The Ongoing Hopes and Challenges of Cancer

By Kuyler Doyle, Shelly Beer, and Philip Vorhies

Cancer vaccines seem straightforward and elegant in theory, yet the effective application of the concept has been largely elusive. Numerous cancer vaccines have shown promise in early phases of development only to have difficulties meeting endpoints in Phase 3 clinical trials. Despite these shortcomings, established pharmaceutical companies have become increasingly interested in cancer immunotherapies; and currently, there are over 100 immunotherapy products in various stages of development. Of these, many are specific active immunotherapies (vaccines) that have already entered into clinical development, and several, as illustrated in Table 1, are currently in or have recently completed Phase 3 trials.

The discovery of several tumor-associated antigens (TAA) with expression patterns that distinguish them from normal cells—making them plausible targets for an induced immune response—is raising hopes for developers of cancer vaccines. As envisioned by researchers, cancer vaccines hold the potential to be specific, safe, and long-lasting while eliciting minimal associated toxicity.

The idea that the immune system can be engaged to strike a developing tumor has existed since the late 1800s when William Coley, MD, found that sarcoma metastases at several sites regressed after a patient developed a bacterial infection. Coley's discovery of a tumor response in the absence of providing tumor-specific antigens exemplifies the existence of different types of immunotherapy: passive, non-specific active, and specific active (Table 2). This article focuses on the specific active vaccines.

Prophylactic cancer vaccines have already been approved by the U.S. Food and Drug Administration (FDA) to help prevent against specific cancers by inducing an immune response against the viruses known to cause

Table 1. Cancer Vaccines in Phase 3 Clinical Trials

Company (Product)	Description	Indication
Dendreon (Provenge)	Patient dendritic cells treated with prostate alkaline phosphatase (PAP)-GM-CSF fusion protein	Prostate cancer
Avax Technologies (MVax)	Patient tumor cells treated with hapten dinitrophenyl (DNP)	Melanoma
Vaccinogen (OncoVAX)	Patient tumor cells with BCG adjuvant	Colon cancer
Biovest / Accentia (BiovaxID)	Personalized tumor-specific anti-idiotype vaccine conjugated to keyhole limpet hemocyanin (KLH) plus GM-CSF	Non-Hodgkin's lymphoma
GSK (MAGE-A3)	Off the shelf peptide vaccine targeting MAGE-3 antigen	Non-small cell lung cancer; Melanoma
StimuVax (Merck KGaA / Oncothyreon)	MUC-1 peptide antigen in liposome	Non-small cell lung cancer
NovaRx (Lucanix)	Whole tumor cell lines plus TGF-b blocker	Non-small cell lung cancer
KAEL-GemVax (GV1001)	Telomerase peptide antigen vaccine	Pancreatic cancer
Medarex / BMS (MDX-1379 + MDX-01)	Two peptides from gp100 with an anti-CTLA4 Ab	Melanoma
Oxford Biomedica TroVax	Modified Vaccinia Ankara with 5T4 antigen	Renal cell carcinoma
Northwest Biotherapeutics (DCVax Prostate)	Patient dendritic cells treated with prostate membrane specific antigen (PMSA)	Prostate cancer

Table 2. Immunotherapy Categories

Category	Description	Product
Passive	• Infusion of antibodies or immune system cells to neutralize the danger • Does not directly stimulate an immune response	• Intravenous immunoglobulin • Cellular immunotherapy with *ex vivo* activated immune system cells
Non-specific Active	• Infusion of immunostimulatory agents • Help stimulate the immune system so that the body can mount its own response	• Cytokines • Innate immunity (Toll-like receptor) activators • Bacterial extracts
Specific Active	• Infusion of antigens or cells loaded with antigens, typically accompanied by immunostimulatory agents • Stimulates an active immune response against introduced antigens	• Vaccines

