Cancer drug shows promise against graft vs. host disease

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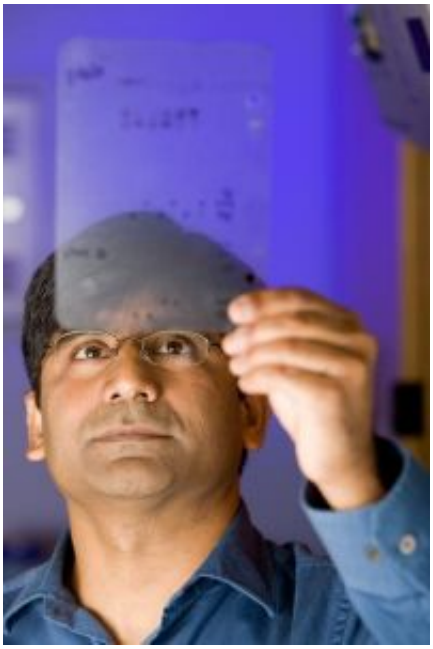

Pavan Reddy, M.D., a University of Michigan researcher, led a study in mice showing that drugs known as HDAC inhibitors show promise in preventing graft vs. host disease. Credit: U-M Photo Services: Martin Vloet

A new University of Michigan study in mice suggests that a drug recently approved to fight cancer tumors is also able to reduce the effects of graft-versus-host disease, a common and sometimes fatal complication for people who have had bone marrow transplants.

Plans are under way at U-M for an initial trial of the drug in people as a

new way to prevent graft-versus-host disease. Researchers expect to begin a trial within a year.

The U-M scientists tested the effects of the drug SAHA, as well as another member of a group of drugs known as HDAC inhibitors, on key immune system cells called dendritic cells. In mice, both drugs were able to significantly diminish the destructive inflammatory effects that these cells cause in graft-versus-host disease.

Graft-versus-host disease occurs when immune cells in the transplanted bone marrow mount a misguided attack on body tissues. If HDAC inhibitors turn out to be safe and effective in people, they might offer a treatment option preferable to the immunosuppressant drugs used now to treat the disease. These leave people vulnerable to infection and have other significant side effects.

"To make bone marrow transplants more effective, we need better control of the very powerful reactions between the immune systems of the donor and recipient. This study shows how drugs like SAHA regulate those reactions, and takes us a major step closer to bringing this new approach to patients who need transplants," says James L.M. Ferrara, M.D., director of the U-M Combined Bone Marrow Transplant Program and a senior author on the study. Ferrara is also professor of internal medicine and pediatric and communicable diseases at U-M.

"These HDAC inhibitors were thought to just kill cancer cells, but at lower doses, it's possible they can modulate a number of immune diseases," says Pavan Reddy, M.D., the study's lead and corresponding author, and an assistant professor of internal medicine at the U-M Medical School. "The mechanism we have identified in graft-versus-host disease may be involved in autoimmune diseases as well."

The study appears in the July issue of the *Journal of Clinical*

Investigation.

Context:

Bone marrow stem cell transplants are most commonly used to treat leukemia and lymphoma. By replenishing depleted blood cells, the transplants allow higher doses of chemotherapy to more effectively get rid of cancer cells.

But as many as half of bone marrow transplant recipients develop acute or chronic symptoms of graft-versus-host disease, which can affect the skin, liver and gastrointestinal tract. Reddy calls the disease "the single biggest barrier to bone marrow transplant."

The study suggests a novel way to treat graft-versus-host disease with an already available drug that is stirring considerable interest as an anti-cancer agent. The FDA approved SAHA, marketed under the name Vorinostat, as a treatment for one kind of lymphoma in 2006 and for leukemia in 2007. SAHA is being used off label for other cancers, including lung, brain and colon cancer.

The U-M study adds to a growing body of research suggesting HDAC inhibitors also may be useful tools to reign in misguided immune responses. Researchers elsewhere have recently shown that HDAC inhibitors have been beneficial in animal studies of lupus and inflammatory bowel disease. Other studies suggest the drugs could be useful in regulating the immune response in heart and islet cell transplants.

Research details:

The U-M researchers studied the responses of immune system dendritic cells in mice given SAHA and ITF 2357, another new HDAC inhibitor.

Dendritic cells are important immune system cells whose varied roles are beginning to be fully understood.

The scientists looked at the two HDAC inhibitors' effects on mouse and human dendritic cells in culture. They found that as they suspected, the drugs acted to diminish the dendritic cells' key role in promoting pro-inflammatory proteins called cytokines. Specifically, the researchers found that the HDAC inhibitors increase the expression of IDO, an enzyme which represses dendritic cell activity.

They tested the HDAC inhibitors in mice bred to display the effects of graft -versus-host disease. When they injected the mice with dendritic cells treated with the drugs, they found the drugs were able to reduce the disease's effects.

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