

Landmark approval for Dendreon's cancer vaccine

The April 29 approval of Seattle-based Dendreon's prostate cancer vaccine, Provenge (sipuleucel-T), is being hailed as a victory for cancer immunotherapy. For Dendreon, the US Food and Drug Administration's (FDA) go-ahead marks the end of a tortuous regulatory path, marked not only by missteps by the company but also by controversy at the FDA, not least the decision in 2007 by the Center for Biologics Evaluation and Research (CBER) to act against its advisory panel's positive recommendations. After the turmoil of ad campaigns critical of the agency, picketing and lobbying by patient groups, death threats, lawsuits and even calls for a Congressional investigation (*Nat. Biotechnol.* 26, 1, 2008), the FDA issued a complete response letter on the earlier trials and requested further clinical evidence of efficacy. Dendreon then soldiered on with a phase 3 placebo-controlled trial (Immunotherapy for Prostate Adenocarcinoma Treatment; IMPACT), the results of which were submitted to FDA last November. On the basis of these data, which have yet to be published in a peer-reviewed journal, the agency finally gave Provenge its imprimatur, approving the first therapeutic vaccine for use in individuals with asymptomatic, or minimally symptomatic hormone refractory metastatic prostate cancer.

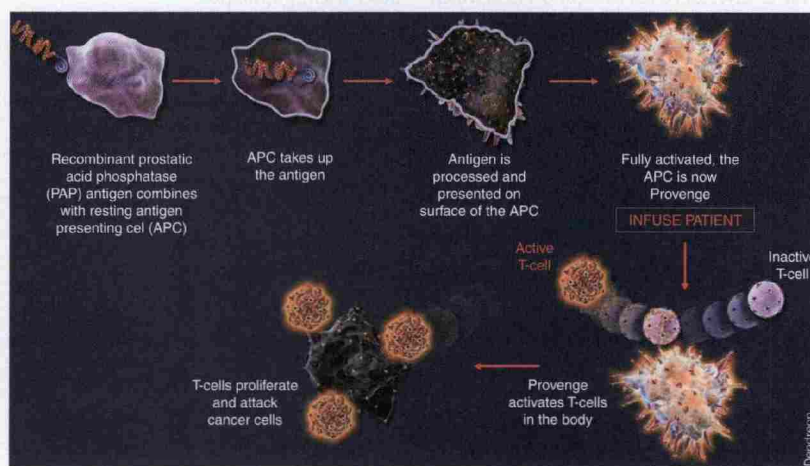
The approval has received an ecstatic reception from patient groups, oncologists and cancer vaccinologists, who view Provenge and potentially other cell vaccines as a valuable and complementary adjunct to the growing list of different cytotoxic and cytostatic therapies used in the fight against cancer. Provenge is being touted as a non-toxic cancer treatment for an underserved population, which in the US alone surpasses 76,000 patients. "It's a hugely exciting time for our field," says Bernard Fox, president of the International Society for Biological Therapy of Cancer. "We've been doing it [immunotherapy] for 25 years, through times that have been very bad for the community. We didn't have much to point to except clinicians that had seen their patients respond."

It remains unclear, however, whether Dendreon's decade-long struggle to pass regulatory muster has clarified the path of oversight for other cancer vaccines or even whether autologous cellular vaccines will rival the success of 'off-the-shelf' vaccines or other types of adjunct therapies, such as antibodies or small molecules. Therapeutic cancer vaccines are a diverse group of products; they can be cellular or acellular (peptides, proteins, DNA), be targeted against a single antigen or groups of antigens, use viruses or other scaffolds to present antigens or use patient cells or cell lines (*Nat. Biotechnol.* 27, 129–139, 2009).

Provenge, unique among cancer vaccines in late-stage clinical trials (Table 1), is an autologous, cell-based therapy created by incubating (activating) the patient's own antigen-presenting cells *ex vivo* with a fusion of prostatic acid phosphatase (an antigen specific to prostate tissue) and granulocyte macrophage colony-stimulating factor, which act to stimulate immune cell responses. This is a first-generation product, but it is both simpler (uses a single antigen) and more complex (works with a mélange of cells) than some of the other products under development.

Dendreon's clinical trial design and analysis of the human data have been dogged by controversy. Two early trials of Provenge showed a benefit in overall survival (OS) but not progression-free survival (PFS), which is unusual according to Don Berry, chairman of biostatistics at MD Anderson Hospital in Houston. "If something is effective in cancer, it inhibits or slows growth and this apparently does not," he says. Unfortunately for Dendreon, PFS was the primary endpoint in these early trials. The FDA refused to move the goalposts, and sent Dendreon back to gather more data, this time using OS as an endpoint in a large (512-patient) phase 3 trial, which was already underway.

Last October, Dendreon announced interim results, essentially priming the pump for investors, if not regulators. (The company raised \$409.5 million in a stock offering the following month.) The release of interim results to the company by the data monitoring group was unusual, according to Susan Ellenberg of the University of Pennsylvania in Philadelphia, who led the team that wrote the guidance for placebo-controlled trials when she was at CBER. Apparently in this case it was done with the consent of the FDA. The interim data had not achieved statistical



The making of a cancer vaccine. The precise mechanism of Provenge in prostate cancer has not been established.

