

## Treatment of Children with Thalassemia Major Using Umbilical Cord Blood Stem Cells from Unrelated Donors (PCRC 1579)

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### Synopsis:

Hematopoietic cell transplantation (HCT) is the only curative therapy for thalassemia major. The safety and long-term success of HCT is excellent in younger children with thalassemia when hematopoietic stem cells from bone marrow or umbilical cord blood (UCB) from HLA-identical sibling donors are used. Unfortunately, 65 to 70% of patients with thalassemia lack a suitable HLA-identical sibling donor. The results of HCT with alternative stem cell donors have been disappointing due to problems of graft versus host disease (GVHD) and graft rejection with recurrence of thalassemia. We hypothesize that the use of unrelated UCB, a widely available source of stem cells, in combination with augmented immunosuppression can overcome these limitations.

The purpose of this investigation is to evaluate the risks and benefits of unrelated UCB transplantation in patients who have thalassemia major. Patients who lack suitable family member donors will be eligible for enrollment, and primary transplantation outcomes of engraftment, GVHD and survival will be measured. To enhance the safety of the study, stringent rules for donor selection that include a minimum degree of HLA-matching and a minimum UCB cell dose requirement have been integrated in the study design. To assess the cause of graft failure if it occurs after transplantation, early markers of rejection such as donor-host chimerism and gene expression profiling of peripheral blood cells will be analyzed prospectively. If successful, the results of this study might expand the availability of stem cell transplantation to more children with thalassemia major.

Specifically, we propose to conduct a pilot phase I-II investigation of unrelated umbilical cord blood transplantation for thalassemia major, utilizing a myeloablative combination of busulfan, cyclophosphamide and rabbit anti-thymocyte globulin (rATG) before transplantation, and a combination of mycophenolate mofetil and cyclosporine for post-grafting immunosuppression.

Clinical and laboratory data will be collected before and after transplantation in order to:

1. Define the event-free survival after unrelated cord blood transplantation for thalassemia major, where an event is the occurrence of graft rejection, disease recurrence or death.
2. Prospectively identify gene expression profiles of peripheral blood cells with DNA microarrays which might be predictive of graft rejection through correlation with donor-host chimerism and circulating lymphocyte subsets identified by flow cytometry.
3. Evaluate the effect of donor engraftment on the following clinical and laboratory manifestations of thalassemia major:
  - a. Patient survival, incidence of graft rejection, incidence of platelet and RBC engraftment, and incidence of RBC transfusion.
  - b. Incidence and severity of acute and chronic graft-versus-host disease (GVHD).
  - c. Incidence of complications, including infection, veno-occlusive disease, interstitial pneumonitis, secondary malignancies, lymphoproliferative disorders, and post-transplant myelodysplasia.
  - d. Characteristics of immune reconstitution.