Title: A Prospective Study of Optimal Cord Selection for Haplo-Cord Transplantation: targeting the Inherited Paternal Antigen (IPA) and Matching for the Non-Inherited Maternal Antigen (NIMA)

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Weill Cornell Medical College

TITLE: A Prospective Study of Optimal Cord Selection for Haplo-Cord Transplantation: targeting the Inherited Paternal Antigen (IPA) and Matching for the Non-Inherited Maternal Antigen (NIMA)

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STUDY SCHEMA

1. **INCLUSION/EXCLUSION: See Section 3**

2. **ENROLLMENT:** All potential participants will have complete human leukocyte antigen (HLA) typing and determination of HLA antibodies.

3. **TREATMENT PLAN:**

Conditioning Regimen:

	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1 or day 0
Fludarabine	30 mg/m^2	30 mg/m^2	30 mg/m^2	30 mg/m^2	30mg/m^2			Haplo Stemcell	UCB stem cell
Melphalan						140 mg/m^2			
rATG			1.5 mg/**kg**		1.5 mg/**kg**		1.5 mg/**kg**		
TBI*				2Gray	2Gray				

Fludarabine: 30 mg/m2 /day IV x 5 days total dose 150 mg/m2. Fludarabine will be dosed according to actual body weight.

Melphalan: 140mg/m2/day IV x 1 day. Melphalan will be dosed according to actual body weight. Cryotherapy with ice chips will be administered to prevent mucositis.

Rabbit ATG (rATG): 1.5 mg/kg/day IV x x3 days total 4.5 mg/kg for all patients. ATG will be dosed according to actual body weight. The first dose will be infused over at least six hours, and subsequent doses over at least 4 hours. Pre-medications include acetaminophen 650 mg PO, diphenhydramine 25-50 mg PO/IV, and methylprednisolone 2 mg/kg (1 mg/ kg at the initiation and 1 mg/kg half-way through anti-thymocyte globulin administration).
Circumstances may require minor changes in scheduling of chemotherapy. Variations of up to 24 hours in scheduling will be acceptable.

Rituximab for prevention of PTLD: All patients not previously exposed to rituximab or who have not received rituximab in the six months prior to transplant, will receive one dose of rituximab 375 mg/m^2 prior to or upon admission.

TBI*: Because of occasional cases of graft failure, condition has been intensified for certain groups of patients. Patients at high risk for CNS relapse (e.g ALL or Burkitt's), or patients at high risk for graft rejection (i.e., donor-specific HLA antibodies, patients with severe aplastic anemia or hemoglobinopathies) may receive 2 doses of TBI as part of the conditioning

GVHD Prophylaxis:
Tacrolimus: 0.03 mg/kg/day IV continuous infusion (CI) over 24 hr from 4 PM Day -2 until engraftment or when subject is able to take PO, then tacrolimus approximately 0.09 mg/kg PO in

2 divided doses. Tacrolimus should be given at full dose to maintain levels of 5-15 ng/mL through day 180, tapered by 20% every week thereafter. Infection, toxicity or other clinical circumstances may prompt earlier discontinuation or adjustment of doses. In the presence of GVHD, a clinical decision by the attending physician will determine if tacrolimus can be tapered or should be continued. PO tacrolimus can be used when IV access for CI tacrolimus is unavailable.

Mycophenolate Mofetil (MMF): will be started on day -2 and given at a dose of 1000 mg q 8 hours until day 28. MMF can be given PO or IV. Infection, toxicity, very low patient weight (<50kg) may prompt earlier discontinuation or adjustment of doses.

Note: Patient specific circumstances may mandate minor variations in conditioning regimen and/or GVHD prophylaxis, such as reduction of some of the doses of medications, changes in schedule or-rarely- substitution of a particular drug. These changes will be noted and justified, but will not require IRB approval. Refer to Section 2.9.4 for further details.

Stem Cell infusion:
The infusion of UCB and the haplo-identical units will be separated by at least 2 hours and preferably they will occur on successive days (Day 0 and Day 1). The order of infusion is not specified.

Supportive care:

In case of cytomegalovirus (CMV) sero-positivity of donor and/or recipient, CMV prophylaxis will use high dose ganciclovir and (val) acyclovir as outlined below. Adjustment for renal dysfunction should follow institutional guidelines.

Supportive Care Schedule

Admission to Day -2	Day -1 until engraftment	Engraftment until Day 210	Day 210
Ganciclovir 5mg/kg IV q 12hrs	Acyclovir 500mg/m2 IV q 8hrs (or equivalent PO)	Valacyclovir 2gm PO QID	Acyclovir 400 mg po TID (or equivalent IV)

CMV seronegative donor and recipients: Acylovir 400 mg po TID or IV equivalent.

