Denise Myshko

The New FRONTIER of Therapeutic Vaccines

Researchers continue to evaluate the sustainability of powering the immune system to treat cancers and other serious diseases.

For years researchers have been trying to find a way to trigger the body's immune system to recognize cancers and other diseases. Early attempts to use cytokines, proteins, peptides, and immune stimulants as effective cancer therapies often failed in Phase III trials to show any benefit to the patient, mainly because researchers didn't understand how cancer functions.

"In the 1980s and 1990s, researchers were using peptides or fragments of peptides," says Michael Kranda, CEO of Vaccinogen. "There were multiple companies investigating this research approach, but they didn't have the right technology or they didn't have the right peptide. We've come to better understand that cancer involves random mutations and that it is hard to pick a target ahead of time and build an effective therapy."

Today, the immunotherapy field is experiencing a renaissance, says Robert Kirkman, M.D., CEO of Oncothyreon.

"There is a renewed effort to develop off-the-shelf vaccines as well as those that can be used as individual therapies," he says. "There is a lot of work going on that combines various approaches in an effort to deliver immunotherapies. For example, vaccines are being combined with nonspecific boosters of T-cell activity and combinations of antigens are being used. There are many different approaches."

One positive development was the U.S. approval of Provenge in April 2010. Provenge is the world's first patient-specific prostate cancer immunotherapy. It uses a patient's own tumor cells to create a vaccine, which is designed to induce an immune response against an antigen expressed in most prostate cancers.

Marc Mansour, Ph.D., chief science officer and chief operating officer of Immunovaccine, says Provenge reinvigorated the field of immunotherapies.

"The research around Provenge reawakened interest in cancer vaccines and provided a proof of concept that a cancer vaccine can work," he says. "In many ways, this is reminiscent of the monoclonal antibody field. People were initially excited about the science in the 1990s, but there were challenges with clinical development and people lost confidence. But within five years of the first approval of a monoclonal antibody, five more were approved and now this is a multibillion-dollar industry."

"We think of vaccines generally for prevention," Dr. Mansour continues. "Using vaccines therapeutically to treat cancer is a change in the approach to developing cancer treatments. The idea is to use a vaccine to reactivate the immune system in order to delay the progression of the cancer."

The therapeutic vaccine market was estimated to be valued at $137 million in 2010; BCC Research analysts say it is expected to increase to almost $3.1 billion in 2014, for a four-year CAGR of 117.7%. The largest segment in this market is cancer vaccine products, which is expected to have a four-year CAGR of 115.3%, reaching $2.9 billion in 2014.

According to BCC Research, this period of expected dynamic growth in the therapeutic vaccines market is due to the anticipated rollout of eight products before 2015. Further back in the pipeline, therapeutic vaccines are also in development to treat infectious diseases, such as HIV and hepatitis C; neurological disorders, such as Alzheimer's disease; autoimmune disorders, such as rheumatoid arthritis and multiple sclerosis; and other conditions such as hypertension.

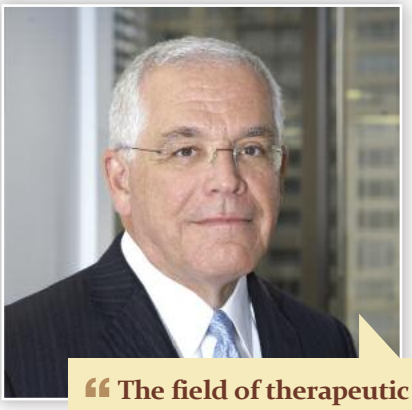
Research Approaches

Several companies are taking different approaches to develop therapeutic vaccines.

For example, Dendreon's Provenge uses cells from a patient's own immune system, along with an immune stimulant, to target and attack prostate cancer. Treatment includes three doses given about two weeks apart. Once a patient's immune cells are collected, they are shipped to a Dendreon manufacturing facility, where they are combined with a protein that is found in most prostate cancers linked to an immune stimulating agent.

Dr. Mansour says the immune system tar-

> "There is interest now in harnessing the power of the immune system to have a meaningful effect on cancer and have immunotherapies provide a clinical benefit."
>
> **DR. MARC MANSOUR**
> Immunovaccine



> "The field of therapeutic vaccine research is experiencing a bit of a renaissance."
>
> **DR. ROBERT KIRKMAN** / Oncothyreon

gets the site where the patient is vaccinated; an immune response is then turned on against the target that is in the vaccine.