Table 1 Selected cancer vaccines in phase 3 clinical trials

Company (location)	Product description	Indication
Antigenics (Lexington, Massachusetts)	HSPPC-96 Oncophage: heat-shock protein vaccine isolated from patient tumor cells	Melanoma Glioma Renal cell carcinoma
BioVest International (Tampa, Florida)	BioVaxid: patient-specific immunoglobulin idiotype vaccine conjugated to the immunogenic protein KLH	Non-Hodgkin's lymphoma
Genitope (Fremont, California)	Patient-specific immunoglobulin idiotype-KLH conjugate	Non-Hodgkin's lymphoma
GlaxoSmithKline (Brentford, UK)	MAGE: liposomally packaged tumor-specific antigen	Melanoma Lung cancer
Northwest Biotherapeutics (Bethesda, Maryland)	DCVax: patient-derived dendritic cells loaded with cancer proteins or lysates	Prostate cancer Brain cancer
NovaRX (San Diego)	Lucanix: four cell lines carrying antisense oligos against transforming growth factor	Lung cancer
Oncothyreon (Seattle)	Stimuvax: liposomal vaccine with a synthetic peptide derived from tumor-specific antigen MUC-1	Lung cancer
Oxford Biomedica (Oxford, UK)	TroVax: pox viral vector carrying tumor-associated antigen 5T4	Renal cell carcinoma

significance (Dendreon needed to achieve 22.5% improvement in OS but at that time, they were only at 20%). Dendreon researchers were confident, based on their prior experience from randomized trials, however, that once all the results had been collected, the data would meet the mark, which was, in fact, the case.

As reported at the American Society of Clinical Oncology (ASCO) 2010 Genitourinary Cancers Symposium, held March 5–7 in San Francisco, three-year OS rates were 38% higher among men who received the drug than those who received placebo. Provenge showed a median OS benefit of 4.1 months compared with the placebo ($P = 0.032$).

On the basis of these results, the FDA declined to convene an advisory panel, although rumors circulated in March that one might take place. Dendreon's stock price took a hit, as investors tried to second-guess which way the winds were blowing at the agency. But as the previous panel had voted for approval with clinical data that fell short of statistical significance, it seemed unlikely that agency officials would convene a panel again. Indeed, at the end of the next month, FDA finally gave the formal green light, announcing marketing authorization for Provenge.

One further complication with the IMPACT data has had statisticians scratching their heads. This is the use of previously frozen Provenge—which some are calling Frovenge—as the salvage protocol for patients who progressed on the placebo arm. Those on the experimental arm whose disease progressed received chemotherapy with docetaxel. Offering progressors alternative therapies is common, but giving an unproven therapy, which on top of being unproven, is different from the product

given to the experimental arm, introduces an uncontrolled variable and confounds analysis when the endpoint had yet to be met (death).

Mark Frohlich, Dendreon's chief medical officer, explains that using Frovenge was preferable to creating the vaccine anew from trial participants. Each patient, regardless of which arm they were on, had to undergo three leukophereses, an invasive procedure, to isolate the cells necessary for the therapy or the placebo. According to Frohlich, Frovenge met the same specifications as Provenge, "Scientifically there is really no biological or scientific rationale as to why a product that meets the same release specs would be deleterious to the patient," he says. Furthermore, when the trial started, there was no therapy available for progressors; docetaxol was approved only later for use in this patient population.

Another factor tempering enthusiasm in some quarters is the fact that, at least for now, the data have only been reviewed by the FDA and Dendreon, which presented a summary of the data at ASCO. (Frohlich says Dendreon intends to publish the data in a peer-reviewed journal, but has not indicated when.) Steven Rosenberg, chief of surgery at the National Cancer Institute, who has been working on immunotherapies for over 20 years, finds it strange that the data have not been released, given the newness of the approach that Provenge represents. "Particularly for a field that has had a rash of negative results, it's important for the scientific community to see the data. That's how science works," he says.

From the viewpoint of vaccine developers, the 'rocky' ride that Provenge received during FDA review also poses some questions. For example, Dendreon's Frohlich challenges

the conventional wisdom that assessments of efficacy should be the same for vaccines as for more conventional oncology treatments, such as chemotherapy. Until now, the gold standard used by regulators has been the shrinkage of tumors or the downregulation of tumor markers. In such a system, even if a cancer vaccine has a positive effect on OS, "you don't necessarily expect" to see an effect on tumor shrinkage/burden, Frohlich says. Howard Scher of Sloan Kettering Cancer Institute in New York concurs. He encourages sponsors "not to mandate stopping therapy at the first sign that [the signs are seemingly going in the wrong direction. We just have to be smarter on how we measure [response]." Scher was one of four dissenting votes on the 2007 advisory panel that gave Provenge the green light.

After the slog over the regulatory finish line, Dendreon is now faced with the Herculean effort of producing an autologous cell therapy on a large scale. The company started to ramp up its manufacturing capacity before approval, with \$630 million raised in two follow-on stock offerings last year. Even so, the firm plans to commence commercialization with dosing of only 2,000 patients—a fraction of the population indicated on the label. The \$93,000 price tag for three infusions may also dictate who gets the treatment. According to Frohlich, Dendreon is in discussions with the Center for Medicare and Medicaid Services, as the majority of Provenge's target patient population is over 65. Eric Schmidt, an analyst with Cowen and Company in Boston, predicted that the price tag would be high, but feels it's appropriate for a product with proven efficacy and a great safety profile, with no added expense from supportive care. "Price is not a factor," he believes.

Whether Provenge's approval heralds a new era for cellular cancer vaccines remains to be seen. It seems likely that off-the-shelf products that are simpler to produce, such as tumor antigens targeted to dendritic cells by way of antibody moieties, are likely to supersede more complex cellular products that often suffer from batch-to-batch variability. MD Anderson's Berry remains guarded about the field's prospects. "It will still be a hard road to approval for companies with vaccines because the vaccine batting average is still very low. But one hit is better than none," he says. Fox is more sanguine. "There is a lesson here for us to look at what some might think are crazy ideas. I don't think a lot of people would have thought it was going to work." But although it is an important step, he adds, "People are still dying on [Provenge]."

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