Constructing a Vaccine Against Cancer: a Complex Path to a Simple Goal

The possibility of destroying and/or preventing neoplastic disease by enlisting the patient’s own immune system has intrigued and excited clinical scientists for decades. However, the complexity of the human immune response, coupled with the innate characteristics of the tumor cells themselves, has made success elusive.

If there is a known etiologic agent for a disease, such as influenza or polio, vaccines are designed to be preventive and are administered to healthy people to protect against future exposures. In the case of cancer, however, few etiologic agents have been explicitly connected with specific cancers. Thus, most cancer vaccines have been designed as therapeutic agents, targeting tumor antigens instead of infectious agents and being administered to patients who usually have a significant tumor burden. Such vaccines, if successful at eliminating cancer cells, would have significant advantages over other treatment modalities currently available: they would be easy to administer and, because of their specificity, would be expected to have few significant side effects.

The human immune system can mount either a humoral or a cellular defense against foreign invaders. In the humoral response, important for traditional vaccines, B cells interact directly with unprocessed antigens, subsequently differentiating into either antibody-secreting plasma cells or long-lasting memory cells. In the cellular response, antigens are processed into small pieces, complexed with major histocompatibility
complex (MHC) proteins, and presented to T cells on the surface of professional antigen-presenting cells such as dendritic cells. Most strategies for constructing therapeutic vaccines against cancer are focused on eliciting a cellular response against cancer-specific antigens, typically the production of cytotoxic CD8+ T cells.

The basic concept of developing a vaccine that targets a specific tumor cell antigen is a simple one. Until recently, however, the history of research in this field has been one of limited success and unexpected difficulties. To construct an effective vaccine, researchers must address several problems. An appropriate antigen, or group of antigens, must be selected. The antigen must be effectively presented to the correct T cells. And regardless of the antigen selected or the type of vaccine constructed, specific cell types and substances that suppress any immune response against the tumor must be overcome.

During the last 10 years, new and powerful tools in molecular biology have allowed a more complete understanding of the immune process and the design of better strategies for vaccine development. In this issue, we review some of the exciting research and clinical trials in cancer vaccine development underway at Baylor Charles A. Sammons Cancer Center at Baylor University Medical Center at Dallas.
Is This the Year?

The cover of Time on March 29, 1954 had a picture of Jonas Salk and, in large type, “POLIO FIGHTER SALK.” In smaller type was the question, “Is this the year?” In regard to cancer vaccines, this question is repeated annually.

For those of us born in the baby boomer generation and subsequently, immunization for a variety of infectious diseases is routine. In my early memories, visits to the doctor always held the dread of getting “a shot,” whether it was the Salk vaccine, tetanus, or measles. As a child, I remember the elation that my friends and I felt when Sabin produced an oral vaccine.

The history of vaccines dates to the late 1700s and Jenner’s work in smallpox. The list of infectious agents for which successful immunization exists is long, but the search for cancer vaccines has been elusive. Unlike infections, cancer arises from an individual’s own cells. This increases the challenges when one directs the immune system to attack the cancer, because normal cells need to be spared.

Initial successes of vaccines against cancer came via the secondary benefit of developing immunity against viruses known to predispose to cancer. The first came in 1981 with the approval of a vaccine for hepatitis B virus, followed more recently by vaccines against human papillomavirus linked to cervical cancer. The challenges still lie in developing a vaccine that helps to cause a direct attack on an existing cancer. Recently the U.S. Food and Drug Administration approved a dendritic cell-based vaccine for prostate cancer, the first to be approved for cancer treatment (see page 14).

Researchers at Baylor Charles A. Sammons Cancer Center at Dallas, Baylor Institute for Immunology Research, Texas Oncology, and Mary Crowley Cancer Research Center are involved in a broad array of vaccine development and trials. Several of these are highlighted in the pages of this issue of Cancer Update. We hope that, through these efforts and those of others, it won’t be long until we can provide an affirmative answer to the question, “Is this the year?”

New Appointments at Baylor University Medical Center at Dallas

Congratulations to three new medical directors recently appointed at Baylor Dallas. Kartik Konduri, MD, is the new co-medical director of the Lung Cancer Center of Excellence. Carolyn Matthews, MD, is the new medical director of the Integrative Medicine Program. Dan McCoy, MD, is the new medical director of the Melanoma and Skin Tumor Clinic.

