# Haploidentical Transplant for Patients with Chronic Granulomatous Disease (CGD) using Post-Transplant Cyclophosphamide

**NIAID Protocol Number**: **15-I-0007**

**Sponsored by:**
**National Institute of Allergy and Infectious Diseases (NIAID)**

**Principal Investigator: Elizabeth Kang**

**Version Number: 6.0**

**4 April 2018**

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event/Adverse Experience |
| ß-hCG | beta-human chorionic gonadotropin |
| CBC | Complete blood count |
| CFR | Code of Federal Regulations |
| CGD | Chronic Granulomatous Disease |
| CMV | Cytomegalovirus |
| CRF | Case Report Form |
| DHR | Dihydrorhodamine 123 assay |
| DSMB | Data and Safety Monitoring Board |
| EBV | Epstein Barr Virus |
| ECOG | Eastern Cooperative Oncology Group |
| ESR | Erythrocyte sedimentation rate |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte Colony Stimulating Factor |
| GTT | Green Top Tube |
| GvHD | graft versus host disease |
| HLA | human leukocyte antigen |
| HSC | Hematopoietic stem cells |
| IB | Investigator's Brochure |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| LHD | Laboratory of Host Defenses |
| MUD | Matched unrelated donor |
| MUGA | multi-acquisition gated |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| OHRP | Office for Human Research Protections |
| PBSC | Peripheral Blood Stem Cell |
| PI | Principal Investigator |
| PID | Primary Immune Deficiency |
| PTLD | post-transplant lymphoproliferative disease |
| RCHSPB | Regulatory Compliance and Human Subjects Protection Branch |
| RCHSPP | Regulatory Compliance and Human Subjects Protection Program |
| RTT | Red Top tube |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SCID | severe combined immunodeficiency |
| SMC | Safety Monitoring Committee |
| TB | Tuberculosis |
| TBI | Total Body Irradiation |
| TREC | T-cell Receptor Excision Circles |
| TTVs | Transfusion-transmitted viruses |
| UP | Unanticipated Problem |
| UPnonAE | Unanticipated Problem that is not an Adverse Event |

## PROTOCOL SUMMARY

**Full Title**: **Haploidentical Transplant for Patients with Chronic Granulomatous Disease (CGD) using Post-Transplant Cyclophosphamide**

| | |
|---|---|
| **Short Title:** | Haplo Transplant with Cyclophosphamide for CGD |
| **Clinical Phase:** | 0 (Pilot study) |
| **IND Sponsor:** | Elizabeth Kang, MD |
| **Conducted by:** | Laboratory of Host Defenses |
| **Principal Investigator:** | Elizabeth Kang, MD |
| **Sample Size:** | N=10 CGD recipients |
| **Accrual Ceiling:** | 20 |
| **Study Population:** | Patients with CGD and no human leukocyte antigen (HLA) fully matched donor |
| **Study Design:** | To perform a haploidentical transplant for patients with CGD who have an ongoing infection refractory to standard medical intervention. |
| **Study Duration:** | Start Date: 1 October 2014<br>End Date: 1 January 2024 |
| **Study Agent/ Intervention Description:** | Post-transplant cyclophosphamide |
| **Primary Objective:** | To determine the efficacy of this allogeneic transplant approach in reconstituting normal hematopoiesis and reversing the clinical phenotype of CGD |
| **Secondary Objectives:** | To determine the safety of this allogeneic HSCT approach in patients with CGD including transplant related toxicity, the incidence of acute and chronic graft-versus-host disease, immune reconstitution, overall and disease-free survival |

## PRÉCIS

Allogeneic transplant using HLA matched donors, both related and unrelated, has proven curative for patients with various immunodeficiencies, including those with ongoing infections. However donor availability remains a limiting factor in the application of this treatment modality. The use of haploidentical related donors has in the past been fraught with a greater rate of complications related to both higher rates of GvHD and delayed immunorecovery. Newer transplant regimens appear to have diminished these risks and improved outcomes. We propose using a reduced intensity conditioning regimen followed by post-transplant cyclophosphamide for patients with CGD who do not have an HLA matched donor but whose circumstances necessitate the use of a potentially curative, albeit high-risk treatment modality.

# BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 1.1 Background Information

Description of the Study Agent/Intervention(s)

This is an open-label pilot study using haploidentical transplantation (Hematopoietic transplantation using a related donor that matches at least ½ by Human leukocyte antigen (HLA) typing) to treat patients with CGD. The conditioning regimen will consist of standard FDA approved drugs, but the unmanipulated graft will be followed by cyclophosphamide to prevent graft versus host disease.

Chronic Granulomatous Disease (CGD)
CGD is one of a group of inherited disorders affecting neutrophil function. Due to mutations in one of the genes encoding the phagocyte NADPH oxidase, patients with CGD are susceptible to recurrent bacterial and fungal infections. Besides life threatening infections, these patients develop granulomas that can result in genitourinary or gastrointestinal tract obstruction. Iatrogenic or infection related end organ damage has also been seen in long-term survivors of CGD. Despite improvements in infection prevention and control, 2% of patients with CGD die each year, and few patients survive to age 50.(3)

Treatment of CGD - Prophylactic Antibiotics and Interferon gamma
All CGD patients receive prophylactic antibiotic coverage with agents such as trimethoprim/sulfamethoxazole. Prophylactic Interferon gamma therapy has been shown to decrease the incidence of infection but it is not well tolerated, and long-term compliance is rare. When infections do arise, emphasis is placed on identifying the pathogen and treating with the appropriate antibiotic for a prolonged period of time. When granuloma formation complicates an infection, a course of steroids is often effective.(1)

Gene Therapy for CGD
The genes responsible for the 4 most common forms of CGD have been cloned. A fifth type of CGD with a mutation in the P40 gene has also been described but only 2 patients have been documented with this form of CGD. A number of small animal studies including xenogeneic models have shown proof of principal using vectors corrective for both the p47 mutation and the gp91 mutation.(2-4) Results of a Phase I clinical trial of gene therapy for patients with the p47-deficient form of CGD have also been reported as well as a more recent study treating patients with the gp91 mutations. (5) The authors demonstrated that autologous hematopoietic progenitors can be transduced with a retroviral vector containing the missing gene. These progenitor cells were then safely infused back into the patient, and small numbers of gene-corrected neutrophils were detectable in the peripheral blood for up to 6 months. However, without a selective advantage conferred upon the transduced cells, there was insufficient engraftment and/or proliferation to sustain a long-term cure. In 2006, a German-Swiss collaborative study resulted in two patients achieving clinical benefit after receiving genetically transduced cells with the use of busulfan preconditioning. Both

patients maintained a level of 20% of corrected cells in the peripheral blood (6); however the first patient succumbed to a CGD related infection felt to be secondary to poor expression of the gp91 protein on a per cell level and both patients developed a myelodysplasia as well as evidence of silencing of the vector-derived gene. At the NIH, we initiated a clinical protocol treating 3 patients with X-linked CGD using a retroviral vector. One patient expired of his infection after apparently rejecting the genetically modified cells. The other two remain marked albeit at low levels including one patient who is 7 years post gene therapy who still has 0.5% marking. This is the highest level of long term marking in any patient to date. We are now in the process of establishing a new clinical gene therapy trial for patients with X-linked CGD using a lentiviral vector. The protocol is designed for patients who have an underlying infection without an available HLA matched donor, related or unrelated, but is still awaiting FDA approval.