"This is the beauty of vaccines," he says. "The approach is similar to that of a flu shot, in which the immune system is 'trained' to recognize the flu virus. The idea is to train the immune system to recognize a cancer target, although it is much more difficult to teach the immune system to recognize a cancer target. While there is growing evidence that the immune system can be used in the treatment of cancer, the questions now are: when to apply a vaccine, in what setting, and where along the disease progression does a vaccine fit in the current treatment of cancer?"

Vaccinogen is also developing an autologous vaccine, OncoVAX, that uses the patient's own cells to manufacture a personalized product. Following surgery to remove the Stage II colon cancer, the tumor cells are processed in Vaccinogen's facility in the Netherlands.

OncoVAX completed its first Phase IIIa

trial in Stage II colon cancer. The product also is in Phase I/II trials for treating melanoma and renal cell carcinoma.

(Please see the digital edition of PharmaVOICE for more information about this and the other clinical programs of the companies interviewed for this article.)

Mr. Kranda says Vaccinogen has completed one Phase III trial; the data showed a 50% increase in recurrence-free survival at five years.

"We're in the process of raising money to initiate the second Phase III trial," he says. "This is a pivotal trial. We believe if the outcomes from the original study are repeated, we'll have a very strong filing in the 2014-2015 time frame."

Other companies, such as Oncothyreon and Immunovaccine, are using different approaches to developing therapeutic vaccines. They are working to develop an off-the-shelf product containing several tumor antigens.

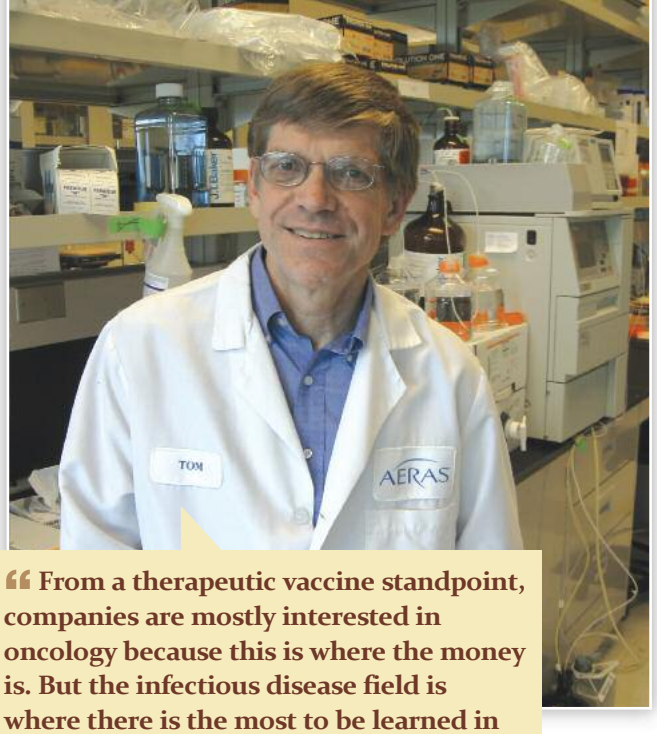
Immunovaccine's DPX-0907 completed a Phase I clinical trial to treat patients with advanced-stage breast, ovarian, and prostate cancers. DPX-0907 combines seven peptide antigens plus an adjuvant using Immunovaccine's DepoVax delivery platform.

"In the case of DPX-0907, we took a multitargeted approach," Dr. Mansour says. "Some patients may have one antigen and not the others. Other patients may have another set of antigens.This is one way to get around the fact that patients have different antigens. As long as a given patient has at least one target, the vaccine will be applicable."

Additionally, he says the company's delivery system is designed as a vaccine enhancement platform.

"The formulation technology holds the antigens at the site of vaccination for a long time, which exposes the immune system to the targets and other immune activating ingredients in a prolonged fashion," he says.

Another area of research is being explored by Oncothyreon and Merck KGaA, which are co-developing Stimuvax, which is designed to stimulate an individual's immune system to recognize cancer cells that express MUC1, a protein antigen widely expressed on common cancers, including lung, breast, prostate, and colorectal.



> **"From a therapeutic vaccine standpoint, companies are mostly interested in oncology because this is where the money is. But the infectious disease field is where there is the most to be learned in terms of proof of concept and science."**
>
> **DR. THOMAS EVANS**
> Aeras

Challenges with Developing Immunotherapies

Dr. Kirkman says one of the challenges involved with developing therapeutic vaccines is that surrogate markers that represent the activity of the vaccine aren't very good, which hinders translating a vaccine into a clinical benefit.

"There isn't an immune assay that clearly correlates with a clinical outcome," he says. "Without a solid assay, every question has to be based on a survival endpoint. This has been a problem for the whole field. Vaccines are not like small-molecule development programs where there is a clear pharmacodynamic endpoint that demonstrates the molecule is active. There are all types of assays that measure immune response, but what we don't know is how they correlate with the desired outcome."

