Cancer vaccines based on dendritic cells—the immune system’s first responders to foreign invaders—grabbed the spotlight this summer. Several vaccines showed remarkable responses in early clinical trials in patients with advanced tumors, and in one animal study, a dendritic cell vaccine wiped out tumors in mice with melanoma.

At this point, it is anybody’s guess which, if any, of several approaches to vaccination using dendritic cells will make a difference for cancer patients. The scientists who are doing the work mix terms like “cautious optimism” and “potentially promising” with “uphill battle” and “suboptimal process.”

“We’re learning how to find tumor antigens, how to make more effective vaccines and make them more potent, and how to block or turn off negative regulatory mechanisms of tumors,” said Jay A. Berzofsky, M.D., Ph.D., chief of the Vaccine Branch at the National Cancer Institute.

“Dendritic cells are clearly the most important modulator of immune responses in the body,” said David E. Avigan, M.D., director of bone marrow transplantation at Beth Israel Deaconess Medical Center in Boston. They roam the circulatory system to collect foreign invaders or other antigens and carry them to the lymph nodes, where they present them to the T cells. This primes the T cells to mount an attack against those antigens. Cancer cells have found ways to evade the immune system, but specially programming a patient’s own dendritic cells may be one way to unmask the tumor and alert the body to mount a strong defense.

During the past decade, scientists have devised a dozen different ways to make dendritic cell vaccines. They have linked dendritic cells with all kinds of antigens, including peptides derived from gene mutations, tumor RNA, viral vectors, and with whole tumors. And they are adding cytokines such as granulocyte–macrophage colony-stimulating factor (GM-CSF) or interleukin 4 during dendritic cell growth or maturation or at the site of vaccination to try to boost response.

“We’re still learning the best way to make the dendritic cells, send them to the right place in the body, and use the biological stage of development that is most suited to stimulate a response,” Avigan explained.

**Tumor Cell Vaccines**

Instead of relying on one antigen to prime the dendritic cells, Avigan and Donald Kufe, M.D., professor of medicine at Dana-Farber Cancer Institute and Harvard University in Boston, are fusing whole tumor cells to the dendritic cells. They hope to express the entire repertoire of the tumor’s antigens—including those as yet unknown—and avoid the tumor’s ability to downregulate expression of a single antigen to escape the immune response.

In a phase I study published in *Clinical Cancer Research* in July, the researchers gave the fusion cell vaccine to 10 patients with metastatic breast cancer and 13 patients with metastatic renal cancer. Two patients with breast cancer had disease regression, including one woman whose large mass in her chest wall regressed by 90%. She showed no evidence of new disease for 2 years after vaccination. Five patients with renal cancer and one with breast cancer had disease stabilization. In about half of the patients, the scientists detected a heightened reaction by the immune system that was targeted at antigens on the tumor cells. Toxic effects were minimal and no autoimmune reactions occurred.

Avigan pointed out several lessons learned in this early phase study. “We learned what kind of lesions produce an adequate number of cells to make the vaccine, and that needle biopsy, in general, didn’t yield enough cells,” he said. “We saw individual biological differences between patients—some tumor cells last and some don’t.” His group has new trials under way, attempting to boost the vaccine’s efficacy by changing how the dendritic cells are made and by maturing them with different cytokines. In a breast cancer trial, they will add interleukin 12 to the vaccine. For renal cancer and myeloma, they will add GM-CSF.

Stanford University scientists have had success treating patients with follicular lymphoma with a single-antigen–based dendritic cell vaccine that is loaded with idiotype (Id), a protein specific to B-cell lymphomas. Twenty-two percent of patients given the vaccine had tumor regression, and for 70% of patients, their disease remained stable for a median of 43 months after chemotherapy. Six patients with disease progression received a booster injection of Id plus a carrier protein (Id-KLH), and three experienced tumor regression.

John M. Timmerman, M.D., who was on the Stanford team and is now at the University of California at Los Angeles Jonsson Cancer Center, marvels at the impact of the booster shot. “We think that the dendritic cells stimulated memory T cells. So when we injected Id-KLH protein, it wasn’t the first time the immune system had encountered that, and it made a vigorous response immediately.”