Cheryl Sampson, CCRP, MBA, joined Baylor Dallas as the new director of clinical oncology research coordination. In her new role, Ms. Sampson is responsible for the coordination and oversight of all oncology research conducted at Baylor Dallas, as well as the coordination of oncology research associated with non-Baylor entities such as Mary Crowley Cancer Research Center, Texas Oncology, US Oncology, and others that work collaboratively with Baylor Dallas. She will oversee oncology research among all parties to provide efficiency, lack of duplication, consistent communication, progress reports, adherence to stated goals and objectives, and complete follow-up.

(Continued on page 4)
Building Better Cancer Vaccines: Researchers on the Baylor Dallas Campus Are Using Diverse Approaches to Optimize Immune Response

According to Jacques Banchereau, PhD, director of the Baylor Institute for Immunology Research (BIIR), the field of cancer vaccines is in a renaissance mode. Researchers at Baylor Dallas are exploring multiple strategies to overcome the difficulties involved in constructing therapeutic vaccines against various types of cancer. Dendritic cells, the primary antigen-presenting cells central to the cellular immune response, are being grown and manipulated in the laboratory for use as vaccines against cancer. Innovative molecular biology techniques are being used to unravel immune alterations in cancer as well as identify biomarkers of clinical efficacy. Modern approaches are being used to stimulate the immune response and to reduce or eliminate naturally occurring immune suppressive factors. And recombinant off-shelf vaccines based on tumor-specific antigens grown in plants are being tested in multi-institutional clinical trials.

Dendritic Cell Vaccines

Under the direction of Dr. Banchereau, Karolina Palucka, MD, PhD, and Joseph Fay, MD, researchers at BIIR are developing and testing vaccines based on dendritic cells to treat a variety of cancers, including melanoma, pancreatic cancer, and breast cancer.

Dendritic cells are the master controllers of immune processes in the human body, critical for both creating and curtailing immunity. They are found in all tissues and in the blood, but are especially prevalent in peripheral tissues that interface with the environment (e.g., skin, mucosa). There, they act as highly motile sentinels, continuously sampling their environment for potentially dangerous cells or molecules. They capture and process foreign antigens, then migrate to secondary lymph organs where they activate other immune cells against the antigen. Dendritic cells are also important in the development of immune tolerance, preventing the immune system from attacking harmless substances or cells in the body.

New Appointments at Baylor University Medical Center at Dallas

Jennifer Williams has been named oncology events and community relations coordinator for Baylor Charles A. Sammons Cancer Center at Dallas. She will coordinate health fairs and screenings throughout the community to raise awareness of cancer prevention, detection, and research advances. An important function in this new position will be the dissemination of information about cancer clinical trials at Baylor Dallas to help further these advances.

Baylor Health Care System has collaborated with Pathologists Biomedical Laboratories, US Oncology, and Texas Oncology to establish med fusion, an advanced medical testing and clinical trials company located in Lewisville, Texas. The new company, which opened this spring, is focused on the emerging fields of molecular diagnostics and pharmacogenomics, including the analysis of the genetic makeup of tumors to guide treatment decisions. These high-end tests, which have previously been sent out of state for processing, will now be handled locally, resulting in faster results for patients and physicians.
All vaccines act through dendritic cells. Even skin vaccinations depend on the vaccine encountering dendritic cells in the skin in order to elicit an immune response. Because of this critical role in directing the body’s immune defense system, manipulating dendritic cells is an important strategy to pursue for cancer vaccine development.

The Biology of Dendritic Cells

A key characteristic of dendritic cells that can be exploited in the construction of vaccines is their plasticity: they will mature differently in response to different growth factors and cytokines. This variation is associated with different types of T cell-mediated immune responses.

In the skin, dendritic cells are present in different variants (subsets), including those called Langerhans cells, which induce the proliferation of cytotoxic CD8+ T cells.

The maturation of dendritic cells involves two distinct aspects of immunogenicity that occur sequentially. Immature (nonactivated) dendritic cells have the ability to process antigens and to form peptide-MHC complexes. However, they do not have the ability to produce the costimulatory molecules needed for an immunogenic response in T cells. They present self-antigens and other harmless molecules to the T cells to induce immune tolerance.

Captured infections and other foreign antigens induce the further maturation of dendritic cells, which are now able to produce the costimulatory molecules needed to influence T cell response. Activation factors for this process can include whole bacteria or bacterial antigens, inflammatory cytokines, or viral products, such as double-stranded RNA. Different maturation factors result in dendritic cells that direct different types of subsequent lymphocyte responses.

