

Preclinical evaluation of gene therapy for Sickle Cell Disease

P.I.: Victor Garcia, Ph.D.

In recent years, the life expectancy and symptoms of patients with sickle cell disease (SCD) have improved significantly. These improvements have been due to clinical, genetic and molecular advances that have revealed basic aspects of the pathophysiology of SCD. In spite of these advances, SCD remains associated with significant mortality and morbidity. The large body of data with autologous stem cell bone marrow transplantation has shown to be effective for a certain number of patients with SCD but early mortality, the availability of suitable donors and patient selection remain limiting factors. Alternatively, genetic correction of SCD offers hope as a potential curative approach. Recent progress in the development of SCD mouse models and vector design have provided strong rationale and impetus for preclinical implementation of gene therapy approaches for SCD. In this proposal, we address three important challenges to the successful genetic correction of SCD. We first develop lentivirus-based vectors for the transduction of globin genes that include all critical regulatory elements for high level single copy gene expression. We then evaluate their transduction efficiency into stem cells from SC patients and finally we evaluate these transduced cells in vivo using a human/mouse xenograft model of bone marrow transplantation. The preclinical data obtained while conducting these experiments will serve as the rationale basis for the implementation of clinical gene therapy protocols aimed at the genetic correction of sickle cell disease.

Specific Aims:

1. To develop lentivirus vectors for the efficient transduction of human β -globin genes that express at high level when integrated as single copy genes.
2. To evaluate, in vitro, the human β -globin vectors developed in specific aim 1 using hematopoietic progenitor cells from SC patients.
3. To perform the preclinical evaluation of SC gene therapy using a human/mouse xenograft model of bone marrow transplantation.