

The Science Behind Developing Active Immunotherapies:

A Look at NHL
and Prostate Cancer
Therapeutic Vaccines

By Dianne Spena





Therapeutic vaccines for cancer have been “just over the horizon” for decades. Thanks to an explosion of knowledge in the area of immunology, as well as the availability of new production technologies, the prospects for bringing a therapeutic cancer vaccine to market in 2007-2008 are tantalizingly close.

Several compounds are in Phase III development with Fast Track designation from the FDA. But, what exactly will it take for one or more of these compounds to successfully reach the market?

The first step for developers of therapeutic vaccines is to identify an antigen that is specific to a particular tumor type, and to find a way to package it so that it delivers maximum antigenicity and leverages the natural properties of the immune system. Most therapeutic vaccines for cancer consist of one or more antigens, which are often modified to increase immunogenicity and are combined with adjuvants and/or co-stimulatory molecules to boost immune cell function. (See sidebar: Antigen, Adjuvants, and Co-stimulators.)

According to Dan Gold, founder and Chief Scientific Officer of Favril, Inc., the choice of antigen is a huge issue in the development of a successful therapeutic cancer vaccine. Because cancer cells arise from normal cells and the

immune system is designed to prevent reactivity against self, individuals’ immune systems tend to tolerate cancer cells. For a therapeutic cancer vaccine to succeed, it must be able to overcome this tolerance and evoke a potent T-cell response to the patients’ cancer cells. The ideal antigen, therefore, should be highly immunogenic as well as tumor-specific.

In the case of lymphoma, lymphoma cells produce an antibody with a unique signature, or idotype, which is not found in normal tissues. Using the idotype from a patient’s own lymphoma cells and conjugating it with an adjuvant to enhance its antigenicity (keyhole limpet hemocyanin or KLH), then co-administering granulocyte macrophage colony-stimulating factor (GM-CSF) to stimulate the proliferation of antigen presenting cells, results in an autologous (patient-specific) vaccine therapy designed to elicit a vigorous, specific immune response against the patient’s lymphoma cells.

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The choice of which cancer type to target may be another key to success. B-cell non-Hodgkin's lymphomas (NHLs) may well be ideal targets for a therapeutic vaccine for several reasons. According to Dr. Gold, the idiotype proteins produced by B-cell lymphomas are "one of the few, if not the only, truly validated cancer antigens in human beings." Decades of testing at Stanford University and the National Cancer Institute (NCI) have shown that the idiotype proteins produced by B-cell lymphomas are highly antigenic, and capable of inducing a marked response by T-cells in humans. Indolent (slow-growing) B-cell NHLs have been a particularly attractive target for initial studies precisely because they grow slowly. This allows time for the patient to mount an immune response and for clinical benefits to emerge.

Genitope, Biovest, and Favrilite are three companies with therapeutic vaccines in Phase III trials for B-cell NHL. Although all three B-cell NHL vaccines use a similar antigenic strategy, there are essential differences in how they are formulated and produced, including the type of cell line used to produce the patient-specific idiotype, which may influence antigenicity, the technologies used to produce and manufacture the vaccine, and dosage and administration. There are also key differences in how these products are being studied in clinical trials.

Genitope is presently conducting a Phase III study of MyVax® Personalized Immunotherapy (GTOP-99) in previously-untreated patients with follicular NHL (f-NHL), an indolent form of NHL. Following 8 cycles of CVP (cyclophosphamide, vincristine, prednisone) chemotherapy to induce remission, patients who respond are randomized to receive 7 immunizations of MyVax (patient-specific idiotype + KLH) in conjunction with injections of GM-CSF or non-specific immunotherapy (KLH + GM-CSF) over a 24-month period. (A six-month rest period between the end of chemotherapy and the initiation of MyVax therapy allows the immune system to recover from chemotherapy.)

The primary endpoint is progression-free survival. Long-term follow-up from an open-label Phase II study of patients with follicular B-cell NHL in first remission following chemotherapy showed a significant increase in time-to-progression of NHL compared with historical controls.

Also in Phase III development is Biovest's BiovaxID®. In the BiovaxID Phase III protocol, patients with f-NHL undergo chemotherapy with cyclophosphamide, doxorubicin, etoposide, and prednisone to induce remission. After a six-month rest period, patients are randomized to receive either a series of patient-derived idiotype-specific vaccinations plus KLH and GM-CSF or KLH and GM-CSF alone. The primary endpoint of this study is disease-free survival. This trial is still currently enrolling patients.

