

I. Scientific Abstract

When expressed in otherwise permissive cells, dominant-negative HIV *tat* and *rev* genes can confer resistance to HIV infection in culture. Pediatric HIV infection presents a unique opportunity to exploit these mutants in gene therapy. Cord blood hematopoietic stem cells may be particularly good as targets for genetic manipulation by retrovirus vectors. We have developed a unique vector that expresses a double transdominant fusion protein (Trev) capable of inhibiting both Tat- and Rev-mediated viral functions. In culture, this construct decreases viral gene expression and makes cells resistant to viral-induced cytopathicity. We have also shown that the vector can be introduced into human cord blood hematopoietic progenitors. We plan to conduct a Phase I clinical protocol to test the safety and some aspects of *in vivo* biological activity of this vector. The proposal consists of five components: (1) storage of cord blood mononuclear cells from a cohort of infants at risk for maternally-transmitted HIV infection; (2) identification of infants with HIV infection demonstrable within the first year of life; (3) transduction of autologous cord blood CD34+ hematopoietic progenitors with both the Trev vector and an inactive control vector followed by infusion into infected infants; (4) serial evaluation of the *in vivo* persistence of the Trev vector-transduced cells compared to the control vector transduced cells in each patient; (5) evaluation of the potential immune response of the patients to Trev. These studies will indicate whether expression of Trev is, itself, deleterious to progenitor and mature hematolymphoid cells and whether Trev elicits a potentially problematic immune response. The long term aim of these studies is to test whether it is feasible to create an effective gene-based therapy for Pediatric AIDS using transdominant inhibitors of HIV.