Allogeneic (Allo) Transplantation

Allogeneic transplantation (transplant of hematopoietic derived stem cells from a related or unrelated donor) has been used successfully to cure patients with CGD. The best donors are those who match as closely as possible by HLA typing (Human leukocyte antigen). These are a set of proteins or markers that determine immune reactions within the body. The vast majority of successful transplants have also used myeloablative conditioning regimens (regimens that essentially wipe out the marrow necessitating replacement with new cells). The toxicity and associated morbidity and mortality of these regimens, however, have limited the widespread use of allo transplants as a therapeutic option for many patients and their referring physicians. More recent efforts using reduced intensity and nonmyeloablative regimens have reduced mortality and morbidity, but these regimens have simultaneously incurred an increased rate of graft rejection. In addition, despite an overall reduction in toxicity, patients still experienced significant GvHD as in the study performed here, where 2 of 15 patients died within one year of transplantation.(7) A third patient died suddenly from sepsis 2 years post-transplant, although there was no obvious evidence of GvHD and the patient had had a successful engraftment. However of the remaining patients, including those who did not engraft, all are alive. A number of these survivors have successfully undergone second transplants with good results. Thus, alternative regimens are needed to improve initial engraftment and further reduce GvHD incidence.

Matched Unrelated Donor Transplantation

Matched unrelated donor transplantation has also been shown to be curative of CGD. Gungor et al recently published results in 54 patients (35 using unrelated donors, 19 with related donors) transplanted in 16 different centres using targeted dose busulfan (AUC target 45-64mg*h/L or 10976-15854 min*uMol/L.)(8)

Under NIH Protocol 07-I-0075, using a nonmyeloablative conditioning regimen, we have transplanted 34 patients to date (thus the largest single centre for CGD transplant to date) using unrelated donors with no patient developing greater than grade 2 acute graft versus host disease with the initial transplant. Included in this group were 28 patients considered high risk due either to the presence of ongoing infection and/or active inflammation from autoimmune disease. (In patients receiving a stem cell boost for graft loss, we have seen Grade 3 GvHD). We have also had only one patient develop

chronic graft versus host disease, which responded well to treatment. This data is similar to the results obtained by Gungor et al.(8) which had an overall 96% survival in a less high risk population compared to the NIH group. Thus for patients without an HLA matched sibling donor, using an unrelated HLA matched donor is a reasonable option and preferable to a haploidentical transplant. However, the ability to find a donor is always a limiting option for this form of therapy and more difficult for patients of less common or mixed ethnicity. Although we have had good success in finding donors for 38 patients, we have had 5 patients with no available HLA matched donor in our searching.

Haploidentical Transplantation

Although, there is almost universal availability of a haploidentical related donor for any given patient, other than for patients with severe combined immunodeficiency (SCID), haploidentical transplantation has been used only when there is no available HLA matched donor. In most cases, haploidentical transplants have been associated with higher rates of graft rejection, as well as graft versus host disease and slow immune reconstitution. Novel techniques are now expanding the application of haploidentical transplantation and have been used to transplant a number of patients with immunodeficiencies who do not have an available HLA matched donor. Further, using older techniques, the rates of success between mismatched unrelated donor and haploidentical related donor transplant has been similar. Thus, with improvements in haploidentical transplantation, the readily available haploidentical related donor may be preferable to a mismatched related donor.

## 1.2 Scientific and Clinical Justification

We are proposing this protocol to treat patients with allogeneic transplantation, as it is the only known curative treatment for CGD, using related donors that match at least ½ by HLA typing (haploidentical). Although we have a matched related and unrelated donor protocol available, many patients will not have an available HLA matched donor. In order to provide this curative option, we need to use a haploidentical graft in order to treat patients whose clinical condition justifies higher risk but potentially curative treatment.

This protocol aims to decrease the risk of transplant related mortality associated with haploidentical transplantation, while offering the potential for cure of CGD.

As described previously, matched related donor transplantation is curative for patients with CGD as well as for other Primary Immune Deficiencies (PIDs), and for those patients who lack an HLA-matched sibling donor. Matched unrelated donor (MUD) transplantation has also been used. In a retrospective study that reviewed patients with various types of SCID, the survival of patients was 80% at 168 months post transplantation. Most deaths were related to either GvHD or infection, and 3 of 41 patients experienced graft failures. There was a 73% incidence of GvHD, but only 22% of patients had Grade 3 or higher. As this study was retrospective, the conditioning regimens and GvHD prophylaxis differed amongst the centers and patients, so the effects of conditioning cannot be determined from this study.(9)

Matched unrelated donor and umbilical cord transplantations have also been used in patients with immunodeficiencies, although the number of patients is limited, particularly in CGD.

Umbilical cord blood is an attractive option as there is data to suggest that there is less risk of GvHD induction, given the immunologic immaturity of these cells. It is also possible to transplant across more HLA mismatches with less risk of GvHD or rejection. However, the disadvantages to using cord blood have been related to the smaller number of grafted cells and the resultant delayed immune recovery post-transplant. In a 1997 analysis, better survival was associated with: age less than 6 years, weight less than 20 kg, an infusion of greater than 37 million nucleated cells per kg, and a CMV (cytomegalovirus) negative donor.(10) Hence, cord blood transplant has been traditionally limited to recipients of young age and low body mass. In an effort to increase the cell dose, the University of Minnesota in particular has been using more than one cord blood product per patient, with very promising results. In these patients with high-risk hematologic malignancies, the disease free survival was 57% at 1 year, and 72% overall survival for patients transplanted while in remission.(11)

Cord blood from an HLA matched sibling was used in 1 patient with CGD after a busulfan based conditioning regimen. One year post-transplant, the patient appeared to have a Dihydrorhodamine 123 assay (DHR) of 92% and normal T and B cell numbers.

In addition, transplantation centers have been developing reduced intensity (or nonmyeloablative conditioning regimens) for use in MUD and umbilical cord blood transplantation, and have applied these methods to both adults and children. With a median nucleated cell dose of $3.7 \times 10^7$/kg recipient body weight, the overall engraftment was between 76% and 95% depending on the conditioning regimen used in a single center trial. The incidence of GvHD was 9% and survival was 39% in this high-risk group of patients.(12) However, in our experience at the NIH, 2 patients with CGD rejected cord blood grafts. Further, data from Duke suggests that a myeloablative regimen is necessary for engraftment with a cord blood transplant(13), thus making this less desirable for patients with a progressive infection. Further, hematopoietic recovery is also significantly slower when using cord blood products, which is also problematic in the face of an ongoing infection in the recipient.

Only 25% of patients have a matched sibling, and in the setting of a congenital disorder, this is reduced to 10-15%, and only one-half of individuals have a matched unrelated donor. Alternative options include mismatched unrelated donors, and haplotype ( a type of mismatched) related donors. The particular advantage of a haplotype family member include: donor availability for almost all patients, ability to select the best donor family member, and the absence of delay in obtaining the graft source.(14) Historically, the major drawback of haploidentical related donor transplant has been the very strong graft-versus-host and host-versus-graft allo-responses due to the high frequency of T cells that recognize major class I or class II disparities between donor and recipient (15)

but when T cell depletion was used to modify the donor graft, there was a high rate of rejection of the donor grafts.(16)

In recent years there has been a renewed interest in both T cell depleted and T-cell replete full haplotype mismatched allogeneic transplant.(17, 18) With T-cell depleted haploidentical transplant, the major problem remains rejection and delayed immune reconstitution. Infection is a major problem in immunodeficiency diseases where patients may enter transplant with serious opportunistic infections. Moreover, T-cell depletion has not been shown to improve outcomes after HLA-mismatched allogeneic transplant.