Favrilite, on the other hand, is taking a different approach altogether with its ongoing Phase III study of FavID®. This study includes mostly treatment-naïve patients (80%) and some relapsed/refractory patients with f-NHL. Patients are first treated with the monoclonal antibody Rituxan® [rituximab; Genentech] to induce remission. After 8 weeks, patients who respond to Rituxan therapy are randomized to receive a series of treatments with FavID (patient-specific idiotype plus KLH) in conjunction with GM-CSF or placebo in conjunction with GM-CSF.

Dr. Gold of Favrilite believes that the use of Rituxan rather than cytotoxic chemotherapy to induce remission in FavID clinical trials sets it apart from Genitope's and Biovest's products. Because Rituxan has become the standard of care for newly-diagnosed f-NHL, he maintains that this protocol better reflects real-life treatment of f-NHL. The primary endpoint for this trial is time-to-disease progression (TTP). In an interim analysis from December 2006, the Data Monitoring Committee reported that there was no difference in the secondary endpoint of response improvement. Nonetheless, the company expects to be able to meet its primary endpoint when final data are reviewed in 2007.

Genitope, Biovest, and Favrilite are three companies with therapeutic vaccines in Phase III trials for B-cell NHL.

While the anti-idiotypic approach is appropriate for B-cell NHL and other immune system cancers, other cancer types may require different antigen strategies. That's the challenge facing developers of therapeutic vaccines for prostate cancer. Because the antigens that have been identified in human prostate cancer tend to be expressed in normal tissues and over-expressed in cancer cells, there is greater natural tolerance to these antigens, and thus, a higher hurdle to overcome in eliciting an immune response strong enough to produce clinical benefits. Nevertheless, according to Charles Ryan, an oncologist specializing in prostate cancer at UCSF, animal models have identified several prostate-associated antigens capable of eliciting T-cell responses. These findings are facilitating development of a therapeutic vaccine for prostate cancer.

There are three compounds currently in Phase III development for advanced prostate cancer, each using a different antigen plus adjuvant. Some of these vaccines are autologous while others are allogeneic (non-patient-specific). Provenge® [sipuleucel-T; Dendreon Corp.] uses an autologous approach. First, dendritic cells (DCs) are extracted from the patient's blood through a process called leukapheresis. DCs are professional antigen-presenting cells that facilitate the development of an immune response to the antigen. These dendritic cells are then exposed *ex vivo* to a prostate-associated antigen, prostatic acid phosphatase (PAP), and GM-CSF, resulting in primed, patient-specific DCs that are sensitized to PAP.

In one Phase III study (D9901) in patients with asymptomatic androgen-independent prostatic cancer (AIPC), sipuleucel-T was associated with a trend toward benefit in the primary endpoint, time-to-objective disease progression (TTP). Long-term follow-up data showed a significant increase in overall survival for patients who received sipuleucel-T. These follow-up survival data form the basis for Dendreon's Biologics License Application (BLA), which has received Priority Review status from the FDA.

A separate Phase III study in similar patients (D9902A) was halted early so that the protocol could be amended to

measure survival, resulting in D9902A being underpowered. Although D9902A showed no difference between the sipuleucel-T and placebo groups for the primary or secondary endpoints, there was a trend in favor of sipuleucel-T. These promising, but inconclusive, results have prompted a larger, redesigned Phase III study, the IMPACT study, which is currently enrolling patients.

Other therapeutic vaccines for prostatic cancer take the allogeneic road. GVAX® [Cell Genesys] is an allogeneic whole-cell vaccine consisting of tumor cells genetically modified to secrete GM-CSF. Because it is not limited to a particular prostate-associated antigen, GVAX vaccine elicits T-cell responses against a broader array of tumor-associated antigens and may be more likely to elicit B-cell responses as well. According to Dr. Ryan, there may be advantages to the broader coverage of antigens provided by GVAX compared with Provenge, which "puts all its eggs in the prostatic acid phosphatase basket." Whether this broader antigen approach results in identifiable clinical benefits is unclear.

GVAX is presently being studied in two Phase III trials: VITAL-1 is comparing GVAX with docetaxel administered with prednisone in asymptomatic metastatic HRPC patients; VITAL-2 is comparing GVAX plus docetaxel to docetaxel plus prednisone in symptomatic metastatic HRPC patients. Both studies are designed with test survival benefits.

