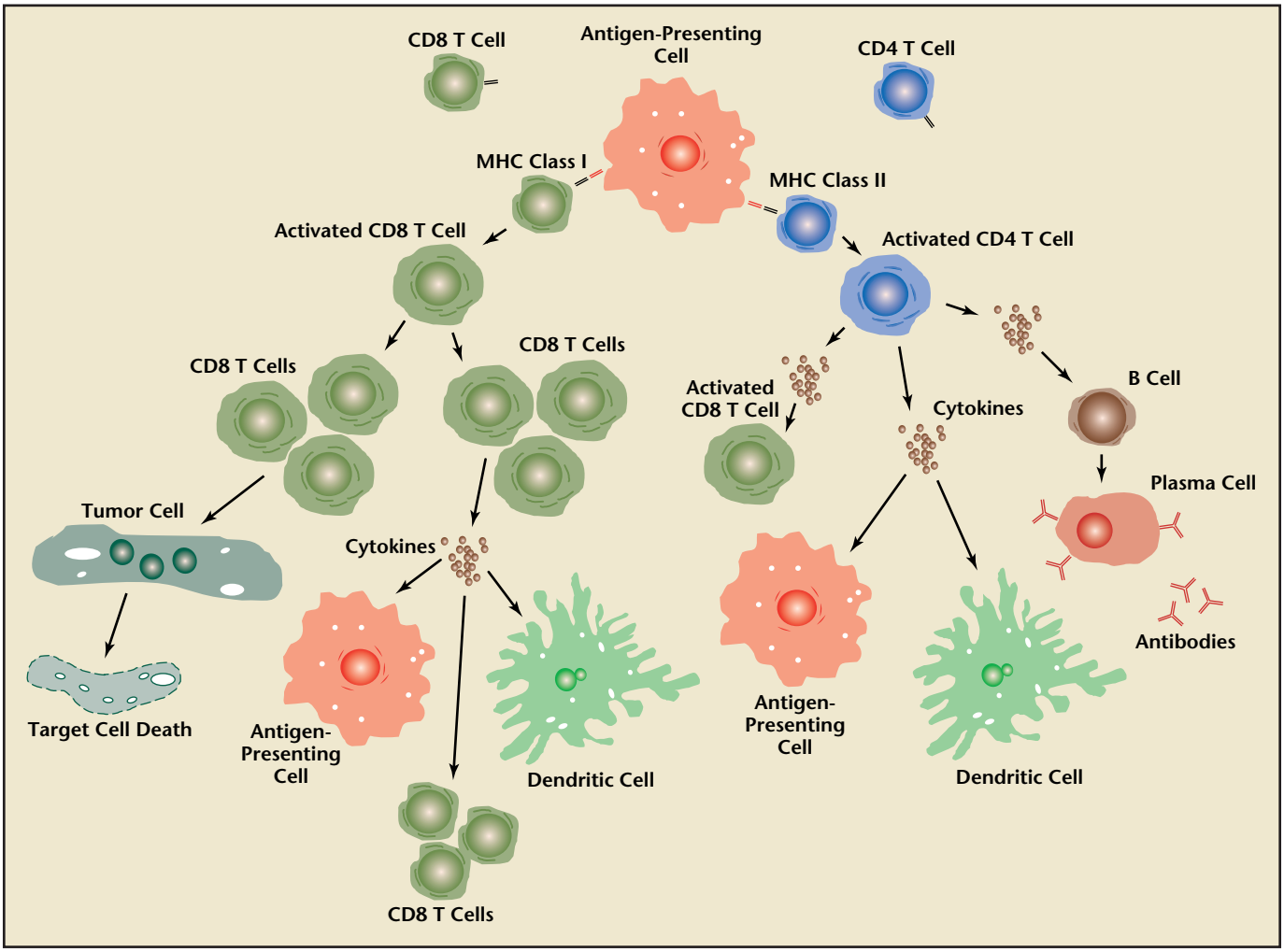
Prostate Cancer Vaccines

In contrast to the unspecific immune activation achieved by CTLA-4 or 4-1BB targeted therapy, therapeutic cancer vaccines are capable of inducing T cell responses with exquisite specificity for cell surface–based or even intracellular TAAs. Cancer vaccination exerts immunologic activity by priming naïve T cells that bind to TAAs in context with molecules of the major histocompatibility complex (MHC). Each T cell receptor binds exclusively to its cognate MHC–antigen complex,

which ensures the specificity typical of cellular immunity. Mechanisms that facilitate efficient T cell recognition rely on (a) effective antigen presentation, (b) MHC class I and II expression by tumor cells, and (c) costimulation during dendritic cell (DC)–T cell interaction in lymphatic organs. Also, it is known that endogenously synthesized antigens (membrane proteins) are presented on MHC class I, but not on MHC class II, molecules, while exogenous proteins (secretory and some membrane proteins) that are internalized by fluid phase absorption or receptor-mediated endocytosis are presented mainly in context with MHC class II, and to a lesser extent, with MHC class I, molecules[20] (Figure 1).