Vaccines

tumor development. Merck's Gardasil® and GSK's Cervarix® protect from infection with Human Papilloma Virus (HPV) strains associated with cervical cancer, and hepatitis B vaccines such as Merck's Recombivax HB® and GSK's Engerix-B® protect from chronic infection that can lead to liver cancer. cont. on pg 28 >>

Table 3. Types of Cancer Vaccines

	Therapy Type	Description	Ongoing Clinical Development	Development Ceased
Personalized	**Cellular Immunotherapy**	Immune system cells (typically "antigen presenting" dendritic cells) from patient's blood are stimulated with cancer antigens and re-injected to activate the immune response against the cancer	Dendreon Provenge; Northwest Biotherapeutics DCVax; Geron GRNVAC1; Argos Therapeutics AGS-003; ImmunoCellular Therapeutics ICT-107; Bellicum Pharmaceuticals BP-GMAX-CD1	Genzyme Melan-A/ MART-1 and gp100; Genzyme Dendritic / Tumor Cell Fusion; IDM Pharma UVIDEM and COLLIDEM
	Whole Cell Tumor Derived - Autologous	Patients' cancer cells are removed during surgery, cells modified to attenuate, create lysates, or isolate antigens (such as heat-shock protein-peptide complexes), and re-injected to activate the immune system against the patients' specific cancer antigens	Vaccinogen Oncovax; AVAX MVax; Antigenics Oncophage	LipoNova Reniale
	Anti-idiotype	Specific for cancers derived from immune system B-lymphocytes (e.g., non-Hodgkin's lymphoma) that display a unique antibody "idiotype" (antigen-binding structure) on their surface. Following cancer cell harvest and laboratory manipulation, patients are vaccinated with the specific cancer idiotype, leading to an immune response against the cancer cells	Biovest/Accentia BioVaxID	Favrille FavID; Genitope MyVax
"Off-the-Shelf"	**Whole Cell Tumor Derived - Allogenic**	Modified tumor cell lines (not from patient) are injected into patient to activate the immune response against the shared antigens for the type of cancer	Onyvax Onyvax-P; NovaRx Lucanix; New Link Genetics HyperAcute	Cell Genesys GVAX; CancerVax/Serono Canvaxin; Corixa Melacine
	Antigen	Use of specific proteins or peptides (protein fragments) that can flag the immune system, frequently in combination with an adjuvant to stimulate the immune system to fight tumor cells that express that antigen	Merck KGaA/Oncothyreon Stimuvax; GSK MAGE-A3; Celldex CDX-110; KAEL-GemVax GV1001; Medarex/BMS MDX-1379+MDX-010; CG Therapeutics CG201; Aphthera NeuVax	Aphton Insegia; Breakthrough Therapeutics ABLVAX
	Anti-idiotype	Uses anti-idiotype antibodies to mimic tumor antigens and activate an immune response against cancer cells		Imclone Mitumomab; Titan Pharmaceuticals CeaVac; Onyvax-105; Menarini abagovomab
	DNA	Circular DNA "plasmids" encoding tumor-associated antigens are injected into the patient. When the DNA reaches the inside of cells, the tumor antigen is expressed and stimulates an immune response	Eisai Amolimogene; Oxford Biomedica Hi-8 MEL (DNA prime followed by recombinant microorganism boost)	AVI Biopharma Avicine
	Recombinant microorganism	Use of microorganisms, such as bacteria, yeast, or replication-defective viruses, to deliver genes coding for tumor-associated antigens into the patient to stimulate an immune response	Oxford Biomedica TroVax; Advaxis ADXS11-001; Sanofi Pasteur MEL11; Transgene TG 4010; GlobeImmune Tarmogen GI-4000; Cytos CYT004-MelQbG10; Bavarian Nordic PROSTVAC	Therion PANVAC-VF

However, most cancer vaccines currently in development are being created as *therapeutic vaccines* that work to stimulate the immune response against tumors in patients who already have cancer (rather than prevent the disease). Broadly speaking, the therapeutic approaches can be divided into *personalized* vaccines that make use of patients' cells and *off-the-shelf* vaccines that do not rely on material from the patient (Table 3).