Melanoma Vaccines

Clinical studies in patients with stage IV melanoma. Three approaches to melanoma vaccines have been and/or are being investigated: (1) injecting a tumor-specific antigen with adjuvant, resulting in random in vivo targeting of dendritic cells; (2) injecting dendritic cells generated ex vivo from progenitor cells and loaded with tumor-specific antigen; and (3) injecting chimeric proteins resulting from the fusion of antidendritic cell antibodies and tumor-specific antigens, resulting in specific in vivo targeting of dendritic cells.

At BIIR, researchers have been working for over 10 years on dendritic cell vaccines that target melanoma. To date, most studies at BIIR have focused on the ex vivo generation and antigen loading of dendritic cells. For this procedure, either CD34+ stem cells or monocytes are removed from the patient’s blood by apheresis and grown in culture with selected

An Early Success Story that Fueled a Dream

Patient B was the first recipient of the dendritic cell-based cancer vaccine for melanoma. At the age of 59, he was diagnosed with melanoma that had metastasized to the brain. That tumor was removed, but he already had another lesion and was given only 3 to 6 months to live. In March of 1999, he began the dendritic cell vaccine program and received the first vaccine injection in April of that year. By summer, blood tests indicated that the vaccine had elicited a strong immune response, and magnetic resonance imaging and computed tomography scans showed that the lesion had disappeared. He continues to do well, with no evidence of disease.

New Grant Funded for Melanoma Vaccine

Karolina Palucka, MD, PhD of the Baylor Institute for Immunology Research has received a grant from the National Cancer Institute to carry out a phase I/I clinical trial with a second generation dendritic cell vaccine for melanoma.
growth factors that affect differentiation and maturation. Manipulation of these ex vivo growth requirements has been directed towards achieving the desired end product: dendritic cells that are functionally similar to Langerhans cells, capable of activating CD8⁺ cytotoxic T cells.

The first vaccine of this type that was tested in a clinical trial at BIIIR used CD34⁺ precursor cells, grown with granulocyte macrophage colony-stimulating factor (GM-CSF), fetal liver tyrosine kinase 3 (FLT3) ligand, and tumor necrosis factor α (TNFα) to yield dendritic cells. (In this protocol, TNFα also serves as a maturation factor for dendritic cells.) For the vaccine, the cells were loaded with control proteins and with peptides derived from 4 melanoma antigens. An enhanced immune response to >2 melanoma antigens was seen in 10 out of 16 immunologically responding patients, and cytolytic DC8⁺ T cell precursors specific for melanoma antigens were observed in 9 of 12 patients analyzed. At 10 weeks from study entry, 3 patients had no progression of disease, 4 patients with multiple lesions had regression at one or more disease sites, and 3 patients with only limited disease cleared any evidence of disease.

The analysis of long-term outcomes revealed an association between the breadth of melanoma-specific immunity and survival, i.e., patients who survived longer were those who showed the expansion of a broad repertoire of antigen-specific CD8⁺ T cells (>2 melanoma antigens presented on the DC vaccine). Three of these patients who were vaccinated between March 1999 and March 2000 are alive as of November 2009 and show no evidence of disease.

For a second clinical trial, several important parameters in this protocol were changed. First, monocytes were used as...
the precursor cells and grown with GM-CSF and interleukin 4 (IL4) to yield dendritic cells. These cells were activated with TNFα and CD40 ligand (a member of the TNF family) and then loaded with whole killed tumor cells, rather than individual peptides. This increases the number of potential antigens that might trigger an immune response and also increases the probability that the dendritic cells would present the antigens in a way that would be likely to generate cytotoxic CD8+ T cells. CD8+ immunity to the melanoma-specific antigen MART-1 was observed in 3 of 13 analyzed patients.

Two patients who mounted potent melanoma antigen-specific immune responses showed durable objective tumor regressions, i.e., a complete response (18 months) and a near complete response (55+ months) (overall 10% objective response rate). Both patients had failed other therapies while in stage IV.

Altogether, retrospective analysis of overall survival in a cohort of 66 patients accrued between 1999 and 2003 showed 20% long-term survival. These data now need to be confirmed in prospective randomized trials testing survival as a predefined clinical endpoint.

