Prototype drug targets metabolism, halts disease that limits bone marrow transplantation

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(PhysOrg.com) -- A prototype drug already shown to hold promise for treating autoimmune disorders like lupus, arthritis and psoriasis halts established graft-versus-host disease (GVHD) in mouse models of bone marrow transplantation, research at the University of Michigan and the University of Florida shows.

The research, published in the Jan. 26 issue of *Science Translational Medicine*, also offers new insights into how the cells that cause GVHD and other immune disorders make adenosine-5'-triphosphate (ATP), the fuel cells use to survive and carry out their prescribed functions. These findings challenge a long-standing model of how activated cells of the immune system make ATP, opening the door for fundamentally new approaches to combat immune diseases.

Bone marrow is the soft tissue that helps form blood cells, including the white cells that fight disease and infection. Bone marrow transplantation is a life-saving procedure used to treat diseases once thought incurable, including leukemia, aplastic anemia, Hodgkin's disease, multiple myeloma, immune deficiency disorders, and some solid tumors. During what's known as allogeneic bone marrow transplantation, healthy bone marrow stem cells from a donor are transfused into a patient, replacing marrow that is either not working properly or has been destroyed by chemotherapy or radiation.

The new donor bone marrow must precisely match the genetic makeup of the patient's own marrow. If the donor's bone marrow is not perfectly matched, as is often the case, it can perceive the patient's body as foreign material to be attacked and destroyed. This condition, known as GVHD, is often life-threatening and greatly limits the use of allogeneic bone marrow transplantation.

Currently, allogeneic bone marrow transplant recipients are given drugs that suppress the immune system in order to lessen the effects of GVHD. In many cases, these drugs are simply ineffective at preventing or treating GVHD. They also cause serious side effects, such as lowering a person's resistance to infection and making infections more difficult to treat.

In the new work, a research team led by U-M faculty members Gary Glick and James Ferrara tested a compound called Bz-423 in several mouse models of bone marrow transplantation. A chemical cousin of anti-anxiety medications such as Valium and Xanax, Bz-423 sets off a chain of events that results in a type of cell death called apoptosis in donor T-cells, the immune cells that cause GVHD.

"We've been working on the chemistry and biology of Bz-423 for several years, and have identified what it binds to and how it works in cells, said Glick, who is the Werner E. Bachmann Collegiate Professor of Chemistry and a professor of biological chemistry. "Bz-423 controls an enzyme involved in metabolism, and because our previous work with lupus showed that the compound targets disease-causing cells without harming normal cells, that led us to believe there may be differences in metabolism between normal and disease-causing immune cells."

The researchers turned their attention to GVHD because it's an important medical problem and also because in animal models, disease-causing cells can easily be distinguished from normal cells. As suspected,

they found that the rogue T cells involved in GVHD do differ metabolically from normal white blood cells.

"Cells make energy through one of two processes: glycolysis or oxidative phosphorylation," Glick said. "Others have shown that normal T cells, which are important for fighting bacteria and viruses, use glycolysis. However, we found that disease-causing T cells use oxidative phosphorylation." In addition, the aberrant T cells have reduced levels of antioxidants.

"This combination of decreased antioxidants and oxidative phosphorylation seems to be a unique property of pathogenic T cells, compared to normal white blood cells, heart cells, brain cells and other body cells," Glick said. The unusual metabolic profile of troublemaking T cells provides the basis for selective targeting by drugs like Bz-423 that modulate metabolism.

"Bz-423 provides a much higher level of selectivity for silencing disease-causing cells than is seen with the immunosuppressive drugs typically used for diseases like GVHD," Glick said. In the experiments described in the paper, Bz-423 arrested GVHD in mice by selectively killing disease-causing T cells, with no adverse effects on normal cells or bone marrow transplant success.

"Now that we've made these observations about the role of metabolism in immunology, particularly as it relates to disease, there's much more work to be done to learn why these differences occur in diseased cells," Glick said. "Understanding that should reveal other ways to intervene therapeutically."

Research on compounds with similar properties to Bz-423 is ongoing at Lycera Corp., a Plymouth, Michigan-based company that Glick and U-M associate professor of obstetrics and gynecology Anthony Opipari

founded in 2006.

"Lycera is moving toward clinical trials with molecules that control the same cellular enzyme as Bz-423, but that have better drug like properties, including oral bioavailability," Glick said.

More information: Science Translational Medicine
stm.sciencemag.org/

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