Recent insights into the molecular pathways that control the growth of human tumors have provided new opportunities to develop vaccine-based strategies that not only target TAAs, but also cellular proteins with critical roles in oncogenesis. Mechanisms that regulate tumor cell proliferation, control resistance to apoptotic signals, enable escape from the immune response, promote new blood vessel formation, and facilitate stromal–epithelial interactions are increasingly well-understood. As a result, immune-based approaches that specifically target these individual pathways have been developed and

Figure 1. *Regulation of immune responses by antigen-presenting cells (APCs). APCs such as dendritic cells acquire antigens from pathogens or malignant cells. These antigens are then presented in context with MHC molecules to either CD8+ T cells (cytotoxic T lymphocytes) or to CD4+ T helper cells. Upon DC-T-cell contact, T cells become activated and acquire specificity for the antigen presented by the APCs. CD8+ T cells travel via the peripheral bloodstream to tumor sites or virally infected cells (target cells) and upon cell contact exert their destruction. Activated CD4+ T cells augment CD8+ T-cell responses through release of cytokines such as IL-2. They can also mediate antibody responses against tumors by activation of B-cells and plasma cells. DC, dendritic cell; MHC, major histocompatibility complex.*



are currently undergoing clinical evaluation.

Several vaccine approaches against prostate cancer have successfully moved on to the final phase of human testing and are currently being considered for drug approval. These approaches entail either cell-based vaccines using autologous or allogenic cellular products in the form of antigen-loaded DCs or gene-modified tumor vaccines (GMTVs). In addition, the therapeutic potential of recombinant gene technologies has recently been realized in numerous clinical trials around the globe. Future success of these biologic products and their regulatory approval will facilitate the development of emerging classes of immunotherapeutic drugs for prostate and other cancers. The following is a discussion of 4 vaccine strategies that serve as examples for the many biologic drugs that are relevant to the treatment of metastatic prostate cancer.

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Sipuleucel-T (APC8015, Provenge®; Dendreon Corporation, Seattle, WA) is an active cellular immunotherapy product that consists of autologous antigen-presenting cells (APCs) that have been generated from peripheral blood mononuclear cells (PBMCs) using a proprietary elutriation process. The apheresis-derived APCs are loaded and activated in vitro using a recombinant fusion protein composed of human prostatic acid phosphatase (PAP) linked to GM-CSF. The rationale for using PAP as a target antigen is based on the fact that PAP is overexpressed in more than 95% of prostate cancers[21] and that it contains several epitopes that can be recognized by MHC class I–restricted cytotoxic lymphocytes.[22,23] Sipuleucel-T is administered as a freshly manufactured product to patients via intravenous infusion for a total of 3 applications every other week. A large body of preclinical studies has demonstrated that the loading of APCs with the PAP/GM-CSF fusion protein leads to their activation, as evidenced by upregulation of the cell adhesion molecule CD54. Most importantly, the PAP-loaded APCs have shown their capability to stimulate proliferation of PAP-specific T-cells in vitro.

Several clinical studies conducted in recent years have shown that intravenous administration of sipuleucel-T is generally well tolerated, with mild-to-moderate infusion-related fevers and rigors as the most common adverse events. This vaccine approach has also demonstrated biological activity by stimulating PAP-specific T cell responses in HPRC patients. In one published study, PAP was immunologically recognized as a target antigen in 40% of the patients, and 3 out of 20 subjects exhibited a decline in serum PSA levels of more than 50%.[24]

Data as evidence for the clinical activity of sipuleucel-T are derived from 2 identically designed phase III randomized multicenter trials conducted in men with asymptomatic metastatic HRPC. Both studies enrolled 127 and 98 subjects, respectively, that were treated with sipuleucel-T or placebo, using time to disease progression as the primary endpoint. Although both studies failed to meet the primary endpoint, there was a statistically significant improvement in patient survival for men treated with the drug, compared with those who received placebo. The median survival of men treated with sipuleucel-T was 26 months, 4.5 months more than patients who received the placebo vaccine. Based on these results, the company is currently enrolling additional HRPC patients into another, ongoing phase III registration study that includes overall survival as the primary endpoint. Although at present no prospective data exist to confirm the clinical activity of sipuleucel-T, the company plans to file a biologic licensing application with the FDA in 2007. This vaccine is currently on the FDA "fast track" for approval and, if successful, it would become the first clinically available therapeutic cancer vaccine in the United States.

