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### **Improving the Odds**

#### **A new method for bone marrow transplantation from mismatched donors restores the immune system faster**

Although bone marrow transplants have long been standard for acute leukemia, current treatments still rely on exact matches between donor and patient. Now, scientists at the University of Perugia, Italy, and the Weizmann Institute of Science have improved on a method of transplanting bone marrow-based stem cells from a mismatched donor, making it safer for use when no exact match exists. They were invited to present their findings at the recent annual American Society of Hematology conference in New Orleans.

More than a decade ago, Prof. Yair Reisner of the Weizmann Institute's Immunology Department pioneered a method for transplanting stem cells from family members who are a partial match. Based on these studies (in mice), he joined forces with Prof. Massimo F. Martelli, Head of the Hematology and Clinical Immunology Section at the University of Perugia, to demonstrate in more than 300 patients that the cure rate of these so-called "mega dose" transplants is similar to that of transplants from matched, unrelated donors picked from international bone marrow donor registries. To combat the body's tendency to reject the foreign cells, these stem cells are stripped of immune cells called T cells and given in high doses that overwhelm the host's own immune system. Although removing donor T cells from the bone marrow reduces the risk of graft-versus-host disease – caused when the T cells attack the recipient's tissues – the immune system is slow to recover after the transplant, leaving the patient at risk of serious infection. Doctors are faced with a difficult choice: Either remove the T cells from the bone marrow, increasing the risk of infection, or leave the T cells in the graft, putting the patient at risk for lethal graft-versus-host disease.

Martelli, working with Reisner, has now found a way to facilitate the recovery of the immune responses in recipients of T cell-depleted bone marrow transplants. In a clinical trial, 25 of 26 leukemia and lymphoma patients who received mismatched mega dose T cell-depleted stem cell transplants from relatives showed prompt immune recovery, and their immune systems were functioning well several months later.

The scientists knew that certain regulatory T cells (T regs), rather than causing graft-versus-host disease, could actually help to prevent it in mice. T regs have also been shown to keep other immune responses in check, including preventing autoimmune attacks on the body's own cells. In the present study, after purifying T regs from the donor's blood, the cells were infused intravenously into the cancer patients, who had previously undergone standard radiation and chemotherapy treatments. Three days later, the patients received the donor stem cells, along with another kind of T cell – those that fight disease.

The patients who underwent this procedure showed quick, lasting improvements in immune activity; most experienced no symptoms even though they received large doses of the T cells that are generally associated with lethal graft-versus-host disease.

Further follow up on these patients and additional clinical trials will be needed before the procedure can be widely adopted. But these results strongly suggest that T regs used in mega-dose stem cells will further enhance the cure rate for bone marrow transplant patients without a matched donor in the family.

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*Prof. Reisner is the incumbent of the Henry H. Drake Professorial Chair in Immunology.*

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