



SCID Q & A with Sung-Yun Pai, MD

Sung-Yun Pai, MD, a pediatric hematologist/oncologist at Dana-Farber/Boston Children's Cancer and Blood Disorders Center, was lead author on two articles published last year on Severe Combined Immune Deficiency (SCID) in *The New England Journal of Medicine*: "Transplantation Outcomes for Severe Combined Immunodeficiency, 2000–2009" July 31, 2014 and "A Modified γ -Retrovirus Vector for X-Linked Severe Combined Immunodeficiency" October 9, 2014. The first reviewed outcomes after bone marrow transplantation; the second reported the first results of a new international gene therapy trial for X-linked SCID.

Q. What is SCID?

A. SCID is a group of disorders that compromise the blood's T cells, a key component of the immune system that helps the body fight common viral infections, other opportunistic infections and fungal infections. They are also important for the development of antibody responses to bacteria and other micro-organisms. A baby born with SCID appears healthy at birth. Once the maternal antibodies that the baby is born with start to wane, the infant is at risk of life-threatening infections. Unless diagnosed and treated with a stem cell transplant from a healthy donor or a more experimental therapy like gene therapy, babies with SCID typically die before their first birthday.

Q. How is stem cell transplant used to treat children with SCID?

A. Transplantation using healthy donor cells derived from a variety of sources has been described for SCID since 1968. The ideal donor is a healthy sibling donor with a matched tissue type. However, only 25 percent or less of siblings will be matched to the patient, and fewer siblings still will be healthy and suitable to donate. For most patients, the donor is a parent, an unrelated suitably matched adult or umbilical cord donor.

Q. Please describe your paper on transplant outcomes.

A. We examined outcomes for 240 patients transplanted in North America between 2000 and 2010. Virtually all patients with a matched sibling donor survived, but only half of babies who were actively infected at the time of transplant survived. Babies who had never suffered an infection or whose infection had resolved prior to transplant had excellent survival, regardless of age or donor source. Actively infected babies who got chemotherapy or immunosuppressive conditioning prior to transplant had lower survival compared to those who received no conditioning. While overall we found better immune system recovery in surviving babies who received

chemotherapy conditioning, this benefit must be weighed against the long and short-term toxicities of chemotherapy. The longer you wait for transplant, the more likely it is that a baby with SCID will develop an infection, making it important to transplant babies as soon after birth as possible. Newborn screening in all 50 states is critical for this.

Q. What is gene therapy?

A. Gene therapy is an experimental treatment currently available for X-linked and adenosine deaminase deficient SCID (ADA SCID). Clinicians harvest the patient's own blood stem cells, introduce a corrected copy of the gene using a specially designed virus called a vector, and give those cells to the patient through a transplant. Because the patient's own cells are used, gene therapy eliminates the risk of graft-versus-host disease.

Q. Please describe your paper on gene therapy.

A. The new trial for X-linked SCID was designed to avoid the treatment-related leukemia that developed in one-quarter of patients in earlier European trials. We found that a redesigned vector is as effective in curing the SCID, and we have preliminary evidence that it is safer. Although our patients have not yet cleared the two-to-six year window in which the leukemia developed, molecular analysis shows that the new vector did not lead to the proliferation of cells driven by over-activity of cancer-causing genes that was seen in the earlier trials.

Q. Which patients should consider conventional transplant, and which should consider gene therapy?

A. If you have a matched sibling donor you should go with that. These transplants are almost always performed without chemotherapy, so even babies with an active infection do well. These patients are at substantially lower risk of graft-versus-host disease and rarely get its severe form. Examples of candidates for gene therapy include patients who lack a matched sibling donor, as well as those with an active infection. While most patients who undergo transplant do not develop severe graft-versus-host disease, for those that do, the consequences can be debilitating. Gene therapy trials for ADA SCID have yielded positive results and are beginning to be covered by insurance.

Q. Looking ahead, what do you see?

A. Given the toxicity of chemotherapy conditioning, we would like to determine the minimal dose needed to give patients the best chance of having normal immune systems. In gene therapy, we are working on the next generation vector, which we hope will be even less prone to the development of leukemia, and plan to introduce a low dose of chemotherapy conditioning to promote better immune system recovery. Both avenues of treatment are clearly advancing. It's too soon to say whether one will take over for the other. Ultimately I hope to see that all babies with SCID can be cured.

IDF SCID Newborn Screening Campaign Update

For many years, the Immune Deficiency Foundation (IDF) has strongly supported and worked tirelessly toward establishing SCID newborn screening programs in all 50 states to save lives. With more than 40 states either currently screening or planning to begin screening, the goal is within reach, but much work needs to be done.

To stay up-to-date and learn how to get involved, visit the IDF SCID Newborn Screening Blog: www.idfscidnewbornscreening.org.

The IDF SCID Newborn Screening Blog is sponsored in part by PerkinElmer and Sigma-Tau Pharmaceuticals, Inc.