Thomas Evans, M.D., chief scientific officer of Aeras, agrees that researchers often don't know the immune response they want to achieve.

"Since there is an iterative process to figuring out the immune response to be induced and developing good biomarkers, we're still shooting in the dark until these issues are resolved," he says.

Dr. Evans says for TB vaccines specifically, there haven't been many trials, so the endpoints are not quite as clear as they might be for some other diseases.

"The endpoints are clear for melanoma studies or prostate cancer studies," he says. "For TB vaccines, the endpoints are being defined as we go along. This makes for some regulatory uncertainty."

Industry experts say with therapeutic vaccines it's important that clinical trials are adequately powered to answer the questions being asked.

Dr. Mansour suggests that more rigorous Phase II trials might be the way foward to address this concern.

"In general, cancer research has focused on small, single-arm uncontrolled clinical trials, so the usability of these data are unclear," he says. "A better approach would be a Phase II randomized trial with a reasonable number of patients."

Dr. Mansour says a great deal of money has been wasted in progressing products to Phase III without having solid Phase II data.

He adds that the up-front costs for more robust Phase II trials may be higher, but in the long run, companies will have answers sooner rather than later as to the viability of the product and won't spend unnecessary money developing a product that isn't viable.

Going forward, U.S. regulators are considering tightening the standards for accelerated approval of new cancer products. In February, the FDA's Oncologic Drugs Advisory Committee recommended that sponsors should generally conduct randomized trials rather than single-arm studies — trials without a control — and that there should be more extensive postmarketing studies to confirm clinical benefit. PV

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EXPERTS

THOMAS EVANS, M.D. Chief Scientific Officer, Aeras, a nonprofit organization dedicated to the development of effective tuberculosis (TB) vaccines and biologics to prevent TB. For more information, visit aeras.org.

ROBERT KIRKMAN, M.D. CEO, Oncothyreon Inc., a biotechnology company specializing in the development of innovative therapeutic products for the treatment of cancer. For more information, visit oncothyreon.com.

MICHAEL KRANDA. CEO, Vaccinogen Inc., which is developing autologous cancer vaccines and other immunotherapeutic products. For more information, visit vaccinogeninc.com.

MARC MANSOUR, PH.D. Chief Science Officer and Chief Operating Officer, Immunovaccine Inc., a clinical-stage vaccine company focused on the commercialization of its patented DepoVax vaccine delivery technology and product candidates. For more information, visit imvaccine.com.

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Selected Vaccine Development Programs

Several companies are actively working in the therapeutic vaccine space. The following outlines their development programs.

Aeras

Tuberculosis is the world's second deadliest infectious disease, with almost 9.4 million new cases diagnosed in 2009. According to the World Health Organization, an estimated 1.7 million people died from TB in 2009.

Aeras is a nonprofit research organization developing new tuberculosis vaccines.

"TB vaccines try to induce cellular immune responses similar to the therapeutic vaccines," says Thomas Evans, M.D., chief scientific officer of Aeras. "Almost all licensed vaccines for infectious diseases are based on antibody responses."

He says one vaccine Aeras is studying aims to prevent disease. Another avenue of vaccine research is for those who are already infected, such as with HIV, and whose immune system breaks down. Aeras has products in late-phase development that have been tested with people who have been treated for TB.

An example is AERAS-402/Crucell Ad35, which is being developed with Crucell. The delivery system uses an adenovirus because adeno-vectored vaccines consistently induce high levels of CD8+ T-cell responses.

Immunovaccine Inc.

DPX-0907, a therapeutic cancer vaccine, recently completed a Phase I clinical trial in patients with advanced-stage breast, ovarian, and prostate cancers. DPX-0907 combines seven peptide antigens plus an adjuvant with Immunovaccine's DepoVax delivery platform.

"DepoVax is a vaccine enhancement platform," says Marc Mansour, Ph.D., chief science officer and chief operating officer of Immunovaccine. "Identifying a target is important, but it is also important to deliver it properly to the immune system and be able to activate the immune system again. To do this adjuvants, a delivery system, and the technologies that enhance the delivery of the vaccine and the efficacy of the vaccine are needed."

DepoVax holds the antigens at the site of vaccination for a long time and exposes the immune system to these targets in a prolonged fashion.

Dr. Mansour says DPX-0907 contains seven antigens from seven different proteins.