According to Dr. Ryan, it may be an advantage for Genitope if VITAL-1 and VITAL-2 show that GVAX is effective alone as well as in combination with docetaxel because it increases the clinicians' options in treating metastatic HRPC and may permit reimbursement for both scenarios.

GVAX is also being studied as a way to prime anti-prostate tumor responses before administration of MDX-010 [Medarex], an investigational therapy designed to block CTLA-4, a negative co-regulator that turns off activated T cells. [cont. on pg 14 >>](#)



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Vaccines that use viruses as vectors represent a third avenue for stimulating an immune response. PROSTVAC®-VF [Therion] has three distinct components: two separate viral vectors, an allogeneic prostate-specific antigen, and three co-stimulatory molecules that boost the immune response to the antigen. PROSTVAC-VF is administered in a series, beginning with an initial dose to prime the immune response, followed by repeated booster vaccinations to sustain the response.

Results of a randomized, placebo-controlled Phase III study of PROSTVAC-VF in patients with asymptomatic metastatic AIPC did not meet the primary endpoint: progression-free survival. However, there was a trend toward improved overall survival in a subset of patients who were not taking bisphosphonates at the time of study entry. Based on this positive trend, a Phase III trial is planned in patients with AIPC without overt metastatic disease, who are unlikely to be receiving bisphosphonates. The primary endpoint will be time-to-overt metastatic disease.

The results of these clinical trials may shed light on some of the big questions facing vaccine developers; namely: Is it more effective to target multiple antigens, or a single one? Do the putative advantages of patient-specific versus non-patient-specific vaccines translate into real clinical benefits that justify the additional time and expense required to produce them? The answers to these questions are likely to drive the next wave of therapeutic cancer vaccine development.

Transforming Treatment Paradigms

There's little doubt that therapeutic vaccines have the potential to transform treatment paradigms. For Dr. Ryan, who studies therapeutic vaccines in prostate cancer, they represent a less toxic option that may complement the effects of other strategies for prostate cancer, including chemotherapy. The favorable toxicity profile of therapeutic vaccines is a particular advantage in patients with HRPC,

who tend to be elderly and less able to withstand the rigors of chemotherapy.

With regard to B-cell lymphoma, Dr. Gold believes FavID could transform the way NHL is treated. Hopefully, patients who receive a course of Rituxan followed by FavID will experience prolonged survival without the consequences of cytotoxic chemotherapy, keeping the patient alive longer and with a better quality of life. Furthermore, Dr. Gold says, by giving FavID before chemotherapy, “we haven't burned any boats,” so that the full range of therapeutic options—whether cytotoxic chemotherapy, further doses of Rituxan, or potentially more FavID—remain available to the patient.

Changing How We Think About Therapeutic Cancer Vaccines

Ultimately, another key to the success of therapeutic vaccines may be changing the way we think about them—and study them. There's a growing perception that therapeutic vaccines may be more successful at stabilizing disease or containing small tumors than causing actual tumor regression. In addition, patients who are heavily-pretreated with cytotoxic chemotherapy and/or radiotherapy may be unable to mount an effective immune response in response to vaccination. For these and other reasons, vaccine developers are conducting additional studies in patients with less advanced disease and smaller tumor burden, and testing their compounds before or in combination with cytotoxic chemotherapy, rather than after exhaustive chemotherapy. They are also using endpoints that may more accurately measure how vaccines affect disease (e.g., measuring survival rather than tumor regression).

Clearly, the ultimate measure of success for developers will be the approval and launch of these new therapies. **NS**

Nomenclature

Is it time to change the way we refer to therapeutic cancer vaccines? The very phrase “cancer vaccine” may conjure up images of banishing cancer forever, like the eradication of smallpox, and may blur the distinction between preventive and therapeutic vaccines. Some of the experts consulted for this article, including some vaccine developers, prefer the term “active immunotherapies” when referring to therapeutic vaccines, in part to avoid confusion with vaccines such as Gardasil® (quadrivalent human papilloma virus type 6, 11, 16, 18; Merck) and hepatitis B vaccines that prevent infection with viruses that may lead to the development of cancer.