Excitement Tempered by Long Road Ahead for Dendritic Cell Vaccines
Id-KLH alone is being tested as a vaccine in a multicenter phase III clinical trial, but Timmerman is convinced that “loading ID-KLH into dendritic cells and then giving them to patients is more potent.” He is about to test that assumption in a study ready to launch at UCLA. Thirty-two patients with follicular lymphoma that recurred after one or more treatments will get three monthly infusions of Id-loaded dendritic cells. For patients with less than a complete response at 3 months, a series of six more treatments will get three monthly booster shots will be given. Patients will receive more dendritic cells than in previous studies.

As with the other dendritic cell vaccines, the idiotypic antigen comes from each lymphoma patient’s tumor. Several biotechnology firms are using genetic engineering methods to rapidly produce sufficient amounts of idiotypic antigen to make the vaccine.

**To Each His Own Approach**

Vaccines that aim antibodies at certain dendritic cell receptors to trick the dendritic cells into action hold promise as well. “Dendritic cells express a large number of receptors that can be exploited for [immunotherapy]. It seems that engagement of each of these has a slightly different outcome,” said Larry R. Pease, Ph.D., professor of immunology at the Mayo Clinic. He and colleagues used a human monoclonal immunoglobulin M antibody that crosslinks a receptor on the surface of the dendritic cells, turning on an activation signal that starts a “robust” immune response. Their test of the vaccine in mice with malignant melanoma was published in July in *Cancer Research*. In the two control groups, 25 of 26 mice were riddled with tumors. Of the mice treated with the crosslinked dendritic cells, 11 of 16 were tumor free for several months. “These animals even displayed resistance to a second tumor challenge more than 3 months after the last animal in the control group had developed rapidly growing melanoma,” Pease said.

Berzofsky’s group at NCI is running two clinical trials and several animal model studies using dendritic cells. They are taking a patient’s monocytes and growing them with GM-CSF and interleukin 4 to differentiate them into dendritic cells. Then they mature them with CD-40 ligand. One study pairs the dendritic cells with peptides related to mutations in the ras oncogene for colon cancer patients—one arm with metastatic disease, another arm with no evidence of disease after tumor removal. A second study targets p53 mutations in lung cancer patients. A prostate cancer trial with a “new type of tumor antigen” is being planned.

Berzofsky and most other dendritic cell vaccine researchers mature the dendritic cells outside of the patients because cancer cells make factors, such as vascular endothelial growth factor (VEGF), that inhibit maturation of dendritic cells. Immature dendritic cells cannot present antigens for immune system recognition, and so the body’s immune response to the tumor is stifled. The hope is that by maturing dendritic cells outside of the patient, combining with relevant antigens, then returning them to the patient as an autologous vaccine, “these would be more effective than dendritic cells that matured in the patient where influence of the tumor prevents them from properly maturing,” Berzofsky said.

Eli Gilboa, Ph.D., professor of experimental surgery and immunology at Duke University Medical Center in Durham, N.C., is not so sure. He is injecting immature dendritic cells into sites preexposed to agents that mimic the conditions conducive to *in situ* maturation of the injected dendritic cell. His group has managed to stimulate dendritic cell maturation, migration, and function inside mice, and they hope to translate this simpler approach into human studies.

Nobody expects cancer vaccines to be used as stand-alone therapy. “We’ll need a strategy to remove enough tumor so the immune system has a manageable amount that it can deal with,” Berzofsky explained. “A combination of conventional approaches like surgery or radiation or certain types of chemotherapy that reduce tumor burden combined with an immunotherapy [strategy] that can eradicate any remaining tumor cells or micrometastases is likely to be more effective than either alone.”

Even on the immunotherapy side, one approach will not be enough, according to Gilboa. He wrote an optimistic perspective on cancer vaccines in the May 2004 *Nature Reviews Cancer*, but he is quick to point out the challenges. Most current strategies deal with how to stimulate an immune response. “How to maintain the immune response that you’ve generated is, in my opinion, more important than stimulating a response,” Gilboa said. Add to that the issue of overcoming the immunosuppression induced by the cancer itself, fears of autoimmunity that could potentially be sparked by dendritic cells, and incompatibility of some treatments with immunological treatments.

“I think we’re on the right path,” he continued, “and it’s reasonable to expect that immune intervention can have a dramatic therapeutic benefit for cancer patients, but we are certainly not there and we have a long way to go.”

—Cori Vanchieri