An effort to improve outcomes with haploidentical transplant has been pioneered by a group at Johns Hopkins Hospital, whereby they administer cyclophosphamide (Cytoxan) a few days after the graft has been given. The rationale is that the T cells that become activated post infusion are responsible for the generation of graft versus host disease. These cells are then susceptible to the cyclophosphamide, which is a highly immunosuppressive drug that targets cycling cells as opposed to quiescent non-reactive T cells. This allows the use of a T-replete graft, thus reducing the recovery time for immune recovery, while still decreasing the risk of GvHD. (19) Other centers have started to use this same technique, including investigators in the NCI, where they are treating patients with DOCK8 and GATA2 deficiency who do not have an HLA matched donor, related or otherwise and investigators in NHLBI treating patients with Sickle Cell Disease. Results have been promising, but data is also preliminary with some graft versus host disease, but successful engraftment in all patients to date. As noted previously, patients that appear to have higher resistance to engraftment, such as those with sickle cell anemia, have not had as much success at least with lower doses of cyclophosphamide. Now with higher doses of cyclophosphamide, they have had better engraftment and have not seen any GvHD to date. (Personal communication John Tisdale). Further, there is a report of a haploidentical transplant using post transplant cyclophosphamide being done using the Hopkins protocol for two patients with CGD at Children's Hospital of Pennsylvania, but these patients did not engraft (personal communication, Kathleen Sullivan, ASBMT oral presentation).

We therefore propose using post-transplant cyclophosphamide similar to the Hopkins regimen and also similar to that being used by Dennis Hickstein (principal investigator using haploidentical transplant to treat patients with the disorders of DOCK8 and GATA2 deficiency) and John Tisdale/Courtney Fitzhugh using haploidentical transplant for the treatment of patients with Sickle Cell Anemia. Due to the engraftment difficulties in CGD patients as described, above we are increasing slightly the target AUC of the busulfan compared to the DOCK8 protocol. We are also planning to use mobilized peripheral blood stem cells (as being used in the Sickle Cell Haploidentical protocol) to increase the cell dose and improve the likelihood of engraftment. These two changes should improve the engraftment rates as compared to the results from the patients transplanted at Children's Hospital of Philadelphia.

In the majority of these studies, there has been little to no post-transplant GvHD prophylaxis used, but we will include low dose sirolimus as it is a tolerizing agent (as opposed to calcineurin inhibitors such as tacrolimus or cyclosporine). It is generally well tolerated and may allow us to further decrease the degree of conditioning required for engraftment. This is similar to the NHLBI Sickle Cell protocol which is also using single agent sirolimus.

Finally, the dose of busulfan being used is not fully myeloablative.(20, 21) However our target (4000-6000 uM/min) is higher than that used by Beri et al. (22) (3600-4800 uM/min) as patients with CGD have a higher resistance to engraftment. Therefore this dose is higher than that being used in the standard regimen, but still low enough that we should see autologous recovery in the setting of graft failure. (23) (It is also in fact lower than the targeted dose used in the European nonmyeloablative regimen for transplantation of CGD patients-see above.) Thus this is considered a reduced intensity regimen.(24)

Given this higher dose, when feasible, we will obtain an autologous back up product from the recipient, which would provide a source of rescue cells should autologous recovery not occur; however this is not mandatory as the expectation, consistent with our experience from the matched unrelated donor transplant data whereby patients receiving busulfan in the ranges of 4000-8000uM/min combined with TBI have had autologous recovery, is to have bone marrow recovery in the setting of graft failure.

## STUDY OBJECTIVES

### 1.3 Primary Objective

To determine the efficacy of this allogeneic transplant approach in reconstituting normal hematopoiesis and reversing the clinical phenotype of CGD

### 1.4 Secondary Objectives

To determine the safety of this allogeneic HSCT approach in patients with CGD including transplant related toxicity, the incidence of acute and chronic graft-versus-host disease, immune reconstitution, overall and disease-free survival.

## STUDY DESIGN

### 1.5 Description of the Study Design

This is an open-label study designed to treat patients with CGD using a reduced intensity conditioning regimen and post-transplant cyclophosphamide.

## 1.6 Study Endpoints

Primary Endpoint

Engraftment of a haploidentical graft without incurring graft versus host disease as determined by Day 30

Secondary Endpoints

1) Stable Chimerism as indicated by 30-50% myeloid engraftment and 50% lymphoid engraftment as assessed by 1 year post transplant
2) Immune reconstitution levels with DHR as a marker of normal neutrophil function by 1 year post transplant.

## 1.7 STUDY POPULATION

We will recruit up to 10 patients with CGD who do not have an HLA matched donor but whose circumstances necessitate the use of a potentially curative, albeit high-risk treatment modality. The needed progenitor cells will be provided from a biologically related donor of the affected recipient.

We plan to evaluate both parents and any eligible siblings as potential donors utilizing NIAID LHD screening protocol 05-I-0213 and will use the attached algorithm to determine the best donor when feasible (see Appendix B). Once the determination has been made,the donor will be collected on our NIAID approved apheresis protocol 94-I-0073.

See section 10.10 Stopping/Pausing Rules for Protocol.

## 1.8 Subject Inclusion Criteria

- Must have sufficient complications from underlying disease to warrant undergoing transplantation
- Ages 2 years – 65 years

  No appropriate HLA matched donor (available donor has greater than 1 mismatch or the single mismatch is not at DQ for unrelated donors (including cord blood products), or no available 6 out of 6 HLA matched related donor), or patients who may have an unrelated donor, but whose clinical status is such that the time required to obtain an unrelated donor would be life threatening.

- HLA haploidentical family donor graft available.
- Ability to comprehend and willingness to sign the informed consent or have a parent/guardian consent if the donor is a minor; assent being obtained from minors as appropriate
- Must be HIV negative

- Must not be pregnant (confirmed by a negative serum beta-human chorionic gonadotropin (ß-hCG) for women of child-bearing potential) or breastfeeding
- Must be able to stay within one hour's travel of the NIH for the first 3 months after transplantation and have a family member or other designated companion to stay with during the post-transplant period.
- Must provide a durable power of attorney for health care decisions to an appropriate adult relative or guardian in accordance to NIH Form-200 "NIH Durable Power of Attorney for Health Care Decision Making."
- Where appropriate, subjects must agree to use contraception for 3 months post-transplant

### 1.9 Participant Exclusion Criteria

- Major anticipated illness or organ failure incompatible with survival from Allo-transplant
- Inadequate collection from prospective donors.

## STUDY SCHEDULE

### 1.10 Screening

All Recipients – Initial Screening and Baseline Evaluations

The following will be done to aid in determining study eligibility (results may be obtained on another NIH approved protocol or from an outside source)

- Informed consent signed
- Low resolution molecular HLA typing of patient recipient and as many family members as possible to confirm complete matching of the donor
- Confirmation low resolution molecular HLA typing of selected donor.
- HLA antibody screen
- KIR typing (At the discretion of the PI)
- ABO typing
- CMV antibody testing (If test has been completed at some point in the past and the results are positive, the test does not need to be repeated. Otherwise, tests results must be obtained within 1 month of transplant.)
- Epstein Barr Virus (EBV) antibody testing (If test has been completed at some point in the past and the results are positive, the test does not need to be repeated. Otherwise, tests results must be obtained within 1 month of transplant.)
- Chem 20 panel (or the equivalent as per NIH ordering system)
- Transfusion-transmitted viruses (TTVs) as per Department of Transfusion Medicine (DTM) SOPs.

- Infectious Disease Screening (If test have been completed previously within 3 months of transplant, do not need to be repeated.)
  - May include HSV 1 and 2, Toxoplasmosis, syphilis, TB-anergy panel
  - TB testing will be completed. In countries where the BCG vaccination is administered, Quantiferon testing may be done in place of PPD testing.
- Disease Specific testing
- Serum ß-HCG for women of child-bearing potential
- Cardiac function: EKG, and multi-acquisition gated (MUGA) scan or Echocardiogram
- Durable power of attorney form completed
- Complete medical history and physical examination, including weight.

*Please note: Blood draw amounts will conform with MAS M(95-9) policy.*

### 1.11 Baseline

Recipients Baseline Clinical Safety Evaluations & Procedures

These baseline studies will be performed as medically necessary to ensure no occult infection or other medical condition, which could necessitate delay of the transplant procedure.