Two general observations come from these trials. First, the dendritic cell vaccines are extremely safe. The only common side effects reported were mild flulike symptoms for several days after the injections. Second, although a significant proportion of patients showed a tumor antigen-specific immune response, only a few showed a durable objective tumor regression. Several mechanisms have been considered for the lack of clinical response: (1) the cytotoxic CD8+ T cells may be unable to access the antigens on the tumor cells, e.g., because of low avidity or an inability to penetrate the tumor stroma; and (2) the presence of suppressor/regulatory T cells might inhibit the functions of cytotoxic CD8+ cells in the tumor microenvironment.

Two ongoing clinical trials at BIIR are designed to test whether clinical response rates to dendritic cell vaccines in patients with stage IV melanoma can be increased by pretreating patients with low-dose cyclophosphamide to eliminate or control naturally occurring suppressor T cells.

- In the 06-025 trial, the vaccine comprises dendritic cells generated from autologous monocytes using GM-CSF and interferon alpha, loaded with killed whole allogeneic melanoma cells and activated with lipopolysaccharide.

Patients receive low-dose cyclophosphamide (300 mg/m²) 24 hours prior to the first vaccination.

- In the 06-123 trial, the vaccine comprises dendritic cells generated from autologous CD34+ hematopoietic progenitors, loaded with melanoma peptides and control viral peptides and activated with lipopolysaccharide. Patients receive low-dose cyclophosphamide as described in the first trial.*

*The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

**New clinical study in patients with stage III melanoma.**

For ethical reasons, most phase I/II clinical trials for novel cancer treatments are performed in advanced-stage patients who have a significant tumor burden and whose disease has already progressed or recurred after multiple treatments. Unfortunately, this is the patient group that might be least likely to mount a robust immune response against their tumors, either because of poor physical status or because of depletion of their T-cell population after multiple courses of adjuvant therapy. To address this problem, researchers at BIIR are preparing to launch a clinical trial using a dendritic cell vaccine to treat patients with stage III melanoma. Patients will be recruited for this trial immediately after surgery, when they show minimal residual disease. Because the course of melanoma at this stage is somewhat indolent, a long time line will be required in this trial, with at least a 2-year follow-up.

**Other Dendritic Cell Vaccines**

Although the technology developed at BIIR to construct dendritic cell vaccines has focused on melanoma, it is readily adaptable to other cancer types.

**Pancreatic cancer.** Pancreatic cancer is the fifth most common cause of cancer death in the United States. The recent deaths of high-profile celebrities such as Luciano Pavarotti and Patrick Swayze from pancreatic cancer have sensitized the general public to the grim prognosis associated with this disease and the critical need for more effective treatments. A dendritic cell vaccine against pancreatic cancer should be ready for the clinic next year.

**Breast cancer.** Another cancer in need of more effective treatments is triple-negative breast cancer. This subtype of breast cancer is clinically negative for the expression of receptors for estrogen and progesterone and for the HER2
protein. Thus, although it can be treated with chemotherapy, it is not responsive to tamoxifen or trastuzumab. Triple-negative breast cancer has a high prevalence rate in young women and in women of African descent; it is aggressive and likely to recur after treatment.

Dr. Palucka is working to develop a dendritic cell vaccine against triple-negative tumors based on long peptides. Previous trials have loaded dendritic cells either with individual peptides or with whole killed cells. Using individual peptides is restrictive, but the use of whole cells means that much of the immune response will be difficult to monitor, since it is mounted against unknown antigens. CD8+ T cells typically recognize peptide fragments that are 8 to 10 amino acids long. When loaded with long peptides (20 to 50 amino acids), the dendritic cells take them up and process them into appropriately sized epitopes. In preclinical studies, Dr. Palucka is testing antigens characteristically associated with and overexpressed in cancer cells to select appropriate long peptides for this vaccine.

Human papillomavirus. Under the leadership of Gerald Zurawski, PhD, vaccination with chimeric proteins that fuse antibodies against dendritic cell–specific antigens with tumor cell–specific antigens is currently being investigated in preclinical models. The tumor-specific antigens used for the fused molecule can be either unique to a specific tumor or shared. While unique antigens tend to be more immunogenic, shared antigens lend themselves to a more broadly applicable vaccine that could be reproduced more cost effectively and made available to a wider range of patients. The chimeric approach has resulted in high levels of immune response in the mouse.