Potential Limitations to Cancer Vaccines

The ability of the immune system to recognize countless antigens underlies a critical need to educate itself to differentiate *self* from *non-self*, which occurs through a tolerance training process. Since tumor cells are self-derived cells that have incurred subtle changes, there are initially limited differences that distinguish them from normal cells. It is therefore challenging to develop therapeutic vaccines for cancer, as their function is to trigger an immune response against an intruder that closely resembles self and has already evaded the immune system.

Although tumors express specific antigens that differentiate them from normal cells, it has been discovered that there is a distinction between a tumor being *antigenic*, with the potential to be recognized as foreign, and the tumor being *immunogenic* and actually inducing an immune response. Further, research has demonstrated that conditions in the microenvironment surrounding a tumor can affect the ability to mount an immune response and that tumors have developed means to suppress the immune system. As such, one key to the development of a successful cancer vaccine is the need to balance the need to overcome immune tolerance with avoidance of overstimulation and induction of an autoimmune response against normal cells.

Difficulties with Clinical Development

Several companies successfully ushered cancer vaccines through Phase 2 studies, but faced difficulties in Phase 3 trials. Reasons for development failures have been based upon common themes related to the selection of clinical trial endpoints, disease stage, patient population, and trial duration (Table 4).

Table 4. Challenges in Late Clinical Trials

Challenge	Description	Issue	Possible Solution
Clinical Trial Endpoint	• Surrogate endpoints for survival chosen (such as TTP) • Endpoints based upon tumor size selected	• Cancer vaccines can take extended times to show survival benefits • Tumors could progress before immune response and regression	• Avoid endpoints based upon tumor sizing • Use endpoints focused on overall survival and quality of life
Disease Stage	• Patients with late-stage metastatic disease selected as trial subjects	• Advanced-stage cancer patients frequently immunocompromised due to prior treatments and disease • Conflict between slow response to vaccine and rapid disease progression	• Use patients with minimal residual disease as trial subjects • Conduct trials on patients with minimal prior treatments
Patient Selection	• Patients with correlative immune biomarkers not used in pivotal trials	• Variability of cancers and immune systems make finding the correct patient population critical	• When possible, use tumor or immunological biomarkers to separate more likely responders and increase efficacy
Trial Duration and Early Analysis	• Early analysis of some trials appeared futile, but in retrospect could have yielded different results if allowed to continue	• Primary immune stimulation takes time and may require boosters • Patients response at different time intervals, requiring longer durations to achieve statistically significant results	• Avoid expectations that study subjects will respond with similar kinetics and allow sufficient time for response to vaccine

CLINICAL TRIAL ENDPOINTS

Some of the most promising cancer vaccines have experienced regulatory delays due to problems associated with the choice of primary clinical endpoints. Dendreon's Provenge, for example, is a personalized dendritic cell vaccine that initially was selected for a time to progression (TTP) endpoint in hopes of more rapid results. However, Provenge just missed statistical significance of that readout. Overall survival (OS) analysis of those studies demonstrated a 40% reduction in the risk of death with high statistical significance, but since OS was not pre-specified as a primary endpoint, the FDA insisted that another trial be conducted to confirm survival results. Although Dendreon persevered and is now reporting similar findings in further trials, these additional studies have been extremely costly to the company and frustrating to patients looking for alternative therapies.

Therion Biologics shut down after its Phase 2 prostate cancer vaccine trial (PROSTVAC) failed to demonstrate a reduced TTP, and its pancreatic cancer vaccine study also failed. However, two years after the shutdown it was dis-

covered that PROSTVAC had in fact demonstrated a statistically significant OS rate. New licensee Bavarian Nordic will now pursue Phase 3 studies with the vaccine.