- Coagulation screen
- Complete blood count (CBC) with differential
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein
- WBC short tandem repeat chimerism profile (blood or buccal swab)
- Complete lipid profile with triglycerides
- Bone marrow aspirate
- Collection of 24-hour urine for assessment of creatinine clearance
- Pulmonary Function Test (at the discretion of the PI.)
- Imaging appropriate to assess the status of the patient which may include: CT scan of chest, abdomen, pelvis and sinuses
- Nutritional assessment
- Dental exam and clinical review
- Social worker interview
- Ophthalmology consultation

- Pediatric Consult for patient under 18 years
- Autologous Recipient Collection (back up collection-when feasible): Patient will be consented on to NIH Protocol 94-I-0073

Recipients Baseline Research Evaluation

These will be used to evaluate research study endpoints

- T cell Receptor Vß spectra type
- Lymphocyte phenotype
- T-cell Receptor Excision Circles (TREC)
- Research Blood (1 sodium heparin green top tube (GTT), 1 Red top tube (RTT))
- Quantitative Immunoglobulins

### 1.12 Study Phase

Collection of Donor Cellular Products

Potential donors will be screened under protocol 05-I-0213. An appropriate donor will be selected by the PI using Appendix B of this protocol as guidance. All donors will undergo mobilization and collection of cellular products under protocol 94-I-0073. Products will be processed as per cell processing PSI for protocol 15-I-0007.

Recipient Intervention

Treatment Plan

The Recipient will be admitted to an inpatient unit for a minimum of 13 days prior to PBSC infusion. The total anticipated number of inpatient days is 40. (See Appendix D2-D5: Schedule of Events)

<u>Busulfan test dose (within 1 month starting conditioning.)</u>

Single Busulfan test dose: 0.8 mg/kg IV infusion over 1-2 hours given anytime within 1 month prior to starting conditioning.

Drug (busulfan) levels will be obtained for the single Busulfan test dose at the end of infusion, and approximately 135, 150, 180, 240, 300, 360, and 480 minutes after starting the infusion of the drug.

<u>Day -6 (6 days prior to cell infusion)</u>
Fludarabine 30 mg/m$^2$ over 30 minutes
Cyclophosphamide 14.5 mg/kg IV over one hour
<u>Blood tests+/- 3 days: ESR, CRP</u>

Day -5 (5 days prior to cell infusion)
Fludarabine 30 mg/m$^2$ over 30 minutes
Cyclophosphamide 14.5 mg/kg IV over one hour

Day -4, -3, -2 (2-4 days prior to cell infusion)
Fludarabine 30 mg/m$^2$ over 30 minutes
Busulfan 3.2 mg/kg IV once daily over 2-3 hours (adjusted based on test dose to target AUC of 4000-6000 uM/min)

Drug (busulfan) levels will be obtained on Day -4 prior to the infusion, at the end of infusion, and approximately 135, 150, 180, 240, 300, 360, and 480 minutes after starting the infusion of the drug. (Day -3 and Day -2 do not require Busulfan drug levels.)

Day -1
Total Body Irradiation (TBI) 200cGy (see Appedix E)

Day 0 (Day of Cell Infusion)
Infuse donor graft.
Blood tests: ESR, CRP
Research blood: Red top serum tube (10 ml for adults, 5 ml for pediatric patients). *

Day +1
Blood tests + 3 days: ESR, CRP
Research blood: Red top serum tube (10 ml for adults, 5 ml for pediatric patients). *

Day +2
Intravenous hydration will be started 12 hours prior to cyclophosphamide and will continue for approximately 24 hours after cyclophosphamide infusion.

Day +3 and +4
Cyclophosphamide 50 mg/kg/d IV infused over 90 minutes.
Mesna, 50 mg/kg/day, given over 24 hours.

Lasix to be administered as clinically indicated.

Refer to the “BMT consortium Supportive Care Guidelines: Hemorrhagic Cystitis Prevention with High-Dose Cyclophosphamide” at http://intranet.cc.nih.gov/bmt/education/supportive-care.shtml. (Adjustments may be made to these guidelines based on the clinical status of the patient.)

Day +5
For pediatric patients: Begin sirolimus 1 mg/m$^2$ PO q4h for 3 doses, then 1 mg/m$^2$ once a day (QD).
For adult patients, begin sirolimus 5 mg PO q4h for 3 doses, then 5 mg once a day (QD).

Doses may be adjusted to maintain trough levels between 8-14 ng/mL. Recipients will take sirolimus from Day +5 to at least Day 100 (minimum).

*These will be drawn at the discretion of the PI.

### 1.13 Post-Transplant Follow-up (Week 2 to Discharge)

Hospital Discharge Criteria (anticipated anywhere from Day 21 on)

Recipient will be discharged when the following criteria are fulfilled:

- Recipient afebrile, positive weight balance, no parenteral feeding required.
- Neutrophil count greater than 500 on 3 consecutive days.
- Platelet transfusion requirement absent or manageable as an outpatient.
- Recipient or family able to care for central venous catheter.

The following research labs may be obtained while the Recipient is an inpatient until discharged:

**Table 1**: Research Labs for the Recipient

| LABS | Week 2 | Week 3 | Week 4 | Week 5 |
|---|---|---|---|---|
| ESR | 1 X week | 1 X week | 1 X week | 1 X week |
| CRP | 1 X week | 1 X week | 1 X week | 1 X week |
| Chimerism | | + Day 14 (+/- 4 days) | | + Day 30 (+/- 4 days) |
| Sirolimus Levels | 1 X week | 1 X week | 1 X week | 1 X week |
| Lymph Pheno (BMT) | | + Day 14 (+/- 4days or when absolute lymphocyte count is >0.2 K/uL | | + Day 30 (+/- 4 days) (or when absolute lymphocyte count is >0.2 K/uL |
| DHR | | Day 14 (+/- 4 days) | | Day 30 (+/- 4 days) |

| | | | | |
|---|---|---|---|---|
| Research Labs<br>Red Top Tube; Na Heparin GTT | | Day 14<br>(+/- 4 days) | | Day 30<br>(+/- 4 days) |

- Clinical Safety labs will be obtained. These may include: CBC with differential, DHR in appropriate recipient, Chem 20 panel, CMV/EBV-PCR, Lipid panel and Sirolimus levels to guide dosing.

Discharge to Day 100 (Out-Patient)

- Clinical Safety labs will be obtained at least weekly or in some cases monthly. These may include: CBC with differential, DHR in appropriate recipients, Chem 20 panel, CMV/EBV-PCR, lipid panel, pregnancy test, and Sirolimus levels to guide dosing.

- Research Labs will be obtained as follows:
  - Weekly: ESR, CRP, Serum Quantitative Immunoglobulin levels
  - Day +60 (+/-10 days) and Day +100 (+/- 10 days). Chimerism, DHR, 1-10 ml sodium heparin GTT, 1-10 ml red top serum (pediatric patients may have 5 ml.), Lymphocyte phenotype
  - (D+100 only) will be drawn. A bone marrow aspirate may be obtained on day 100 only.

Beyond Day 100

**At 6, 12, 18, 24, 36, 48, and 60 months (+/- 30 days):**

- Clinical Safety Labs (as specified above)
- Chest CT
- Research Labs - ESR, CRP, Serum Quantitative Immunoglobulin levels, Chimerism, DHR, 1-10 ml sodium heparin GTT, 1-10 ml red top serum (pediatric patients may have 5 ml.), Lymphocyte phenotype
- CMV/EBV (6 months only)
- Vß spectra type or flow at 2 years only
- TREC analysis
- Bone marrow aspirate at 1 year
- Pulmonary function test at 12 and 24 months minimum
- Post immune responses per PI discretion

### 1.14 Final Study Visit

Recipients: Participants will have their final study visit 5 years post-transplant. Visit evaluations are specified above in section 5.4.

