

NON-TECHNICAL ABSTRACT

An enzyme, called adenosine deaminase (ADA), is needed for T and B cells of the immune system to develop. Children born with mutations in the ADA gene and who do not make ADA enzyme have severe combined immunodeficiency (SCID). Children with SCID generally die in the first year of life from severe infections because they do not have immune systems which can fight the infection. SCID can be cured by a bone marrow transplant, but this is an imperfect approach because many children do not have siblings who are tissue matches to serve as bone marrow donors. Transplanting bone marrow from a parent who is only a half match or from a non-family member can lead to significant problems, from rejection of the bone marrow graft to reaction of the donor's immune cells against the SCID patient. There is an effective form of enzyme therapy for ADA-deficient SCID, in which children receive injections of purified ADA enzyme once or twice each week. ADA enzyme injections can allow the immune system to recover to a level that protects the children from infections. However, these injections must continue to be given life-long or the immunity will wane. ADA enzyme therapy is very expensive (\$100,000-300,000 annually).

Gene therapy for ADA-deficient SCID could be performed by introducing a normal copy of the human ADA gene into the patient's blood-forming stem cells which are then transplanted back into the patient. Stem cells are present in bone marrow and also in the umbilical cord blood of newborns. Effective gene therapy for ADA-deficient SCID will require inserting the normal human ADA gene into a sufficient number of the subject's stem cells and expressing the gene to make ADA enzyme in the subject's immune blood cells.

In this study, we will determine whether this gene therapy approach is safe, feasible and effective. We will treat ten subjects, either newborn infants diagnosed prior to birth, or children, with ADA-deficient SCID. Umbilical cord blood/bone marrow will be collected from the infants at birth/during childhood, processed in the laboratory to introduce the normal human ADA gene (using retroviral vectors for gene delivery), followed by return of the cells to the subjects by an intravenous infusion. Two different ADA gene vectors will be used side-by-side, to see if either one works better than the other. The infants will be started (and children maintained) on ADA enzyme therapy, because it is a known, effective therapy. We will examine blood samples taken monthly for the next two years to evaluate side-effects from the procedure, whether the new ADA gene is present in blood cells, and

whether the new ADA gene is working to make ADA enzyme. If we determine that the ADA gene is present and active, we will wean the child from ADA enzyme therapy to determine whether the gene delivery has produced enough corrected cells to let the immune system be protective without the need for further enzyme injections.

These studies will provide information on the safety, feasibility and efficacy of this approach applying gene therapy for ADA-deficient SCID. It may lead to a new treatment for this disease which is safer than bone marrow transplant and more cost-effective than ongoing ADA enzyme replacement therapy.