

Clinical Research Project: Allogeneic Stem Cell Transplantation for adult patients with Sickle Cell Disease

Ablative allogeneic transplantation is used to treat diseases, though the potential severe toxicities of the procedure have precluded its broad use for adults with severe effects from sickle cell disease. The long-term objectives of this project are to reduce the toxicity and improve the overall survival following non-myeloablative allogeneic transplantation for sickle cell disease. The central hypothesis of this project is that allogeneic stem cells infused after a less toxic, non-myeloablative regimen will induce a stable donor hematopoietic state. Two complementary strategies will be pursued in order to test this hypothesis. First, persons with severe illness from sickle cell disease will be transplanted with HLA matched sibling donor peripheral blood stem cells (PBSC) using a less toxic non-myeloablative regimen. The primary purpose of this clinical trial is to assess the feasibility in terms of toxicity and engraftment of a less toxic, nonablative conditioning regimen of *in vivo* alemtuzumab (anti-CD52) monoclonal antibody, moderate dose fludarabine, and cyclophosphamide for patients with sickle cell disease. Early stopping rules for toxicity and failure of donor engraftment are an important part of the IRB approved trial. Clinical outcomes, quality of life, and cost efficiency of the nonmyeloablative transplant will be evaluated.

Secondary objective of this study is to investigate the kinetics of recipient immune reconstitution following transplantation. These measurements will consist of general, antigen specific, and alloreactive immune responses to define the dynamics of immune reconstitution following allogeneic transplantation in this patient population.

Aim #1. Evaluate the safety, feasibility, and engraftment rate of transplantation using *in vivo* alemtuzumab followed by concomitantly administered fludarabine and cyclophosphamide as a conditioning regimen prior to HLA matched sibling peripheral blood progenitor cell infusion with alemtuzumab 'in the bag' (*in vivo* and *in vitro* T cell depletion).

Aim #2. Perform a preliminary cost analysis of non-myeloablative transplantation in sickle cell disease. This determination will be conducted through a comparison of costs associated with treatment of sickle cell disease by non-myeloablative transplantation versus those associated with conventional care of patients with sickle cell disease considered eligible for this trial, but not enrolled.

Aim #3. Define the kinetics of immune reconstitution in sickle cell patients. Immune reconstitution will be measured by recovery of: a) Lymphocyte subsets (CD4 and CD8), b) Mitogen induced proliferation of T lymphocytes, c) Alloreactive T lymphocytes, d) Viral antigen specific T lymphocytes. We will further investigate whether recovery of T-cells occurs through a central (thymic) mechanism or peripheral expansion of donor T-cells using the T-cell receptor excision circle (TRECs) analysis.