### 1.15 Early Termination Visit

Please see below section 10.12 Premature withdrawal of a Participant

### 1.16 Re-contact of Participants after Trial Termination

Participants will be followed on NIAID IRB protocol 05-I-0213 “Screening and Baseline Assessment of Patients with Abnormalities of Immune Function” starting 5 years after transplantation on this study and will continue to be followed annually as long as the patient is willing to return to NIH.

## CLINICAL MANAGEMENT OF RECIPIENT POST-TRANSPLANT

### 1.17 Clinical Management

We will manage the transplant recipient appropriately according to standard of care and “Supportive Care Guidelines of the NIH”* in the event of the medical complications such as those listed below, which are known to occur in this patient population post-transplant, as well as anything not listed but related to the transplant

- Infection
- Fever (including neutropenic fever)
- GvHD (acute and chronic)
- Decrease in patient daily caloric intake
- CMV Reactivation
- Epstein Barr Virus (EBV) associated post-transplant lymphoproliferative disease (PTLD)
- Relapse of Original Disease

*(See also Supportive Care Guidelines, available at http://intranettst2.cc.nih.gov/bmt/clinicalcare)

### 1.18 Laboratory Evaluations

Please see section 5.4.2 for specific laboratory evaluations and the distinction between the research driven evaluations and those done for the clinical/medical management (clinical safety labs) of the participant.

Analysis of the Research Samples

Specimens collected strictly for research purposes will not be read by a pathologist. Samples will be ordered and tracked through the CRIS Research Screens. Should a CRIS screen not be available, the NIH Form 2803-1 will be completed and will accompany the specimen and be filed in the medical record.

### 1.19 Chimerism Studies

We will use PCR analysis of microsatellites to identify the contribution of the donor Hematopoietic stem cells (HSCs) to post-transplant hematopoiesis and to detect donor lymphocytes in the circulation (i.e., donor-recipient chimerism).

### 1.20 Bone Marrow Samples

A volume (up to 25 mL) of bone marrow aspirate will be collected for research studies. These will be used to help elucidate the contribution of the progenitor cells to the circulating component.

## POTENTIAL RISKS AND BENEFITS

### 1.21 Potential Risks to the Recipient

Related to the Transplant

The mortality from conventional BMT may be as high as 40%. Although our data as well as that of others suggest a significant reduction in transplant-related mortality with nonmyeloablative “mini” PBSC transplantation, the procedure nevertheless carries significant risk. It is therefore only appropriate to carry out this experimental procedure in the context of debilitating or life-threatening conditions and with full informed consent from the patient, donor, and immediate family. The specific hazards of this study using a subablative preparative regimen and high HSC-content graft are graft rejection, graft versus host disease, and disease relapse. The major discomforts are those of nausea, anorexia, diarrhea, fever and malaise, and intolerance of the isolation period.

Related to GvHD prophylaxis

Sirolimus: The anticipated toxicities of sirolimus in this trial are those related to its immunosuppressive properties. Please refer to the package insert attached (Attachment A).

Related to the Chemotherapies

**Related to Busulfan**
Busulfan on this study is being used as part of the conditioning regimen for its myelosuppressive properties. Commonly listed adverse events include nausea and vomiting, hair loss, and seizure. The risk of seizure will be minimized by the administration of a prophylactic anticonvulsant medication started prior to busulfan administration. Please refer to the package insert attached (Attachment B).

**Related to Fludarabine**
Fludarabine is being used as part of the immunosuppression required to obtain engraftment of a haploidentical transplant. Please refer to the pack insert attached. (Attachment C).

**Related to Cyclophosphamide**

Cyclophosphamide is intrinsic to the study design as it specifically targets activated T cells, eliminating the cells presumed responsible for GvHD. It is associated with immunosuppression and gonadal dysfunction as well as hemorrhagic cystitis. Mesna and hydration are the best prevention for this complication and will be used in the protocol. Refer to Package insert attached (Attachment D).

Related to line placement and venipuncture

Patients may experience pain, bleeding or bruising, and rarely an infection at the needle insertion site from venipuncture. Lightheadedness or more rarely fainting can also occur with repeated blood draws.
Risks from the catheter itself include pain, bleeding, infection, inflammation of the skin and vein or swelling at the site. A clot may form in the vein and may require the use of anticoagulants. Finally, placement of the line can also cause injury to a nearby artery or nerve.

### 1.22 Potential Benefits to the Recipient

Clinically the approach is ethically acceptable because we are targeting patients with significant disease burden who are incurable with conventional treatments other than allogeneic BMT. Allogeneic transplantation has also been shown to be effective for the treatment of autoimmune complications associated with CGD. For patients with ongoing or refractory disease, HSC transplantation is currently the only curative treatment available. The protocol aims to decrease the risk of transplant related mortality while offering the potential for cure of the disease.

The research, therefore, involves more than a minor increase over minimal risk to subjects with the prospect of direct benefit (45 CFR 46.102)

## RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

- **Intended Use:** Samples and data collected under this protocol may be used to study graft versus host disease as well as rejection/engraftment related to transplant. Genetic testing will be performed for HLA typing as well as confirmation of underlying disease where appropriate.
- **Storage:** Access to stored samples will be limited using either a locked room or a locked freezer. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- **Tracking:** Samples and data acquired will be tracked using BSI.
- **Disposition at the Completion of the Protocol:**
  - In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples and/or data. Any clinical information shared about the sample would similarly require prior IRB approval.
  - At the completion of the protocol (termination), samples and data will either be destroyed, or transferred to NIAID IRB protocol 05-I-0213 “Screening and Baseline Assessment of Patients with Abnormalities of Immune Function.”
- **Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB:**
- Any loss or unanticipated destruction of samples or data (for example, due to freezer malfunction) that meets the definition of Protocol Deviation and/or compromises the scientific integrity of the data collected for the study, will be reported to the NIAID IRB.

- Additionally, participants may decide at any point not to have their samples stored. In this case, the principal investigator will destroy all known remaining samples and report what was done to both the participant and to the IRB. This decision will not affect participation in this protocol or any other protocols at NIH.

## REMUNERATION PLAN FOR PARTICIPANTS

No remuneration will be provided. All medical treatments associated or necessitated by the protocol will be provided without charge to the recipient, including medications taken as an outpatient.

## ASSESSMENT OF SAFETY

### 1.23 Toxicity Scale

The scoring for adverse event from any of the research procedures we will refer to the NCI Common Terminology Criteria for Adverse Events, where the normal value will be determined by the participants baseline and grading will then be adjusted based on the number of deviations from baseline in relation to the deviations from normal values as indicated on the NCI Common Terminology Criteria for Adverse Events. (CTC version 4.0, http://ctep.cancer.gov/forms/CTCAEv3.pdf)

### 1.24 Specification of Safety Parameters

*Policy Link: https://federation.nih.gov/ohsr/nih/pnp.php*

### 1.25 Recording/Documentation

At each contact with the participant, information regarding adverse events will be elicited by appropriate questioning and examinations. All events, both expected/unexpected and related/unrelated will be recorded on a source document. Source documents will include: progress notes, laboratory reports, consult notes, phone call summaries, survey tools and data collection tools. Source documents will be reviewed in a timely manner by the research team. All reportable adverse events that are identified will be recorded in the source documents. The start date, the stop date, the severity of each reportable event, and the PI's judgment of the AEs relationship and expectedness to the study agent/intervention will also be recorded in the source documents.

### 1.26 Recipients' Adverse Events

Adverse events used to evaluate the safety of this protocol regimen will be collected to include any unexpected events, which either occur during the study, having been absent at baseline or if present at baseline, appear to worsen and are determined to be possibly, probably or definitely related to this investigational treatment.