Baylor Research Institute (BRI) recently received funding from the National Institutes of Health to investigate the use of this
approach for the treatment of human papillomavirus (HPV), one of the most common sexually transmitted diseases. HPV affects 20 million people in the United States alone and is associated with nearly 70% of all cervical cancers. Existing vaccines against HPV are preventive and not effective when used in individuals already infected with the virus. With Dr. Zurawski as principal investigator, the funding will be used to create a therapeutic vaccine for the treatment of patients who are already infected with HPV. The vaccine will first be tested in a mouse model and, if successful, will progress to a human model.

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The Future of Dendritic Cell Vaccines

According to Dr. Banchereau, there is growing enthusiasm about the possibility that dendritic cell vaccines will become an important tool in cancer management. Clinical trials have shown promising results and minimal toxicity from first- and second-generation vaccines, and third-generation vaccines are now becoming available. New paradigms involving the treatment of early stage patients will be tested in clinical trials that measure time to progression and survival, rather than laboratory measures of immune response. “We are just at the beginning of a major revolution,” said Dr. Banchereau. “The coming decade will see impressive changes in the way we manage cancer.”

Other Strategies for Vaccines

Vaccine Research at Mary Crowley Cancer Research Center

A two-pronged approach for treating non-small cell lung cancer. Historically, non-small cell lung cancer (NSCLC) has been regarded as a nonimmunogenic cancer, and strategies for developing a vaccine to treat this deadly disease have met with little success. Researchers at Mary Crowley Cancer Research Center (Mary Crowley) are using the tools of molecular biology to genetically modify tumor cells to improve immune response. Under the leadership of Executive Director John Nemunaitis, MD, and Scientific Director Neil Senzer, MD, novel strategies are being pursued to simultaneously activate the immune system and block immune inhibitors produced by cancer cells.

GVAX: genetic manipulation of the immune response. A number of cytokines, including GM-CSF, have a positive impact on immune response, especially when given intracellularly. Based on this observation, the GVAX vaccine was developed by transfecting GM-CSF into autologous cancer cells. The vaccine was tested in a published clinical trial involving 33 patients with NSCLC who had failed previous treatment regimens. After GVAX injection with their own transfected cancer cells, 3 patients had a complete response, and two of these patients continue to be in remission beyond 8 years.

A downside to the use of GVAX is that it requires that a resectable tumor sample be available from which to harvest tumor cells to create the vaccine. This is not possible in all patients, so an allogenic vaccine was developed using cells from four NIH lung cancer cell lines using a different transgene TGFBeta2 antisense gene. The average published response rate to this new vaccine was similar to that seen with the autologous vaccine.

Five studies were carried out at Mary Crowley in which patients with NSCLC were treated with these vaccines, leading to some dramatic results. Six patients are still alive at 5 to 10 years after treatment. Importantly, there were no significant side effects from the vaccine in any patients.

Strategies for blocking immune inhibitors. While these results were promising, and suggest survival advantage measures to possibly increase response rates were of further interest. So, Mary Crowley investigators decided to try another approach: blocking transforming growth factor (TGF) β2, one of the most active inhibitors of the immune response. By incorporating an antisense oligonucleotide against TGF β2 into cancer cell lines, they were able to get a >35% downregulation of TGF β2 production. The 1- and 2-year estimated survival rates were 64% and 47% in the group of stages IIIB and IV NSCLC patients receiving the optimized doses, favorably comparing with an expected 20% survival probability in this same group of patients. A follow up published clinical trial testing efficacy at optimal dose confirmed prolonged survival.
Mary Crowley is on the cusp of new vaccine development for NSCLC. Overall, it is clear that a combination approach—stimulating the immune system and blocking immune suppression—works better than either approach alone. These nontoxic vaccines have been able to generate dramatic durable responses in a subset of patients, and researchers are now measuring components of the immune system to determine how responders differ from nonresponders. This work has also justified current ongoing trials involving a novel combination plasmid of the GMCSF and TGFbeta knockdown genes.

Defining New Targets for Vaccines against Breast Cancer

The HER2 molecule is a human growth factor receptor that can promote tumor cell proliferation in a variety of epithelial cancers, including breast cancer and ovarian cancer. HER2 gene amplification or protein overexpression is associated with an especially aggressive form of breast cancer.

