New therapy from naive cells attacks high-risk viruses in cord blood transplant patients

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Researchers in the Center for Cell and Gene Therapy at Baylor College of Medicine, Houston Methodist and the Texas Children's Hospital have expanded the use of virus-specific cell therapy in cord blood transplant patients to successfully prevent three of the most problematic post-transplant viruses affecting this group of patients that have yet to be addressed clinically - cytomegalovirus (CMV), Epstein-Barr virus (EBV), and adenovirus.

The team published their results of a clinical trial that evaluated the safety and efficacy of the therapy - translating an approach from the bench (published in the journal Blood in 2009) to patients at the bedside—in the journal *Science Translational Medicine*.

Patients undergo stem cell transplant as an often lifesaving treatment for leukemia, lymphoma, sickle cell anemia, and other life-threatening blood and immunodeficient disorders. After the transplant phase, patients, whose immune systems are now depleted, receive specially modified virus-specific T cells (specialized immune cells) that are reprogrammed to target and attack blood cancers and other disorders of the immune system. The new blood-forming cells can come from one of three different sources, including bone marrow, peripheral blood stem cells, and cord blood.

But the lifesaving treatment also comes with serious risk of infections, and up until now there have been no treatment alternatives aside from suboptimal pharmacotherapy that addresses the risk of these viruses - especially for CMV, an infection that poses a higher risk to patients undergoing a cord blood transplant, said Dr. Patrick Hanley, first author of the study and an assistant professor in the division of blood and marrow transplantation at Children's National Medical Center in Washington, D.C. (Hanley conducted a majority of the work while completing his training in the Graduate School of Biomedical Sciences at Baylor and postdoctoral training in the Center for Cell and Gene Therapy.)

Researchers in the Center for Cell and Gene Therapy have pioneered efforts to make specialized T cells that are trained to look out for these infections and have successfully used virus specific therapies attacking multiple problematic viruses from healthy donors.

"In the past we have been able make virus-specific T cells that work well so long as the donor has been exposed to the virus before," said Hanley. "In cord blood transplants, the cells are derived from the umbilical cord of a mother and newborn baby so the cord blood has not built up immunity to these viruses."

Though there may be some antibodies from the baby's mother, most cord blood donors do not have the memory T cells to recognize and attack the viruses if they present, said Dr. Helen Heslop, director of the Center for Cell and Gene Therapy and a co-author on the report.

"Cord blood transplant is an option for patients who need a transplant but do not have a matched family member" said Heslop. "There are some patients, such as those with inherited immunodeficiencies, where we prefer to use cord blood because it is available more quickly than an unrelated donor."

In the study, they also identify a way to expand specialized T cells against CMV from healthy adult donors who have not been exposed to the virus, called CMV-seronegative donors. Like cord blood, these donors have not developed memory T cells to CMV.

CMV, a virus of the Herpes family, can have serious long-term affects including hearing loss, vision loss, mental disability, microcephaly, lack of coordination, cerebral palsy and seizures. The virus can lie dormant in the body for years.

"This is kind of a 'catch 22' because cord blood cells and CMV-seronegative donors do not have memory T cells specific for CMV, therefore the recipient is at the greatest risk as the donor does not offer protection to the transplant recipient," said Hanley. "Moreover, because these donors are sero-negative, no one has been able to grow viral specific T cells for CMV."

In the Center's Good Manufacturing Practice facility using technology first adopted in the lab, the team expanded the way they previously made T cells to create a memory of CMV.

We used specialized antigen-presenting cells and a host of other growth factors to give the cells an extra stimulus in hopes of better mimicking the in-vivo priming conditions of a naïve T cell and it worked, he said.

In a clinical trial of three children (with fanconi anemia, acute lymphoblastic leukemia, and severe combined immunodeficiency) who were at a high risk for CMV infection, the new treatment was determined safe and may be effective at preventing or treating infection.

One patient experienced a reactivation of both cytomegalovirus and adenovirus (another common post-transplant infection), which was resolved with therapy while two patients did not show signs of infection.

"This was a proof of principle, we are no longer limited by T cell memory," said Hanley. "This gives us a platform to generate T cells against tumors, additional viruses, or any antigen where we do not have enriched T cell precursors."

"While T cell therapies from virus experienced donors have shown great efficacy in patients after stem cell transplant, virus infection still remains a huge cause of morbidity and mortality in our transplant patients especially when the donor is negative for the virus," said Dr. Catherine Bollard, director of the Program for Emerging Technologies in Immune Cell Therapies at Children's National Medical Center, and the corresponding author of the study. "Therefore, until now, previous approaches have not solved this problem for preventing life threatening virus-associated diseases in some of our highest risk patients."

In this study, we have shown for the first time that virus killing T cells can be elicited from virus naive adult and cord blood donors and that these naïve-derived virus killing T cells are safe and may prevent infection in these high risk patients, Bollard said. "This work is exciting because we may ultimately be able to use this treatment as a 'prophylactic vaccine' to improve outcomes for all high risk transplant recipients, including patients after solid organ transplantation."

In another significant finding, the team observed that the naïve T cells in cord blood and CMV-seronegative donors recognize and respond differently to CMV than memory T cells from adults. "We are now looking at why that happens," said Hanley.

"Our new Texas Children's Hospital cord blood transplant clinical trials have improved survival considerably on patients with non-malignant pediatric disorders, specially patients with immune deficiencies. The overall survival after cord blood transplantation for patients with non-malignant pediatric disorders has been excellent with minimal toxicity and side effects," said Dr. Caridad Martinez, assistant professor in the Texas Children's Cancer and Hematology Centers and the Center for Cell and Gene Therapy. "Our standard approach now is to perform a cord blood transplantation when no related donor is available in patients with non-malignant diseases, especially in patients with immune and metabolic disorders which timing of transplant is crucial".

More information: CMV-specific T cells generated

from naïve T cells recognize atypical epitopes and may be protective in vivo, *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/… scitranslmed.aaa2546

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