DCVax®-Prostate (Northwest Biotherapeutics, Bothell, WA) is another autologous DC-based vaccination platform that has recently advanced to phase III clinical testing. In contrast to sipuleucel-T, which targets human PAP, DCVax®-Prostate consists of autologous, monocyte-derived dendritic cells that have been loaded with a recombinant form of PSMA. PSMA is highly expressed by prostate tumors and other malignancies (eg, brain, kidney, or bladder), as well as on the surface of new blood vessels induced by neoplastic growth.[25] After antigen loading, the PSMA-expressing cells are cryopreserved and stored until administered to the patient. DCVax®-Prostate is administered via the intradermal route for a total of 4 injections weekly. The skin is critically involved in immune reactivity due to the abundance of professional APCs that effectively prime specific immune responses by capturing,

processing, and presenting antigens to naïve T cells in the draining lymph nodes.[26] Data from an as yet unpublished phase I/II clinical trial enrolling 32 patients with HRPC demonstrated the safety of DCVax®-Prostate, as well as the induction of strong immune responses, with approximately 85% of the patients exhibiting a PSMA-specific T cell response after vaccination. Moreover, this trial suggested delayed time to disease progression, especially in patients with rising PSA but without measurable metastatic disease at study entry. Based on these data, the DCVax®-Prostate manufacturers received recent funding for a phase III clinical trial in men with HRPC that was approved by the FDA in January of 2005. This ongoing trial is a randomized, multicenter, double-blinded clinical trial designed to enroll 612 patients with hormone-refractory, nonmetastatic prostate cancer in the United States. The primary endpoint for this trial is time to disease progression; secondary endpoints include the development of symptomatic disease, induction of immune responses, and overall survival.

GVAX® (Cell Genesys Inc., San Francisco, CA) is a vaccine composed of allogeneic prostate tumor cells, genetically engineered to secrete GM-CSF. GVAX® is, after sipuleucel-T, the second most advanced cancer vaccine platform developed to date. The scientific rationale for the clinical use of GMTV was based on murine studies demonstrating specific and long-lasting antitumor immunity after vaccination with autologous, GM-CSF gene-modified tumor vaccines. These effects were attributed to the influx of DC into the vaccination site, as well as to their activation through locally secreted GM-CSF.[27] Vaccination with GM-CSF secreting GMTV has been evaluated clinically in patients with metastatic tumors including prostate,[28] renal,[29] and other malignancies and has demonstrated safety and preliminary indications for clinical efficacy. Although autologous prostate cancer cells may theoretically be the best source of prostate cancer antigens for eliciting therapeutically useful immune responses, recent studies have demonstrated that allogenic prostate carcinoma cells may also serve as useful sources of prostate cancer antigens for prostate cancer vaccine construction. The important advantage of this approach is the scalability and "off-the-shelf availability" of allogeneic, as opposed to autologous, tumor cells, the latter of which are often unattainable and difficult to culture.

For prostate cancer, an allogenic GVAX® cell product comprising GM-CSF gene-modified LNCaP and PC-3 prostate cancer cells is currently being tested in clinical trials, both as a single agent and in combination with chemotherapy, radiation, molecularly targeted therapies, and other modulators of the immune response. In 2 phase II studies presented at the annual meeting of the 2006 American Urological Association (AUA), GVAX® was shown to be immunogenic and generally well tolerated in HRPC patients with radiologic evidence of disease but without bone pain.[30] No dose-limiting toxicities were observed in a 24-week dose escalation trial that included a prime-boost strategy in patients with metastatic androgen-independent prostate cancer (AIPC). Adverse effects associated with GVAX® administration were mild to moderate, with the most common being flu-like symptoms and injection-site reactions. One of the phase II trials showed that immunization with the vaccine is associated with a median survival of 26.2 months, and the other, larger trial showed stable or decreasing levels of PSA as well as reductions of type I carboxyterminal telopeptide (ICTP), an indicator of osteolytic activity. Considering that the historical average survival for patients using the current standard of care is approximately 18 months, there appears to be a significant benefit, to be confirmed in ongoing phase III trials. It is important, however, to keep in mind that comparing results from an uncontrolled trial to historical figures can be misleading, and no drug effect should be assumed from comparisons with historical control data. GVAX® allogeneic cell therapy is currently being evaluated in 2 ongoing phase III trials in symptomatic and asymptomatic patients with metastatic HRPC and any Gleason score. One trial will compare the vaccine with docetaxel/prednisone chemotherapy while the second study will evaluate whether the vaccine plus chemotherapy improves on chemotherapy alone. Endpoints of both studies include the assessment of overall survival, changes in PSA, time to progression, and survival in subjects receiving the GVAX® vaccine versus patients receiving chemotherapy. In summary, the clinical data available support the notion that GMTVs engineered to secrete GM-CSF are well tolerated and may impact the outcome of patients with metastatic HRPC.