The monoclonal antibody trastuzumab (trade name Herceptin®, Genentech), directed against the extracellular domain of the HER2 molecule, is designed to target and block the function of HER2. Its clinical efficacy is a function of direct binding to HER2, and it appears to be useful only in patients with high levels of HER2 overexpression, roughly 30% of patients with breast cancer. On the other hand, therapeutic vaccines comprising peptides from the extracellular domain of HER2 are designed to educate the immune system to attack breast cancer cells; they do not require a high level of HER2 overexpression and may be effective in 75% to 80% of women with breast cancer.

In early trials, patients vaccinated with the E75 peptide from the HER2 extracellular domain showed increased recurrence-free survival and a decreased rate of recurrence after responding to standard cancer therapies. The pattern of recurrence was significant, in that vaccinated patients did not experience metastasis to the bone, a common site of early metastasis in nonvaccinated patients.

Clinicians at Mary Crowley are currently participating in two clinical trials testing different vaccine strategies for the treatment of HER2-positive patients with high risk breast (studies 08-06 and 08-07) or ovarian cancer (study 08-07). The vaccines used in these trials are made from smaller peptides derived from the same protein as E75. The GP2 peptide is HLA-A2 restricted; because it will be presented in the context of a type I MHC protein, it will serve to activate cytotoxic CD8+ T lymphocytes. The AE37 peptide is not HLA restricted; it will be presented in the context of a type II MHC protein and activate helper CD4+ T lymphocytes. The combination of CD4+ and CD8+ activated T lymphocytes optimizes the immune response.

The Mary Crowley 08-06 trial is part of a single-blinded, multicenter phase II trial sponsored by Brooke Army Medical Center comparing four treatment arms in patients with early stage node-positive or high-risk node-negative breast cancer. HLA-A2-positive patients receive either a vaccine consisting of GP2 in combination with GM-CSF or GM-CSF alone. HLA-A2-negative patients receive either a vaccine with AE37 in combination with GM-CSF or GM-CSF alone. At the time of entry into the trial, patients will have completed standard primary breast cancer therapies as appropriate for their specific cancer. They will be clinically cancer free, but considered to be at high risk for recurrence.

The Mary Crowley 08-07 trial is part of a multicenter phase I study evaluating the use of GP2 and AE37 given together in combination with GM-CSF for the treatment of patients with HLA-A2+ or HLA-A3+ intermediate-to high-risk HER2-positive breast or ovarian cancer. As in the 08-06 trial, breast cancer patients will have completed standard therapies and be clinically disease free. Stage IIIIC or IV ovarian cancer patients will have received optimal debulking surgery and chemotherapy prior to enrollment in the trial. By including two peptides that are believed to activate the immune system in different ways, it is hoped that the potency of the vaccine will be enhanced compared with using either peptide alone.

Mary Crowley is a nonprofit clinical cancer research center offering patients innovative cancer therapies in clinical trials under the oversight of FDA. Mary Crowley focuses on new therapies targeting the molecular pathways that impact cancer
Plant-Based Vaccine Trial at Texas Oncology

Texas Oncology physicians on the medical staff at Baylor Dallas will be participating in a phase I clinical study to evaluate the safety and tolerability of an autologous idiotypic vaccine for patients with relapsed follicular lymphoma who are in complete or partial remission following salvage therapy.

Follicular lymphoma is a generally slow-growing type of non-Hodgkin’s lymphoma that arises in B cells. Every B cell has unique immunoglobulins on the cell surface, and the idiotypic antibodies found on the surface of malignant B cells are highly specific tumor markers. The basis of the vaccine is to isolate these specific proteins from the patient, grow them in vitro, tie them to a carrier, and inject them back into the patient. The vaccine will be produced from the patient’s own blood sample using the MagnaICON™ technology developed by Bayer Innovation GmbH. This process introduces a blueprint for the desired protein into tobacco plants using a species of soil bacterium as a carrier. The plant can quickly produce large quantities of the protein, which is then extracted from the leaves.

Because they produce few symptoms in their early stages, follicular lymphomas are usually not diagnosed until they are in advanced stages. At that point, even if treatment results in a remission, recurrences are very common. The aim in developing this vaccine is to keep patients in remission after they have responded well to chemotherapy. To participate in the trial, patients must have histologically proven follicular lymphoma in its first clinical relapse/progression requiring treatment and must have a lymph node or tumor that can be biopsied for use in manufacture of the vaccine.

Texas Oncology/Sammons Cancer Center is one of only two clinical sites in the United States that will be participating in this international trial.