THERAPEUTIC CANCER VACCINES FOR NHL AND PROSTATE CANCER IN PHASE III DEVELOPMENT

Vaccine	Type of Cancer	Vaccine Strategy	Phase III Trials
BiovaxID™ (Biovest, Mass.)	Follicular B-Cell Non-Hodgkin's Lymphoma	Autologous vaccine using idiotype conjugated to KLH, combined with GM-CSF	Autologous vaccine using idiotype conjugated to KLH, combined with GM-CSF
MyVax® (Genitope Corp., Calif.)	Follicular B-Cell Non-Hodgkin's Lymphoma	Autologous vaccine using idiotype conjugated to KLH, combined with GM-CSF	Currently in trials in previously untreated patients; following debulking treatment with cyclophosphamide, vincristine, prednisone (CVP), patients receive MyVax® and GM-CSF
FavID® (Favrille, Calif.)	Follicular B-Cell Non-Hodgkin's Lymphoma	Autologous vaccine using idiotype conjugated to KLH, combined with GM-CSF	Currently evaluating its use in treatment-naïve and relapsed/refractory patients following Rituxan®
GVAX® (Cell Genesys, Inc., Calif.)	Prostate cancer	Allogeneic vaccine using whole tumor cells altered to secrete GM-CSF	Currently being studied alone versus docetaxel (VITAL-1) or in combination with docetaxel (VITAL-2)
Provenge® (Dendreon, Wash.)	Prostate cancer	Autologous vaccine using patient's dendritic cells pulsed ex vivo with prostate acid phosphatase and GM-CSF	Initial Phase III studies failed primary endpoint but showed trend toward overall survival; currently being evaluated in a redesigned study.
PROSTVAC®-VF (Therion, Mass.)	Prostate cancer	Allogeneic vaccine combining viral vectors, prostate associated antigen, and co-stimulatory molecules	Initial Phase III studies failed to show benefit in symptomatic patients with metastatic AIPC; new studies are underway.

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Antigens, Adjuvants, and Co-Stimulatory Molecules

Many therapeutic cancer vaccines today combine antigens and adjuvants in a way that draws the immune system's attention to the cancer cells and augments its response. Types of **antigens** currently being employed in cancer vaccines include:

- Sialyl Tn (STn), a small, synthetic carbohydrate that mimics the mucin molecules expressed by certain cancer cells.
- Heat shock proteins (HSPs), proteins produced in cells in response to stress signals, such as heat and low glucose levels. HSPs from a patient's tumor can be used as the basis for developing patient-specific vaccines for a variety of cancers, including liver, skin, colon, lung, lymphoma, and prostate cancers.
- Ganglioside molecules (GMs), complex molecules that are incorporated into the outside membrane of a cell, and make it more easily recognizable by antibodies. Because some human cancers express ganglioside molecules, GMs are a potential target for therapeutic vaccines.
- Carcinoembryonic antigen (CEA), a protein found in high levels in colorectal, lung, breast, and pancreatic tumors, which has been shown to stimulate T-cell responses.
- MART-1 and tyrosinase, which are both associated with melanin and are more abundant on melanoma cells than normal cells, and thus have been used in melanoma cancer vaccine development.
- Idiotoxes derived from antibodies produced by certain types of cancer cells.

Adjuvants are used to heighten the immune system's response to the selected antigen. Adjuvants are often weakened proteins or bacteria, and essentially act as a decoy, tricking the immune system into mounting an attack on both the tumor cells expressing the antigen and the decoy. Commonly used adjuvants include:

- Keyhole limpet hemocyanin (KLH), a protein made by a type of mollusk common to the coasts of California and Mexico. KLH causes a robust immune response and may also be used as a carrier for cancer cell antigens to increase their visibility to the immune system.
- Bacillus Calmette Guerin (BCG), an inactivated form of the tuberculosis bacterium that has been used for decades as a tuberculosis vaccine and also as an immunotherapy for bladder cancer. Adding BCG to a cancer vaccine may amplify the immune response.
- Interleukin-2 (IL-2), which has been shown to boost the cancer-killing ability of natural killer cells. When combined with an antigen, it may help direct the activity of natural killer cells against the antigen.

Granulocyte monocyte colony stimulating factor (GM-CSF) is a **co-stimulator**, a cytokine that stimulates the proliferation of antigen-presenting cells, such as dendritic cells. GM-CSF is being studied in therapeutic cancer vaccines, and alone, to augment the patient's immune response to cancer.