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## Immunologic Death Blow to Cancer Cells

Taking a clue from a rare disorder in which the immune system destroys a patient's cancer even as it attacks the nervous system, researchers have devised a new strategy to fight breast and ovarian cancer. The scientists have engineered immune cells that target cells containing a protein found in up to 60 percent of ovarian tumors and 25 percent of breast tumors.

The engineered cells, which recognize a protein that can trigger an autoimmune response in a small percentage of patients with these cancers, attacked and killed tumor cells grown in the laboratory. "These findings have brought us right to the cutting edge of tumor immunotherapy," said Howard Hughes Medical Institute investigator Robert Darnell, who led the research.

The research team published its findings in the November 5, 2007, issue of the *Proceedings of the National Academy of Sciences*. Darnell and his colleagues at The Rockefeller University collaborated on the research with scientists from the National Cancer Institute and the Memorial Sloan-Kettering Cancer Center.

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Scientists have pursued a variety of strategies to help patients mount a strong, targeted immune response against tumors. Much of the research has focused on identifying antigens, proteins on the surface of tumor cells that can stimulate killer T cells to attack the cancer. So far, however, success has been limited. Researchers have found few antigens that elicit an immune response robust enough to cause tumor rejection, Darnell said.

Darnell and his colleagues theorized that they might find such antigens within the cells of people with a rare disorder known as paraneoplastic cerebellar disorder (PCD). PCD arises in patients whose tumors produce antigenic proteins usually found only in the brain. The robust immune response to these

antigens can trigger killer T cells to attack not just the tumors, but also cells in the nervous system, causing neurologic degeneration.

The disorder is associated with a range of cancers, including lymphomas and lung and testicular cancers. Darnell and his colleagues studied cases in which breast and ovarian tumor cells had triggered an autoimmune attack. In these patients, neurological symptoms usually become problematic before cancer has been detected -but probably well after the immune system has first attacked the tumor.

The researchers concentrated on a tumor antigen called cdr2, which, when produced by breast and ovarian tumors, can trigger PCD. It is also made by a large proportion of breast and ovarian tumors in patients who do not develop neurological disease. The researchers screened a large library of slightly different fragments of the cdr2 protein for those that were most strongly recognized by T cells, and identified one particularly potent version called cdr2(290).

The researchers found T cells that responded to cdr2(290) in the blood of patients with PCD, confirming that they had identified a clinically relevant antigen. Darnell said the same molecule the researchers used in these studies to search for cdr(290)-responsive T cells could potentially also be used as a diagnostic in cancer patients to help guide therapy.

The researchers used transgenic mice containing human immune genes to generate killer T cells that specifically targeted cdr2(290), which allowed them to identify the killer T cell genes producing the receptor that recognizes the cdr2 antigen. They used that information to add the cdr(290)-specific T cell receptor to killer T cells from healthy individuals, and demonstrated that the engineered immune cells could recognize and attack cultured tumor cells that naturally make cdr2.

“The most exciting thing to us was that these T cells became killers of ovarian tumor cells that expressed the cdr2 antigen,” said Darnell. “We know that up to 60 percent of ovarian tumors and 25 percent of breast tumors from neurologically normal cancer patients express cdr2. So, we believe that we have found a pathway to immunotherapy that may be clinically relevant,” he said.

Darnell said that clinical trials of the immunotherapy for ovarian and breast cancers could begin soon, after some technical refinement. However, he cautioned that immunotherapy could trigger both the desired reaction against a patient's tumor, and an attack against the patient's own tissues. Thus, said Darnell, physicians will need to monitor patients in the clinical trials very carefully for signs that this type of autoimmune response is occurring, and block it if it occurs.