Adverse Events during the Screening Period

As part of the screening portion of this study, we will conduct diagnostic tests that may lead to the discovery of conditions that may necessitate the stopping of enrollment into

the trial. If any of the following events occur or are discovered that have no relation to the screening interventions, we will document but will not be reporting to the IRB unless they meet the criteria of an SAE:

- Eastern Cooperative Oncology Group (ECOG) or equivalent performance status of 3 or more. (See Supportive Care guidelines, available at http://intranet.cc.nih.gov/bmt/clinicalcare)
- Transaminases > 5x upper limit of normal based on the recipient's clinical situation and at the discretion of the investigator.
- Psychiatric disorder or mental deficiency severe enough as to make compliance with the BMT treatment unlikely, and/or making informed consent impossible.
- Major anticipated illness or organ failure incompatible with survival from AlloPBSC transplant.
- Recipient becomes pregnant
- HIV positive
- Uncontrolled seizure disorder

Adverse Events for Enrolled Recipients

The following expected occurrences will be documented but will not be reported to the IRB unless they meet the criteria of an SAE.

- Transient cardiac arrhythmias
- Transient cardiac insufficiency
- Pulmonary insufficiency
- Neutropenia and its complications
- Thrombocytopenia and its complications
- Anemia and its complications
- Transfusion reactions
- Treatable infections from bacteria, viruses, protozoa, and fungi
- Late effects of transplant regimens including: cataracts, infertility, growth impairment, hypothyroidism, and dental caries.
- Headache, insomnia, psychosis, mood changes, disorientation, seizures from metabolic imbalance.
- Nausea, vomiting, diarrhea, mucositis, weight loss, dry mouth, hiccoughs, constipation.
- Well characterized drug reactions – allergic manifestation, red man syndrome
- Well characterized drug adverse effects from drugs routinely used in transplant recipients (e.g., preparative regimen, immunosuppressive drugs, and antimicrobials).
- Common adverse effects of antiemetics, analgesics, anti-inflammatory agents, and known complications of steroid therapy.
- Complications from intravenous catheters, thrombotic occlusion, infection, local reactions, cardiac arrhythmia.

The following expected occurrences will not be reported to the IRB at each occurrence unless they meet the criteria of an SAE. They will be reported in summary form at the time of continuing review and at termination of the clinical study.

- Acute GvHD
- Chronic GvHD
- Graft failure/graft rejection
- Veno-occlusive disease
- Hemorrhagic cystitis
- Regimen-related toxicity
- CMV disease
- EBV Lymphoproliferative Disease

### 1.27 Definitions

Adverse Event: Any untoward medical occurrence in a research participant, including any abnormal sign, symptom, or disease, temporally associated with the participation in research, whether or not considered related to the participation in the research.

Serious adverse event: Any adverse event that

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred). For the purpose of this study, this type of event is defined as any adverse event that places the subject at immediate risk of death from Haploidentical transplantation. The event that requires life-sustaining intervention (ventilator support, vasopressors, and/or dialysis) as it occurred. A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death (i.e seizures, respiratory distress).;
- *results in inpatient hospitalization or prolongation of existing hospitalization*. For the purpose of the study is for overnight admissions only. Emergency room and day or night visits are not considered hospitalizations. Any elective hospitalization for a preexisting condition that has not worsened does not constitute a serious adverse event. In addition, hospitalization for ease of administration of standard treatments (i.e. medical treatments to manage complications of transplant) will also not be considered a serious adverse event.;
- results in a persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. *(Examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse)*

Protocol Deviation: Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as

1. Those that occur because a member of the research team deviates from the protocol.
2. Those that are identified before they occur, but cannot be prevented.
3. Those that are discovered after they occur

Serious Protocol Deviation: A deviation that meets the definition of a Serious Adverse Event or compromises the safety, welfare or rights of research participants or others.

Non-compliance: The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as

1. Serious: Non-compliance that
    a. Increases risks, or causes harm, to participants
    b. Decreases potential benefits to participants
    c. Compromises the integrity of the NIH-HRPP
    d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that, is neither serious nor continuing.

Unanticipated Problem (UP): Any incident, experience, or outcome that meets all three of the following criteria would be considered a serious UP:

1. unexpected in terms of nature, severity, or frequency in relation to
    a. the research risks that are described in the IRB-approved research protocol and informed consent document, Investigator's Brochure or other study documents; and
    b. the characteristics of the patient population being studied
2. related or possibly related to participation in the research
3. suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated problem that is not an Adverse Event (UPnonAE): An unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the participant, affect others in the research study, or significantly impact the integrity of research data. These events may involve a greater risk of social or economic harm to study participants or others rather than physical/psychological harm. Such events would be considered a non-serious UP. Examples of a UPnonAE include a breach of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

## 1.28 Reporting Procedures

Expedited Reporting to the NIAID IRB

Serious and non-serious Unanticipated Problems, deaths, serious deviations, and serious or continuing non-compliance will be reported within 7 calendar days of investigator awareness. Serious Adverse Events that are possibly, probably, or definitely related to the research will be reported to the NIAID IRB within 7 calendar days of investigator's awareness, regardless of expectedness.

Waiver of Reporting Anticipated Protocol Deviations, Expected non-UP AEs and Deaths

Anticipated deviations in the conduct of the protocol will not be reported to the IRB. Expected adverse events will not be reported to the IRB. If the rate of these events exceeds the rate expected by the study team, the events will be classified and reported as though they are unanticipated problems. Death unrelated to research (i.e., due to the underlying disease) will only be reported at the time of continuing review.

Annual Reporting to the NIAID IRB

The following items will be reported to the NIAID IRB in summary at the time of Continuing Review:

- Serious and non-serious unanticipated problems
- Expected serious adverse events that are possibly, probably, or definitely related to the research
- Serious adverse events that are not related to the research
- All adverse events, except expected AEs and deaths granted a waiver of reporting.
- Serious and Non-Serious Protocol deviations
- Serious, continuing, and minor non-compliance
- Any trends or events which in the opinion of the investigator should be reported

Reporting Serious Adverse Events to the Principal Investigator

All SAEs will be reported to:
Elizabeth Kang, M.D.
Building 10-CRC, 6W- Room 63752
Phone: 301-402-7567
Email: Ekang@niaid.nih.gov

## 1.29 Type and Duration of the Follow-up of Participant after Adverse Events

Any adverse event experienced by the patient resulting from the haploidentical transplant will be followed by the protocol investigator until such time it is resolved or is sufficiently stable to allow the patient to be treated by his local physicians.

## 1.30 Safety Monitoring Plan

*NIAID Intramural Data and Safety Monitoring Board (DSMB):* While the NIAID Intramural Data and Safety Monitoring Board (DSMB) is required to monitor studies that use gene therapy methodology or involve multi-center studies presenting more than minimal risk to subjects or that generate randomized blinded data, there is provision that allows DSMB to monitor studies that pose more than minimal risk to its subjects.

This study involves pediatric patients as young as 2 years who will undergo a haploidentical bone marrow transplantation, which carries a risk of mortality. While this study aims to decrease the risk of transplant related mortality with the use of cyclophosphamide post cell infusion day, this regimen is a novel approach to patients with this disease process. Because this study poses more than a minimal risk to subjects, it falls under the NIAID DSMB policy on studies that may require DSMB monitoring.

The NIAID DSMB will review the data and analysis plans of all intramural NIAID clinical studies that require DSMB oversight. The DSMB consists of experts in transplant related infectious diseases, biostatistics, and clinical trials. After the initial review, which occurs prior to opening the study to enrollment, the DSMB will review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial on a semi-annual basis. All serious adverse events (SAEs) will be included in these interim reviews. All cumulative safety data reports from the trial will be submitted to the Board within 14 business days prior to the review. The DSMB will also assess the performance of overall study operations and any other relevant issues, as necessary. The DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review is sufficient for evaluation of the safety and welfare of study participants.