The company also is conducting a Phase I/II clinical study with DPX-Survivac, which is being tested for ovarian cancer. The DPX-Survivac vaccine candidate uses antigens from survivin (licensed from Merck KGaA), which are formulated using the DepoVax vaccine delivery platform.

Survivin is a tumor-associated antigen that is present in cancer cells and generally not expressed in normal cells.

"Survivin is a very exciting antigen," Dr. Mansour says. "There has been a lot of research on survivin, which is essential for cancer cells to survive. The more advanced the cancer, the more of this protein is present. Survivin is involved in several mechanisms of action inside the cell. This is why it's hard for the cell to rid itself of survivin because it is central to so many different pathways in the cancer cell."

Oncothyreon Inc.

Oncothyreon is developing Stimuvax, a therapeutic vaccine designed to stimulate an individual's immune system to recognize cancer cells that express MUC1, a protein antigen widely expressed on common cancers. MUC1 is overexpressed within lung, breast, prostate, and colorectal cancers.

Stimuvax is being developed by Merck KGaA under a license agreement with Oncothyreon. Merck is currently conducting two Phase III trials of Stimuvax for non-small cell lung cancer. Another indication being pursued is maintenance therapy in Stage III lung cancer.

Robert Kirkman, M.D., CEO of Oncothyreon, says the vaccine is a liposome that includes 25 amino acid peptides that represent the most immunogenic part of a tumor-associated antigen MUC1.

"We also use an adjuvant of immune stimulant, which in this case is called MPL, a commercially available adjuvant from GlaxoSmithKline," Dr. Kirkman adds. "This is the same adjuvant that GSK uses in its cervical cancer vaccine. We take the target and the adjuvant and mix them with three fats to form a liposome. This is then injected subcutaneously with the goal of stimulating the body to make an immune response against that target. We have preclinical data that shows that the vaccine can generate a cellular-mediated response."

Another candidate in development is ONT-10, a therapeutic vaccine designed to direct an individual's immune system to identify and destroy cancer cells.

ONT-10 is designed to produce both an antibody and a T-cell immune response to cancer cells that express the MUC1 target.

Oncothyreon expects to file an investigational new drug application for ONT-10 in the third quarter of 2011 and to begin a Phase I clinical trial by late 2011.

"ONT-10 differs from Stimuvax in two ways," Dr. Kirkman says. "The antigen is a little bigger; it has two copies of the target. And second, it also has sugar on it. The concept is that the antigen is going to produce an antibody response as well as a T-cell response. We have preclinical data that was presented at the AACR meeting this year demonstrating this effect in animals."

Vaccinogen Inc.

Vaccinogen's product, OncoVAX, uses the patient's own cancer cells to block the return of colon cancer following surgery. After removal of the Stage II colon cancer, the tumor cells are processed in Vaccinogen's facility.

The vaccine created in this process is injected into the patient's skin in four doses dur-

ing the first six months after the surgery. The vaccine aims to unleash the body's own immune system to fight a cancer that it otherwise would not have recognized.

OncoVAX has completed its first Phase IIIa trial in Stage II colon cancer.

The Vaccinogen platform also has the potential for treating melanoma and renal cell carcinoma, says Michael Kranda, CEO of Vaccinogen.

"Research into cancer heterogeneity suggests that personalized vaccines — autologous vaccines made from the patient's own tumor expressing their unique set of antigens — have the best chance to promote a robust immune response, especially in a setting of minimum residual disease, in our case post-surgical resection of the tumor," he says. PV

Raising Awareness for Vaccine Research Funding


Dr. Gregory Poland


Dr. Paul Offit

The Foundation for Vaccine Research, an international organization formed by leading scientists and advocacy experts in vaccines and infectious diseases, launched in June. The organization seeks to raise global awareness of the need for increased, long-term, flexible funding to advance and accelerate vaccine research and development against a broad range of infectious diseases around the globe.

"The science and the technology are there to develop lifesaving vaccines for the most challenging infectious diseases," says Founding Board Director Paul Offit, M.D., chief, division of infectious diseases at Children's Hospital of Philadelphia and co-inventor of the rotavirus vaccine. "But the resources often are not, and when they are, they tend to come in bursts. Scientists everywhere need long-term, predictable funding in order to pursue new ideas and promising lines of research without worrying about paying next month's rent."

"Vaccines have saved millions of human lives, more than any other medical intervention," notes Founding Board Director Gregory Poland, M.D., professor and director with the Mayo Clinic and editor-in-chief of the journal Vaccine. "With a sustained two- to threefold increase in funding for vaccine research, I believe that we can eliminate infectious diseases as the primary cause of morbidity and mortality from the planet within our children's lifetime."

For more information, visit vaccinefoundation.org.