DISEASE STAGE

Therion Biologics' PANVAC-VF vaccine was an off-the-shelf vaccine consisting of attenuated poxviruses carrying genes encoding two tumor-associated antigens and three immunostimulatory molecules for use in advanced pancreatic cancer. Despite promising early results, the vaccine did not meet its primary endpoint of longer OS in patients that had failed gemcitabine treatment when compared with chemotherapy or best supportive care. This trial demonstrated the difficulties of vaccines being considered for second-line settings and for patients with high tumor burdens or fast-progressing cancers.

A survey of failed trials provided evidence that new cancer vaccine trials should use a homogenous patient population...

PATIENT SELECTION

CancerVax's Canvaxin was an off-the-shelf mix of three irradiated melanoma cell lines (whole cell mixture) for stage III melanoma. Although some HLA variants were identified in Phase 2 as potentially correlated with clinical benefit, the Phase 3 study did not exclusively recruit those subjects. In the trials, post-surgical patients treated with Canvaxin exhibited worse outcomes for OS and progression free survival (PFS) than patients receiving placebo.

In another example, Corixa's off-the-shelf Melacine demonstrated clinical benefit in certain HLA types for melanoma and was approved in Canada, but the FDA did not allow the retrospective analysis and requested a new trial in the U.S. that would have taken 8-10 years to complete, helping seal the fate of the vaccine.

TRIAL DURATION AND EARLY ANALYSIS ISSUES

Some clinical studies of cancer vaccines have been terminated when interim analysis suggested the trial would not meet its endpoints. Cell Genesys recently terminated a trial of its GVAX vaccine for prostate cancer early based upon results from a previously unplanned futility analysis that suggested the trial had less than a 30% chance of meeting its predefined primary endpoint of OS when compared with Taxotere® and prednisone. However, results from further analysis of the study demonstrated that there was in fact a delayed benefit in survival when compared to the more rapidly acting chemotherapy.

CANCER VACCINE SECTOR TRENDS

With recurrent issues leading to the demise of several investigational programs and companies, the Cancer Vaccine Clinical Trial Working Group (CVCTWG), with representatives from the biotechnology/pharmaceutical industry, academia, and participation from the FDA, developed and published a new paradigm for cancer vaccine trials (*J Immunother.* 2007;30:1).

A survey of failed trials provided evidence that new cancer vaccine trials should use a homogenous patient population, focus on containing minimum residual disease where vaccines seemed most effective, not use endpoints related to tumor shrinkage, and provide sufficient time for a patient response as there are no perfect surrogate markers for efficacy and it simply takes time to see OS results. In addition, the CVCTWG group suggested that vaccines would most likely need to be used in combination with other therapies to help boost the immune response and break the immune tolerance to tumors. It was also suggested that new studies use more rigorous randomized Phase 2 trials and be adaptable for expansion to test adequate subjects to provide statistical power to demonstrate significance.

With kinks conceptually worked out from the clinical development protocols, big pharmaceutical companies have been making moves into the cancer vaccine space in the last few years (Table 5).

At the same time, some smaller companies that have worked in the sector for many years are retreating. Although the CVCTWG paradigm for cont. on pg 30 >>

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Table 5. Cancer Vaccine Activities by Pharmaceutical Companies

Pharmaceutical Company	Cancer Vaccines in Development	Partners	Acquisitions
Pfizer	CDX-110	CellDex Therapeutics; Cytos Biotechnology	Coley Pharmaceutical Group (immunostimulators/ adjuvants); PowderMed (DNA vaccine delivery)
Merck	V934/V935	Geron; Inovio (DNA delivery); Idera (adjuvant)	—
Merck KGaA (EMD-Serono)	Stimuvax	Oncothyreon	—
Kirin	AGS-003	Argos	—
Bristol-Myers Squibb	MDX-1379 + MDX-010	Medarex	—
Celgene	GI-4000	GlobeImmune	—
GlaxoSmithKline	MAGE-A3, WT1	—	—
sanofi-aventis	MEL11	—	—

clinical trials should have a positive impact on study design for vaccines, clearly these recommendations will significantly increase complexity and development costs through need to screen patients, to test combination therapies, and to include more patients and longer timelines. After selling off manufacturing rights to Merck KGaA for its lung cancer vaccine Stimuvax, Oncothyreon recently made the decision to leave the cancer vaccine space to work on more traditional cancer therapeutics. Cancer vaccine companies Genitope, Favrille, CancerVax, Aphton, LipoNova and Pharmexa all had Phase 3 vaccines and no longer exist today to continue development of these products.