Expedited Reporting to the NIAID DSMB

Serious and non-serious Unanticipated Problems, deaths, serious deviations, and serious or continuing non-compliance will be reported within 7 calendar days of investigator awareness via the DSMB Executive Secretary. Serious Adverse Events that are possibly, probably, or definitely related to the research will be reported to the NIAID DSMB within 7 calendar days of investigator's awareness, regardless of expectedness. The DSMB may recommend early termination of the study for considerations of safety and efficacy.

## 1.31 Stopping/Pausing Rules for the Protocol

The study will be paused after the third CGD patient has completed the 100 day post-transplant assessment. The outcome data and status of the three individuals will be reported to the NIAID DSMB and the NIAID IRB, unless a more timely report is more warranted.

The study will also be paused if there are 2 patients experiencing either a protocol related death, graft failure, or grade 3 or 4 GvHD, and will be resumed only after agreement with the IRB.

## 1.32 Halting Rules for the Protocol

The NIAID- IRB, or other government agencies, as part of their duties to ensure that research participants are protected; may discontinue the study at any time. Subsequent review of serious, unexpected and related adverse events by the Medical Monitor, Data and Safety Monitoring Board (DSMB), ethics review committee or IRB, and other regulatory authorities may also result in suspension of further trial interventions/administration of study agent. The FDA and other regulatory authorities, retain the authority to suspend additional enrollment and Study Agent(s)/Intervention(s) administration for the entire study as applicable.

## 1.33 Study Discontinuation

### Graft Rejection

This transplant study uses a reduced intensity preparative regimen. Therefore, autologous recovery is anticipated in the recipients should they fail to engraft.

## 1.34 Premature Withdrawal of a Participant

Recipient Voluntary Withdrawal

The Recipient will be allowed to withdraw at any time, even after receiving the conditioning regimen (as autologous recovery is expected) or after receiving the allograft, although withdrawal at this stage would be highly discouraged. Once the conditioning regimen is complete and/or allograft infused, if the Recipient wishes to withdraw, he or she will have to remain within the care of the study physicians until either autologous or graft-mediated recovery is attained.

**Post – Infusion Obligations**

The Recipient will be required to report to the clinic for follow-up assessments as specified in the study guidelines and Section 5.4

Involuntary Withdrawal of a Recipient

- The Recipient may be withdrawn from the study if an inadequate number of cells is collected from the Donor and if cell collection is inadequate in a second donor or if a second donor is not available.
- If the Recipient develops a medical condition or circumstance where, in the opinion of the investigator, it is in the subject's best interest to discontinue participation in the study.

## 1.35 Involuntary Participant Withdrawal

Participants who fail to demonstrate donor cell engraftment will be taken off this study but we will continue to monitor for 6 months post transplant for possible infectious complications related to the conditioning regimen. Participants may be offered other therapies as appropriate. If they do not proceed with other treatments, the participants will be referred

back to their primary physician after the 6 month monitoring period for ongoing care. .

Participants with disease relapse will be taken off of the study protocol.. The participant will then be presented with the opportunity to enroll onto the NIAID IRB Protocol 05-I-0213: Screening and Baseline Assessment of Participants with Abnormalities of Immune Function. This will be offered if the participant is not already enrolled in other alternative treatments or referred back to his/her referring physician, depending on what is considered to be in the best interest of the participant.

Participants will be removed from the protocol in any situation where the investigator, the sponsor or any regulatory agency terminates the entire study for any reason.

If a subject becomes pregnant, she will be taken off of the study protocol and referred back to their primary physician for further therapy but will have contact follow-up by the study staff to document the outcome of the pregnancy.

If a participant develops a medical condition or circumstance where, in the opinion of the investigator, it is in the subject's best interest to discontinue participation in the study, they will be withdrawn off the study.

**Clinical Monitoring Structure**

### 1.36 Site Monitoring Plan

This study monitoring will be conducted according to the "NIAID Intramural Clinical Monitoring Guidelines".

Monitors under contract to the NIAID/RCHSPB will visit the clinical research site to monitor several aspects of the study in accordance with the appropriate regulations and the approved protocol. Only pediatric subjects will be monitored and the objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the IC process for each monitored pediatric subject; 2) to verify AEs and SAEs, including the prompt reporting of all SAEs; 3) to compare applicable electronic research data abstracts with individual participants' records and source documents (participants' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators' are in compliance with the protocol.

The investigator (and/or designee) will make study documents (e.g., consent forms, electronic research data abstracts and pertinent NIH Clinical Center or outside medical records readily available for inspection by the local IRB the site monitors, and the NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the Principal Investigator and study staff prior to enrollment. The plan will outline the frequency of monitoring visits

based on such factors as study enrollment, data collection status and regulatory obligations.

**STATISTICAL CONSIDERATIONS**

This is an open-label pilot study. The primary goal is to evaluate the ability to achieve engraftment with minimal graft versus host disease by using a reduced intensity conditioning regimen followed by post-transplant cyclophosphamide for haploidentical transplant CGD patients. We will transplant 3 patients as an initial pilot and then consider expansion after discussion with the IRB for amending the protocol.
This trial will be paused if at any time 2 or more grade III or IV GvHD events are observed.

For different values of grade III-IV GvHD probability, the following table is given the probability of stopping this trial earlier.

**Table 2: Probability of Stopping the Trial Earlier**

| | | | | |
|---|---|---|---|---|
| Grade II-IV GvHD probability | 0.05 | 0.1 | 0.15 | 0.2 |
| Stop earlier | 0.09 | 0.26 | 0.46 | 0.62 |

If 10, 9 or 8 engraftments are observed out of 10 transplant patients, then the 95% confidence intervals for the engraftment rate are, respectively, (0.73, 1), (0.56, 1) and (0.44, 0.96).

If no grade III-IV GvHD is observed after 10 recipients, the 90%, 95% and 99% confidence intervals for the grade III-IV GvHD probability are, respectively, (0, 0.21), (0, 0.26) and (0, 0.37).

The statistical analysis and stopping rules applies for 10 patients enrolled.

ETHICS/PROTECTION OF HUMAN SUBJECTS

### 1.37 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate in a research trial. It is an on-going conversation between the human research participant and the researchers which begins before consent is given and continues until the end of the participant's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, experimental procedures, alternatives, risks and benefits. Participants will be given the opportunity to ask questions and have them answered.

The participant will sign the informed consent document prior to undergoing any research procedures. The participant may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participant for their records. The researcher will document the signing of the consent form in the participant's research record. The rights and welfare of the participant will be protected by emphasizing to him or her that the quality of his or her medical care will not be adversely affected if he or she declines to participate in this study.

The Principal and/or Authorized Delegate will counsel the participant and his or her parents to obtain the consent during a face-to-face interview when consenting a minor participant.

During this study, all new information relating to risks and/or adverse events will be provided orally and/or in writing to all the study participants. Documentation will be provided to the IRB and if necessary, the informed consent document will be amended to reflect relevant information.

Non-English–Speaking Participants

If a non-English speaking participant is unexpectedly eligible for enrollment, the participant will be provided with the CC Short Written Consent Form for Non-English Speaking Research Participants in the participant's native language and a verbal explanation of the purpose, procedures and risks of the study as described in MAS Policy M77-2, NIH HRPP SOP 12 and 45 CFR 46.117(b)(2). The IRB-approved English consent form will serve as basis for the verbal explanation of the study. The investigator will obtain an interpreter unless the investigator is fluent in the prospective participant's language. Preferably, the interpreter will be someone who is independent of the participant (i.e., not a family member). Interpreters provided by the CC will be used whenever possible. The interpreters will translate the IRB-approved English consent form verbatim and facilitate discussion between the participant and investigator.

The IRB-approved English consent form will be signed by the investigator obtaining consent and a witness to the oral presentation. The CC Short Written Consent Form will be signed by the participant and a witness who observed the presentation of information. The interpreter may sign the consent document as the witness and, in this case, will note "Interpreter" under the signature line. A copy of both signed forms will be provided to the participant to take home.