Cancer research studies on the Baylor Dallas campus are conducted through Baylor Research Institute, Mary Crowley Cancer Research Center, Texas Oncology, and US Oncology. Each reviews, approves, and conducts clinical trials independently.
Clinical Trials on the Baylor Dallas Campus: Studies Investigating Cancer Vaccines

The following clinical trials at component institutions of Baylor Dallas are currently open and recruiting patients.

For more information about any of these trials, including additional information about inclusion and exclusion criteria, contact the Office of Clinical Oncology Research Coordination at 214.818.8472, or send an e-mail to cancer.trials@baylorhealth.edu.

Melanoma

**Study title:** Combined-modality treatment for patients with stage IV melanoma: cyclophosphamide and a dendritic cell vaccine loaded with killed allogeneic melanoma cells—a phase I/IIa trial.

**Study ID number:** BRI IRB# 006-025

**Principal investigator:** Joseph W. Fay, MD

**Sponsor:** Baylor Institute for Immunology Research

**Participating site:** Baylor Institute for Immunology Research

**Brief description of study:** The vaccine comprises dendritic cells generated from autologous monocytes using GM-CSF and interferon alpha, loaded with killed whole allogeneic melanoma cells and activated with lipopolysaccharide. Patients receive low-dose cyclophosphamide 24 hours prior to the first vaccination to eliminate or control naturally occurring suppressor T cells.

**Outcome measures:** Safety and tolerability of combination therapy; feasibility of combination therapy; objective clinical response according to RECIST criteria.

**Volunteers needed:** Patients with stage M1a-c biopsy-proven metastatic melanoma, aged 21 to 75 years, ECOG performance status 0 to 1.
**Study title:** Melanoma peptide-loaded dendritic cell vaccine in HLA-A*0201 patients with stage IV melanoma: a phase II randomized trial to compare vaccination with and without cyclophosphamide treatment.

**Study ID number:** BRI IRB#006-123  
**Principal investigator:** Joseph W. Fay, MD  
**Sponsor:** Baylor Institute for Immunology Research  
**Participating site:** Baylor Institute for Immunology Research

**Brief description of study:** The vaccine comprises dendritic cells generated from autologous CD34+ hematopoietic progenitors and pulsed with melanoma and viral peptides. Patients receive low-dose cyclophosphamide 24 hours prior to the first vaccination to eliminate or control naturally occurring suppressor T cells.

**Outcome measures:** Induction of melanoma-specific CD8+ T cell immunity; objective clinical response according to RECIST criteria.

**Volunteers needed:** HLA-A*0201-positive patients with stage IV melanoma between 21 and 75 years of age, ECOG performance status 0 to 1.

In the description of this study, the content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

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**Non-Small Cell Lung Cancer**

**Study title:** Phase III Lucanix™ vaccine therapy in advanced non-small cell lung cancer (NSCLC) following front-line chemotherapy (STOP).  
**Study ID number:** MCCRC IRB# 08-21  
**Principal investigator:** John Nemunaitis, MD  
**Sponsor:** NovaRx Corporation  
**Participating site:** Mary Crowley Cancer Research Center

**Brief description of study:** Belagenpumatucel-L (Lucanix™) is a nonviral gene-based allogeneic tumor cell vaccine that demonstrates enhancement of tumor antigen recognition as a result of TGF β2 inhibition. TGF β2, produced by tumor cells, is one of the most active inhibitors of the immune response.

**Outcome measures:** Overall survival; progression-free survival; quality of life; time to progression; overall tumor response.

**Volunteers needed:** Patients with stage IIIA (T3N2 only), stage IIIB, or stage IV NSCLC, 18 to 75 years of age, with stable disease or an objective response to a prior first-line platinum-based chemotherapy regimen, ECOG performance status ≤2.

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**Breast Cancer**

**Study title:** Prospective, randomized, single-blinded, multicenter phase II trial of the HER2/neu peptide GP2 plus GM-CSF vaccine versus GM-CSF alone in HLA-A2-positive or the modified HER2/neu peptide AE37 plus GM-CSF vaccine versus GM-CSF alone in HLA-A2-negative node-positive and high-risk node-negative breast cancer patients to prevent recurrence.