With lessons learned from the failed trials of the past, there is still hope for the future of cancer vaccines. However, further challenges related to the commercialization of these products could remain. These in addition to recommendations will be covered in the second article of this two-part series. KD SB PV

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Compiled by Nancy J. Ciancaglini

ASCO (Alexandria, Va.)

The ASCO Cancer Foundation (TACF) appointed **Nancy Riese Daly, MS, MPH,** as its new Executive Director, and **Martin J. Murphy, Jr., PhD, DMedSc,** assumed his new role as the Chair of TACF's Board of Directors. Also appointed to the TACF Board are **Richard L. Schilsky, MD** and **Thomas A. Marsland, MD. Stephen A. Cannistra, MD,** Professor of Medicine at Harvard Medical School will become Editor-in-Chief of ASCO's peer-reviewed publication, The Journal of Clinical Oncology (JCO) in May 2011. Dr. Cannistra has served JCO in various capacities since 1989. He will replace **Daniel G. Haller, MD**.

ASH (Washington, D.C.)

The American Society of Hematology (ASH) welcomed to its Executive Committee **Armand Keating, MD,** who will serve a one-year term as Vice President; and new Councillors **Marilyn J. Telen, MD,** and **Kenneth C. Anderson, MD,** will serve four-year terms, while **Mohandas Narla, DSc,** will serve as Councillor for a one-year term. The 2009 Lasker-De-Bakey Clinical Medical Research Award was given to **Brian Druker, MD,** of the Oregon Health & Science University, and **Charles L. Sawyers, MD,** of the Memorial Sloan-Kettering Cancer Center, for their research on Gleevec®.

Amgen Inc. (Thousand Oaks, Calif.)

The company was honored with two 2009 Scrip Awards: Best Overall Pipeline and Best New Drug for Nplate®. Amgen's focus on satisfying unmet clinical need was singled out by the judges in making their selection for both awards. Nplate, designated an orphan drug, also won the Best New Drug honor due to its novel mode of action. It is the first treatment specifically developed to treat chronic immune thrombocytopenic purpura (ITP), a rare autoimmune disorder which can lead to serious bleeding events.

Baylor Charles A. Sammons Cancer Center (Dallas, Tex.)

The Cancer Center became a full member of Southwest Oncology Group (SWOG), one of the largest cancer clinical trials cooperative groups in the U.S. SWOG is comprised of more than 5,000 physician researchers at 516 institutions.

Cancer*Care*® (New York, N.Y.)

Cancer*Care* named **Helen H. Miller, LCSW,** as its new Chief Executive Officer (CEO), effective January 4, 2010. Miller most recently served as Executive Director of The Bachmann-Strauss Dystonia & Parkinson Foundation in New York City. She succeeds Cancer*Care*'s longtime CEO, **Diane Blum, MSW**.

Cancer Prevention and Research Institute of Texas (Austin, Tex.)

The Cancer Prevention and Research Institute of Texas (CPRIT) named **Jerald S. Cobbs, MBA**, as Chief Commercialization Officer. Cobbs was most recently a principal and Managing Director of Signet Healthcare Partners, a private equity healthcare venture fund. **Stephen W. Wyatt, DMD, MPH**, Dean of the College of Public Health at the University of Kentucky, has been chosen to chair CPRIT's Prevention Review Council which oversees the selection of prevention grants.