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## Combination Immune Therapy Kills Melanoma in Mice

By simultaneously stimulating the body's natural immune response and dampening a mechanism that normally protects the body from attack by its own immune cells, scientists have developed a promising technique for treating the most aggressive forms of the skin cancer melanoma. The new therapy may also work for prostate cancer.

"This two-pronged approach not only kills tumors in mice, but it also produces a characteristic response that we see in the few humans with aggressive melanoma who survive the disease, whether through therapy or spontaneous remission," said James Allison, a Howard Hughes Medical Institute investigator at the University of California, Berkeley. "This is a very exciting result, and we hope to begin human clinical trials by the end of the year."

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**"I am optimistic that human trials of the combination therapy will begin later this year."**

— James P. Allison

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Allison, who has been developing the new therapy for three years, reported his team's results in the August 2, 1999, issue of the *Journal of Experimental Medicine*. Andrea van Elsas and Arthur Hurwitz, postdoctoral fellows in Allison's laboratory, were co-authors of the paper.

Over the past decade, cancer researchers have found that tumor cells often bear molecules, or antigens, on their surfaces that the immune system can attack. But this last line of defense against cancer often fails because tumor cells can thwart this nascent immune response by becoming invisible to the immune system.

The tumor cell's cloaking ability rests with a molecule known as cytotoxic lymphocyte-associated antigen 4, or CTLA-4. This molecule, which healthy cells also produce, appears to stop the immune system's response to self cells.

"The body has elaborate controls that prevent the immune system from attacking its own body, otherwise we'd all develop autoimmune diseases," said Allison. "CTLA-4 is one of the regulatory molecules involved in this process." Other autoimmune diseases include rheumatoid arthritis, lupus and

multiple sclerosis.

Allison explained that the flip side of tumor immunity is autoimmunity, since tumor cells, arise from normal cells and therefore differ little from other cells in the body. "The body is trying to balance recognition of self and recognition of altered self, and when that fails in either direction you get autoimmunity or cancer," he said.

He and his colleagues reasoned that blocking CTLA-4's actions on immune cells known as T lymphocytes might allow the killer cells to destroy the cancerous cells rather than fade away after the tumor repels their initial attack. To accomplish this, the investigators raised a monoclonal antibody against CTLA-4 and administered it to mice with various types of cancer.

"CTLA-4 blockade using this monoclonal antibody worked, but not particularly well in anything but the least aggressive types of tumors," said Allison. "We wanted something that would work in tumors that are hard to kill."

At about the same time, other researchers were testing the effectiveness of a vaccine made from melanoma cells that were both irradiated, to kill them, and genetically engineered to produce granulocyte/macrophage colony-stimulating factor (GM-CSF). This compound, which the immune system can produce naturally, triggers scavenger cells known as macrophages to travel to a site of infection and engulf invading microorganisms. Trials with this vaccine, however, produced about the same results as those from Allison's laboratory with CTLA-4 blockade-some success, but mostly failure.

"So we decided to use both approaches, and the results were very positive, much better than with either approach alone," said Allison. Well-developed melanomas vanished in 80 percent of the mice with already established cancer. Moreover, the therapy protected the animals from developing melanoma again even after receiving additional doses of tumor cells.

Particularly encouraging, said Allison, was the fact that more than half of the normally black-haired mice developed patches of white hair after their tumors disappeared. A similar loss of skin pigment, called vitiligo, occurs in many patients who recover successfully from advanced melanoma. "This depigmentation is what has me really excited about this therapy because of the correlation between vitiligo and successful therapy in humans."

One question dogging the researchers is a concern that CTLA-4 blockade might allow the immune system to run amok. But when the investigators examined the overall level of immune response in the mice, they did not find anything unusual. "The effect seems specific for those T cells that respond to what are considered foreign antigens as opposed to self antigens," he explained.

Allison, who is working with two companies to test the combination approach further, says that the current plan is to complete another round of tests in animals this fall. "We then hope to start human trials in patients with

prostate cancer by year's end," he said. Prostate cancer is a reasonable candidate for this approach because investigators have shown that the immune system also starts developing an immune response against the cancer, only to shut down shortly thereafter.