PROSTVAC®-VF (Therion Biologics Corporation, Cambridge, MA) is a vaccination platform developed in partnership with the National Cancer Institute (NCI). PROSTVAC®-VF is a recombinant vaccinia viral expression cassette engineered to contain a copy of the human PSA gene as well as a triad of costimulatory molecules (B7-1, ICAM-1 and LFA-3). The latter is believed to enhance and sustain the antitumor immune response.[31]

PSA has long been a prime antigenic target for prostate cancer vaccination due to the fact that its expression is highly prostate specific and retained even in hormone-refractory disease. Three phase I clinical trials

performed with a prototypic recombinant vaccinia PSA vaccine, termed PROSTVAC, have demonstrated only minimal toxicity in men with HRPC.[32] A major drawback of this particular strategy is that vaccinia viruses are highly immunogenic after previous exposure (vaccination), thereby leading to the generation of neutralizing antibodies and T cell responses against viral proteins expressed by previously infected cells. In order to circumvent this problem, prime-boost strategies using alternate viral vectors have been developed that have shown to enhance antitumor immunity. For example, the combination of a PSA-expressing vaccinia virus cassette (for priming) and a nonreplicating fowlpox virus (for boosting) has recently been studied in clinical trials, and may represent one way to enhance anti-PSA immunity in patients with advanced prostate cancers. In a phase II study, researchers reported stabilized PSA levels and reduced clinical progression in prostate cancer patients following treatment with this "prime–boost" protocol in HRPC patients who have rising PSA levels but no evidence of metastases.[33] At 24 months post-treatment, 53% of patients treated with varying sequential vaccinations of PROSTVAC remained stable (PSA progression-free) for 6 months or more. Additionally, 78% of all patients who received the vaccine remained free of metastatic prostate cancer. Clinical trials designed to evaluate the effects of vaccination in different stages of disease and through different routes of administration have been completed to better define the optimal schedule for PROSTVAC in patients with metastatic prostate cancer, or for those patients at high risk of developing the disease.

Such extensive clinical trials of multiple vaccine components and prototypes have led to further optimization of the vaccine, by modifying the vector to include a triad of costimulatory molecules aside from the PSA gene (PROSTVAC®-VF). Using this novel platform, a phase II randomized, double-blind, placebo-controlled clinical trial of PROSTVAC®-VF was conducted in men with advanced prostate cancer. In this study, 125 patients with asymptomatic HRPC were enrolled. The primary endpoint of the study was progression-free survival, defined as the proportion of patients who remained alive and progression free at the end of the 24-week study. Secondary endpoints included time to onset of pain, time to onset of opiate use, and overall survival. Unfortunately, this trial did not meet its primary efficacy endpoint of improving progression-free survival. However, subgroup analysis suggested that PROSTVAC®-VF was associated with a potential reduction in mortality compared with placebo. At the same time, the company reported negative results of a phase III clinical trial using a similar vaccine targeting carcinoembryonic antigen (CEA) in metastatic pancreatic carcinoma. At present, continued development of this novel vaccination platform is questionable, as the company was recently liquidated, subsequent to the failed trials.

Future Developments

The increasing number of immune-based, biologic therapies that have advanced to later-phase clinical testing is encouraging. Also, novel insights into prostate cancer biology and immunology have accelerated the efforts in many academic and industry research and development programs to bring new prostate cancer therapies into clinical reality. The increasingly large number of biologic therapies currently in clinical testing will, we hope, translate into an increase in the number of effective treatment options available for prostate cancer patients, particularly for the many with advanced or recurrent disease.