The investigator obtaining consent will document the consent process in the participant's research record, including the name of the interpreter. Further, all instances of use of the CC Short Written Consent Form will be reported to the IRB at the time of annual review. If the CC Short Written Consent Form is used three times or more for the same language, this will be reported to the IRB immediately.

### 1.38 Confidentiality

All records will be kept confidential to the extent provided by federal, state and local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, research records. Records will be kept locked and all computer entry and

networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NIAID, and the OHRP.

## DATA HANDLING AND RECORD KEEPING

### 1.39 Data Capture and Management

Study data will be maintained in an electronic records system and collected directly from participants during study visits and telephone calls, or will be abstracted from participants' clinical center or other research related records. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary to confirm the data abstracted for this study. Data entry onto the electronic records system will be performed by authorized individuals. The Investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

### 1.40 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. Study records will be maintained by the PI for a minimum of 3 years and in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator will provide written notification of such intent to RCHSPB/NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. Destruction or relocation of research records will not proceed without written permission from NIAID/RCHSPB.

## Appendix A: Scientific References

1. Johnston RB, Jr. Clinical aspects of chronic granulomatous disease. Curr Opin Hematol. 2001;8(1):17-22. Epub 2001/01/04. PubMed PMID: 11138621.
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## Appendix B: Selection criteria for donor when more than one available

Historically, HLA typing has been the most important predictor of outcome after BMT. Recent data suggest reconsideration of donor prioritization. Clearly, HLA identical siblings will be given priority over any other potential donor. Data from J0457 (still unpublished) showed that that a 1 antigen mismatch in the GVH direction should be avoided if possible. Our current studies give us the guidelines:

**Donor selection criteria, in decreasing order of priority:**

1. **Patient should lack antibodies against donor HLA molecules**. Specifically, complement dependent cytotoxicity and flow cytometric crossmatch assays must be negative, and the mean fluorescence intensity (MFI) of any anti-donor HLA antibody by solid phase immunoassay should be <3000. Consult with Immunogenetics for the clinical significance of any anti-donor antibody. *Desensitization to remove anti-donor antibody should only be performed for patients who have no other donor options*

2. **ABO compatibility (in order of priority).**

    a. Compatible or minor ABO incompatibility
    b. Major ABO incompatibility

3. **CMV status**

The CMV status of the pair donor-recipient is frequently employed to select a potential donor. This is a controversial issue and the data available is somewhat limited (1). The following guidelines are recommended:

a. For a CMV seronegative recipient, use a CMV seronegative donor
b. For a CMV seropositive recipient, use a CMV seropositive donor

In CMV- patients with CMV+ stem-cell donors, primary CMV infection/reactivation develops in about 30% (2). Data from the European Registry shows the following(3): Seropositive patients receiving grafts from CMV+ HLA-identical sibling donors had the same survival as patients grafted from CMV- donors. However, MUD recipients receiving grafts from CMV+ donors had an improved 5-year survival, an improved event-free survival, and a reduced transplant-related mortality. There was no influence on the relapse incidence. The effects of donor CMV status remained in multivariate analyses. The effect of donor status was different among different disease categories. In patients with chronic myelogenous leukemia, T-cell depletion abrogated the beneficial effect of donor status, suggesting that the effect is mediated through transfer of donor immunity. These data suggest that donor CMV status influences outcome of unrelated SCT.

## 4. Other donor characteristics

Donor parity and sex mismatch, have also been associated with an increased risk of a GVHD and decreased survival in some but not all studies(4-8). Donor age and weight should be also taken into consideration.

Suggestions (in no order of priority):

a. Younger (18 years of age or older) and lighter donors should be preferred.
b. If all else is equal, male donors may be preferred over nulliparous female donors who may be preferred over multiparous female donors.

5. Considerations regarding transfusion requirements for ABO mismatched donor/recipient transplants.

| ABO Incompatibility | | Blood Components | Up to Start of Preparative Regimen | Start of Preparative Regimen | Stem Cell Infusion | Original Antibody Undetectable | Original RBCs Undetectable |
|---|---|---|---|---|---|---|---|
| Major Recip | Donor | | | | | | |
| O | A | RBC | O | O | O | A | Not Applicable |
| | | Plts/Plasma | O | A (AB) | A (AB) | A | |
| O | B | RBC | O | O | O | B | Not Applicable |
| | | Plts/Plasma | O | B (AB) | B (AB) | B | |
| A | AB | RBC | A | A | A | AB | Not Applicable |
| | | Plts/Plasma | A | AB (A, B) | AB (A, B) | AB | |
| B | AB | RBC | B | B | B | AB | Not Applicable |
| | | Plts/Plasma | B | AB (B, A) | AB (A,B) | AB | |
| O | AB | RBC | O | O | O | AB | Not Applicable |
| | | Plts/Plasma | O | AB (A, B) | AB (A, B) | AB | |
| Minor Recip | Donor | | | | | | |
| A | O | RBC'S | A | O | O | Not Applicable | O |
| | | Plts/Plasma | A | A (AB) | A (AB) | | O |
| B | O | RBC'S | B | O | O | Not | O |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Plts/Plasma | B | B (AB) | B (AB) | Applicable | O |
| AB | O | RBC'S | AB | O | O | Not Applicable | O |
| | | Plts/Plasma | AB | AB (A, B) | AB(A, B) | | O |
| AB | A | RBC'S | AB | A | A | Not Applicable | A |
| | | Plts/Plasma | AB | AB (A, B) | AB(A, B) | | A |
| AB | B | RBC'S | AB | B | B | Not Applicable | B |
| | | Plts/Plasma | AB | AB (B, A) | AB(B, A) | | B |
| **Major & Minor** | | | | | | | |
| Recip | Donor | | | | | | |
| A | B | RBC'S | A | O | O | B | B |
| | | Plts/Plasma | A | AB (A, B) | AB(A, B) | AB(A, B) | B |
| B | A | RBC'S | B | O | O | A | A |
| | | Plts/Plasma | B | AB (B, A) | AB(B, A) | AB(B, A) | A |
| **Rh Incompatibility** | | **Blood Components** | **Up to Start of Preparative Regimen** | **Start of Preparative Regimen** | **Stem Cell Infusion** | **D Antigen Undetectable** | **D Antigen Detected** |
| Recip | **Donor** | | | | | | |
| Rh pos | Rh neg | RBC | Pos | Neg | Neg | Neg | Neg |
| | | Plts/Plasma | Pos or Neg | Pos or Neg | Pos or Neg | Pos or Neg | Pos or Neg |
| Rh neg | Rh pos | RBC | Neg | Neg | Neg | Neg | Pos |
| | | Plts/Plasma | Pos or Neg | Pos or Neg | Pos or Neg | Pos or Neg | Pos or Neg |

( ) indicates 2nd, then 3rd choices for platelets

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## Appendix C: C1_C5 Recipient SOE Spreadsheet (attached)

## Appendix D: Total Body Irradiation Guidelines

Energy

All recipients should be treated with a linear accelerator using energies higher than 4MV.

Timing

It is anticipated that TBI will be delivered on days -1

Technique

TBI will be delivered with lateral fields using extended SAD values of 600cm. Tissue compensators (head and neck, e.g.) will be used as appropriate for all recipients. Gonadal shielding will be used in male patients if possible. At times, additional modifications may be used to provide optimal dose distribution, such as beam spoilers.

Dose/Fractionation

Treatment will be delivered in a single fraction. Dose will be prescribed to mid plane.

Dose Modifications

Occasionally, the total dose/technique of TBI may require modifications due to patient factors (unexpected or serious (grade 4-5) adverse events, serious medical illnesses not conducive to stable patient transfer, patient refusal, etc) or treatment factors (linear accelerator machine offline, etc.) Modifications to the radiation treatment will be at the discretion of the treating radiation oncologist and will be discussed and with the PI.