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New Treatment Boosts Cancer Vaccine

The first clinical trials of a new type of cancer treatment that releases the “brakes” on immune cells indicate that this approach enhances attacks on tumors while sparing the body's own tissue.

The results of the phase I clinical trials of cytotoxic T-lymphocyte-associated antigen 4 blockade therapy were published online on April 1, 2003, in the Early Edition of the *Proceedings of the National Academy of Sciences*. The researchers involved in the study included [James Allison](#), a Howard Hughes Medical Institute investigator at the University of California, Berkeley, Glenn Dranoff, Steven Hodi and colleagues from the Dana-Farber Cancer Institute (DFCI), Brigham and Women's Hospital, Massachusetts General Hospital and Harvard Medical School.

Over the last decade, basic research in Allison's laboratory and others has shown that the immune-regulating molecule, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), inhibits activated immune system T cells, and prevents them from attacking the body's own tissues. In studies in mice, Allison and his colleagues identified an antibody that blocks CTLA-4 and showed that it enhances the cancer-fighting activity of certain anti-cancer vaccines. Their research showed that blocking CTLA-4 maintains the response of T cells triggered by the vaccines to attack the cancer.

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- James P. Allison

The success of the experiments in mice prompted the researchers to begin initial clinical studies to test whether they could elicit the same kind of response in humans. The phase I clinical trial—which aimed primarily at establishing the safety of the treatment—included nine patients with

advanced cancers who had previously received cancer vaccines.

Three of the patients with metastatic melanoma and two with ovarian cancer had received a vaccine produced by extracting their own cancer cells, engineering the cells to produce the immune-stimulating molecule, granulocyte-macrophage-colony-stimulating factor (GM-CSF), and vaccinating the patients with those cells. This vaccine was developed by Dranoff and his colleagues at DFCI. Four other metastatic melanoma patients had received different vaccines based on immune-stimulating antigens specific to melanomas.

Although the five patients treated with the GM-CSF vaccine had not responded completely to that vaccine, the researchers found clear evidence that the anti-CTLA-4 antibody enhanced the immune system attack on their tumors. However, treatment with the antibodies did not enhance tumor killing in the four melanoma patients treated with the melanoma antigens.

“In the melanoma patients who responded to the anti-CTLA-4 treatment, Dr. Dranoff saw a skin rash, which is a positive reaction,” said Allison. “Such rashes are evidence that the T cells were attacking normal melanocytes in the skin, which is considered a good prognostic sign for people with melanoma. It indicates that the melanoma is being attacked as well. And while the tumor size did not necessarily immediately decrease in these patients, it was clear from pathology studies that tumor cells were being killed and being replaced by these inflammatory T cells.” According to Allison, the patients with ovarian cancer showed an increase in the bloodstream of a marker molecule indicating that the cancer cells were being killed.

Other clinical trials of the anti-CTLA-4 antibody are ongoing, said Allison, and the early results from all the trials make him optimistic that the treatment will prove highly useful. “In my opinion, what is most exciting is that there is no reason that this approach to tumor therapy is limited to any particular kind of cancer,” he said. “However, until we get more experience with the treatment, we should take extreme care before extending CTLA-4 blockade from cancers arising from tissues that are not absolutely essential.”

According to Allison, CTLA-4 blockade could boost anti-cancer immune response to aid several kinds of therapies. “We have preliminary data indicating that the treatment can synergize not only with immunotherapy, but also with radiation and chemotherapy,” he said. “Under circumstances where these treatments also activate the immune system, anti-CTLA-4 therapy could enhance those therapies.”

Allison emphasized that the anti-CTLA-4 antibodies only stimulate the immune system during a narrow window of treatment. “The beauty of this treatment is that the antibodies by themselves are benign. After they clear from the system, immune regulation returns to normal, and the patient is left with an amplified population of anti-tumor T cells.”