This review would be incomplete without a discussion of the future developments that will have major impact on the design and composition of immune-based therapeutics. To date, a host of prostate-associated or prostate cancer–associated antigens have been cloned and are being tested as a component of investigational therapeutic cancer vaccines.[8,20] Although several vaccine approaches target prostate-associated or prostate cancer–associated antigens such as PSA, PAP, or PSMA, prostate cancer is known to be a heterogeneous disease with a number of different genetic/pathophysiologic clusters. Personalized therapeutic strategies guided by the use of novel molecular diagnostic techniques (eg, imaging, gene chips) will be necessary to successfully test and define the utility of "targeted" agents in patients whose tumors depend upon the "target" for tumor growth or survival.

Because multiple pathways are involved to stimulate clinically effective antitumor immunity, achieving clinical success with biologic therapies will require the development of better patient preselection methods and combinatorial treatments that incorporate vaccines with cytokines, antibodies, small molecule–based reagents, or conventional therapies. Critical elements of such combinatorial approach include not only improved vaccine or antibody formulations, but also strategies to reverse tumor-mediated immunosuppression.[34] Fortunately, strategies exist to reduce the numbers of immunosuppressive regulatory T cells or immature myeloid cells in the cancer patient, thereby enhancing the efficacy of cancer vaccines or other immunologic reagents.[35]

It may also prove to be highly advantageous to combine vaccines or

monoclonal antibody drugs with traditional cancer therapies such as radiation therapy or chemotherapy, as these strategies have shown synergy by rendering tumor cells more susceptible to CTL-mediated lysis, by modulating the tumor microenvironment through release of cytokines or recruitment of DC, or by inducing lymphopenia-induced homeostatic proliferation of T cells.[36] Finally, the silencing of genes with immunosuppressive roles through small-interfering RNA (siRNA) or RNA aptamers has shown to improve the effectiveness of cancer immunotherapy in experimental animals or human systems.[37]

Progress to translate effective immunologic treatment combinations into the clinical arena, however, has typically been slow, as drugs are developed for safety reasons as a single agent and only subsequently in combination with other agents.[38] Moreover, access to many immunologic reagents is limited by complex licensing or patent restrictions involving various companies or other parties. Without question, these and other barriers have generated considerable frustration within the academic community, which stands ready to translate emerging new knowledge into effective immunotherapies. Finding solutions to these problems will require concerted and proactive measures from regulatory agencies, in cooperation with academic institutions and industry partners, so that promising reagents can be made available for clinical investigation. New models of meaningful academic–industry collaborations are urgently needed to take full advantage of individual strengths provided by each partner. Clinical assessment of combinatorial approaches through pilot trials that address important aspects of feasibility, safety, and bioactivity would provide important guidance regarding the design of later-phase clinical trials that directly address questions of clinical benefit. Such partnerships may eventually allow testing of combinatorial strategies based on sound scientific principles, rather than on availability of individual agents, which is often a major influence of drug development today. Without question, successful development of cancer vaccines will rely on a thorough understanding of the molecular events that modulate and enhance antitumor immunity and require cooperative efforts that facilitate further clinical translation. A multipronged approach will be necessary to generate superior biologic therapies with therapeutic impact. ■

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Main Points

- Due to the lack of effective treatment options, intense efforts are underway to develop more specific and targeted therapies. These therapies are designed to improve the prognosis and quality of life of patients with advanced or recurrent prostate cancer.
- Cancer vaccines are unusual from several points of view when compared to conventional drugs and even monoclonal antibodies because their mechanism of action is indirect and relies on an intact host immune system.
- A major obstacle hindering the clinical development of novel therapeutics is the fact that advanced prostate cancer is a particularly troublesome disease when it comes to classification and assessment of clinical benefit.
- For patients with metastatic prostate cancer, a variety of monoclonal antibody–based approaches are currently being developed. These include unconjugated antibodies that target and kill cancer cells by enhancing complement fixation or by initiating antibody-dependent cell-mediated cytotoxicity.
- Although several vaccine approaches target prostate- or prostate cancer–associated antigens, prostate cancer is known to be a heterogeneous disease with a number of different genetic/pathophysiologic clusters. Personalized therapeutic strategies guided by the use of novel molecular diagnostic techniques (eg, imaging, gene chips) will be necessary in order to successfully test and define the utility of "targeted" agents.
- Successful development of cancer vaccines will rely on a thorough understanding of the molecular events that modulate and enhance antitumor immunity and require cooperative efforts that facilitate further clinical translation.

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