**Study ID number:** MCCRC IRB# 08-06  
**Principal investigator:** Joyce O'Shaughnessy, MD  
**Sponsor:** George Peoples, MD, Walter Reed Army Medical Center  
**Participating site:** Mary Crowley Cancer Research Center

**Brief description of study:** GP2 and AE37 are pieces of the HER2/neu protein, which is found on 60% to 70% of breast cancer cells. The peptide vaccines are mixed with GM-CSF, which stimulates the immune system.

**Outcome measures:** Disease recurrence; safety; toxicity.

**Volunteers needed:** Patients with HER2/neu-positive, node-positive or high-risk node-negative breast cancer. High risk is defined as any of the following: T2, grade 3, lymphovascular invasion, ER/PR negative, or N0(i+). Patients must be clinically disease-free, with ECOG performance status <2.
**Study title:** A multicenter phase I evaluation of the doublet MHC class I and II HER2/neu peptide vaccines (GP2 and AE37, respectively) in HLA-A2+ or HLA-A3+ patients with intermediate to high-risk breast or ovarian cancer.

**Study ID number:** MCCRC IRB# 08-07; BRI IRB# 010-007

**Principal investigator:** Neil Senzer, MD

**Sponsor:** George Peoples, MD, Walter Reed Army Medical Center

**Participating site:** Mary Crowley Cancer Research Center

**Brief description of study:** This study will evaluate the use of GP2 and AE37 given together in combination with GM-CSF. The two peptides are believed to activate the immune system in different ways, and it is hoped that the potency of the vaccine will be enhanced compared with using either peptide alone.

**Outcome measures:** Side effects and safety; immune parameters; progression-free survival.

**Volunteers needed:** HLA-A2+ or HLA-A3+ patients with HER2/neu-positive intermediate- to high-risk breast or ovarian cancer.

**Study title:** Autologous vaccine for follicular lymphoma.

**Study ID number:** Texas Oncology IRB# T0926

**Principal investigator:** Carlos Becerra, MD

**Sponsor:** Bayer

**Participating site:** Texas Oncology, Baylor Sammons Cancer Center

**Brief description of study:** This trial will test an autologous idiotype vaccine manufactured by magniCON technology for patients with relapsed follicular lymphoma who are in complete or partial remission. This manufacturing process introduces a blueprint for the desired protein into tobacco plants using a species of soil bacterium as a carrier. The plant can quickly produce large quantities of the protein, which is then extracted from the leaves.

**Outcome measures:** Toxicity; humoral idiotype-specific immune response; cellular idiotype-specific immune response; long-term safety/tolerability.

**Volunteers needed:** Patients with histologically proven follicular lymphoma (grade 1 or 2) in first clinical relapse/progression requiring treatment, ECOG performance status of 0 to 2, with at least one 2 x 2 cm lymph node accessible by physical examination for excision.

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**Breakthrough Prostate Cancer Vaccine**

Patients at Baylor Charles A. Sammons Cancer Center at Dallas now have access to Provenge®, a new prostate cancer vaccine. Approved by the U.S. Food and Drug Administration (FDA) in May, it is heralded as a landmark treatment in the fight against cancer.

The FDA approved the use of Provenge® for treatment of advanced stages of prostate cancer and physicians on the medical staff at Baylor University Medical Center at Dallas are the first in the country to be in-serviced and approved to treat patients with the new Provenge® prostate cancer vaccine. Within one week following the FDA approval, the vaccine was received and treatment protocols began with eligible prostate cancer patients. “It’s an innovative new option for treating patients,” said Thomas Hutson, DO, a medical oncologist on the medical staff at Baylor Dallas.

Provenge®, or sipuleucel-T, is a therapeutic vaccine that instructs the body’s immune system to recognize and kill cancer cells. A patient provides a blood sample, from which white blood cells are extracted. The white blood cells are then exposed to the substance found in prostate cancer cells. The process “trains” the immune system to react to prostate cancer cells when it is reintroduced to the patient’s body through an intravenous infusion. This process is then repeated two additional times, two weeks apart, so the patient receives a total of three doses of cells.

“We’re very excited to be the first to offer this new prostate cancer vaccine to our patients,” said Alan Miller, MD, PhD, medical director of the Baylor Sammons Cancer Center and Baylor Health Care System Chief of Oncology. “This vaccine provides an alternative treatment option for patients who otherwise have had limited success with other therapies.”
Recent Publications from Baylor Sammons Cancer Center


Baylor Charles A. Sammons Cancer Center at Dallas

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