SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS DEVELOPING NEW PROCEDURES TO MAKE BONE-MARROW TRANSPLANTS SAFER

DALLAS – Feb. 4, 2003 – Researchers at UT Southwestern Medical Center at Dallas are helping develop new procedures that may reduce infections and diseases resulting from bone-marrow transplants.

The work by Dr. Ellen Vitetta, director of the Cancer Immunobiology Center, and Dr. Robert Collins, director of the UT Southwestern Hematopoietic Cell Transplant Program, is part of research at UT Southwestern designed to identify the problem cells in a bone-marrow transplant and eliminate them before the transplant is carried out.

The latest findings will appear in the Feb. 4 issue of the *Proceedings of the National Academy of Sciences* and online at the journal's Web site.

In a bone-marrow transplant, the patient is treated with very high doses of chemotherapy, with or without radiation, to destroy cancer cells. This process also destroys the bone marrow, which is replaced with healthy marrow cells obtained either from the patient beforehand (autologous) or from a healthy donor (allogenic). Once transplanted, the donated bone-marrow cells multiply and repopulate the patient's blood cells.

Allogenic stem cell transplants are preferred for many hematologic malignancies or inherited disorders. But while this type of transplant often has an anti-leukemic effect, the risk is graft-versus-host disease (GVHD), where the donated immune system (the graft) begins to attack the recipient's body (the host).

If the graft T cells (lymphocytes) are depleted prior to transplant, GVHD is eliminated. However, there is no anti-leukemic effect, and the patients are at-risk for infection.

"Graft-versus-host disease – when T cells are not eliminated and infections when they are – causes significant morbidity and mortality in patients," said Vitetta, the study's senior author.

To combat this problem, Vitetta and Collins are developing and refining an in-vitro procedure to activate the donor T cells responsible for causing GVHD. These activated T cells

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are then eliminated with an immunotoxin against the cellular activation marker, CD25. This removes the cells responsible for GVHD, but spares cells responsible for the anti-leukemic activity and for fighting infections.

Immunotoxins are drugs created by linking an antibody to a portion of bacterial or plant toxin to destroy cells expressing the molecule to which the antibody binds.

"One of the major goals – the Holy Grail of bone-marrow transplantation – is to separate graft-versus-host disease from graft-versus-leukemia, and we're still not sure it can be done. But, what we've seen so far is very encouraging. If this approach proves successful, it would make transplants a lot safer and more widely utilized," said Collins.

In a recent clinical study in France, Vitetta's group showed the incidence of GVHD was greatly reduced in patients who were infused with the treated cells.

"What came out of the French trial is that this procedure is the way to go," Vitetta said. "Now, we're trying to refine our work and see how broadly it can be applied."

A study by Collins will open soon at UT Southwestern involving both related and unrelated bone-marrow transplant recipients. Instead of getting a full complement of T cells from the donor, he said, patients will receive T cells that have been selectively depleted of the allo-reactive T cells that researchers believe cause graft-versus-host disease.

In addition to this work, Vitetta and Collins are investigating whether T cells that cause GVHD can be distinguished from T cells with anti-leukemia activity. This is accomplished by generating clones of the two types of receptors and sequencing them.

Their in-vitro research, featured in the *Proceedings of the National Academy of Sciences* article, has shown there are separate donor T cells that respond to the patient's normal cells and leukemia cells.

"The goal is to get rid of the T cells that cause damage and save the beneficial ones," Vitetta said. "Even though we're in the early days, both in the clinical trials and in the laboratory research, this is very encouraging.

"Importantly, it would really be the first time something like this has been done entirely

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in-house, without companies. We make the immunotoxin, do all the preclinical studies, file and get an IND (Investigational New Drug Application) with the FDA, and do the clinical study, all on-site. We are hoping this will be a flagship for future efforts in this and related areas."

Because a variety of disorders are treated with bone-marrow transplants, the use of immunotoxins to eliminate harmful cells prior to the transplant could have a significant impact in increasing transplant success rates and reducing hospital time.

Bone-marrow transplants can benefit patients with several types of cancers, including leukemia, lymphoma, myeloma or aplastic anemia. Occasionally, those with certain genetic diseases of the blood (such as thalassemia, sickle-cell disease and severe combined immunodeficiency) receive transplants.

"If you can eliminate graft-versus-host disease but retain or even enhance the other beneficial effects of T cells, this could be applied to a variety of malignancies that are sensitive to donor T cells," Collins said. "It could be utilized in patients who have greater degrees of mismatch and in older patients. If this works out and makes transplants a lot safer, then I know we're going to be doing a lot more transplants."

Vitetta hopes to see the procedure expanded into different areas, such as the treatment of breast, prostate and other cancers.

"I'd like to see this apply to all transplants and become standard-operating procedure," she said. "This could establish a new paradigm."

The research was partially supported by a grant from the Leukemia Association of North Central Texas.

Other contributors to the *Proceedings* study included first author Dr. Jaroslav Michalek and Dr. Petra Vaclavkova, postdoctoral research fellows; H. Pasha Durrani, research technician; and L.E. Ruff and Dr. Daniel Douek at the National Institutes of Health.

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