- A prophylactic broad-spectrum antifungal with anti-mold activity is strongly recommended.
- Other infection prophylaxis and supportive care will be as per institutional unit policy.
  In some cases, a drug called filgrastim (G-CSF) may be administered to hasten the recovery of blood counts. Generic formulations of filgrastim may be utilized as required by insurance or pharmacy.
- Blood transfusion policy should follow institutional policy.
- Cytomegalovirus (CMV) monitoring at least weekly until Day 100 and at least monthly until Day 210, regardless of donor/recipient CMV status. Pre-emptive CMV treatment should be strongly considered for any positive result on by DNA testing (i.e, viral load) within the first 100 days of transplant.

- Epstein-Barr virus (EBV) monitoring:
  - EBV viral load monitoring by PCR at least weekly until Day 100 and at least monthly until Day 365 is strongly recommended.
  - Rising EBV titers should warrant investigation for EBV post-transplant lymphoproliferative disorder (PTLD) including CT imaging and PET scanning for positive CT findings. A bone marrow evaluation is recommended if any evidence of PTLD by imaging or on peripheral blood findings
  - Evidence of PTLD or consecutive increases in EBV PCR should lead to treatment with rituximab at a dose and schedule per institutional policy.

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1.0 OBJECTIVES

1.1 Primary Objective

- To provide access to haplo-cord transplants for patients in need of alternative donor transplant and to determine long-term outcomes.

1.2 Secondary Objectives

- To evaluate outcomes of subjects undergoing haplo cord transplants using an optimally matched umbilical cord blood *(*UCB) graft including overall survival, profession-free survival (PFS), relapse, transplant-related mortality (TRM), toxicities, infections and GVHD)
- To determine the proportion of units selected for optimal Inherited Paternal Antigen (IPA) targeted and Non-Inherited Maternal Antigen (NIMA) matched transplant.
- To conduct preliminary studies of the impact of IPA targeting and NIMA matching on transplant outcome
- To evaluate outcomes in specific disease subgroups.

2.0 BACKGROUND

2.1 Umbilical-Cord Blood Transplantation in Hematologic Malignancies

Transplantation of hematopoietic stem cells derived from bone marrow and peripheral blood of siblings and unrelated donors have been successfully used to treat patients with high-risk or recurrent hematological malignancies. However, allogeneic hematopoietic cell transplants (HCT) are limited by the lack of human leukocyte antigen (HLA) matched donors and the high risk of graft-versus-host disease (GVHD) after transplantation. Although there are more than 18 million registered donors worldwide, more than 30% of patients requiring transplants are unable to find a matched donor.[1] This proportion is higher for patients of minority descent. Patients who receive unmatched transplants have decreased survival secondary to severe GVHD (80%) and opportunistic infections.[2]

In order to increase the donor pool, umbilical cord blood (UCB*)* UCB is now being used for transplants. UCB matching is less stringent than for adult donors as matches at class I loci of HLA-A and HLA-B are determined by intermediate resolution techniques, essentially ignoring allele level mismatches. Moreover, HLA-C has generally been ignored until recently. HLA-DRB1 however, is matched at high resolution. Therefore, UCB matching is limited to matching at 6 loci, HLA-A, B, and DRB1 on each haplotype whereas matching for adult unrelated donors considers at least HLA-A, B, C and DRB-1 loci and sometimes additional loci. Unrelated UCB transplants have a low risk of acute GVHD even in the 1-2 HLA mismatched setting in children[3-5] and adults.[6] However, delayed engraftment and associated treatment-related toxicity and opportunistic infections result in high treatment-related mortality from slow engraftment. Most studies show a median time to neutrophil recovery of 16 to 24 days, with a considerable proportion of patients having very delayed neutrophil and platelet recovery. For those whose

neutrophil recovery is delayed beyond approximately 16 days after transplant, the risk for treatment related mortality rapidly increases with further delays.[7;8]

Laughlin et al emphasized the importance of nucleated cell dose as a predictor of hematopoietic recovery. [6] Subsequently Eapen et al showed that HLA matching also affects survival, with 6/6 matches faring better than 5/6 or 4/6 matches.[9] Cell dose was important only with less well matched grafts. In other words, a 6/6 graft with low cell dose ($<2.5 \times 10^7$ total nucleated cells per kilogram) resulted in equivalent outcomes to a 4/6 graft with higher cell doses.

The standard decision algorithm emphasizes cell dose and utilizes $>2.5 \times 10^7$ nucleated cells/kg as a minimum threshold. Using this threshold, 5/6 cords can be identified for approximately 60% of whites, but only approximately 20% of blacks or other minorities.[10]

2.2 Haplo-Cord Transplantation

Disappointed with the delayed engraftment after cord blood transplantation, several groups have tried to enhance recovery by (1) *in vitro* expansion of cords;[8] (2) infusion of multiple cords;[9] or (3) combination of cord blood transplant with cells from other origins.[11] We recently completed a study of haplo-cord transplantation.[12] For a detailed explanation of the procedure we refer to our recent publication. In brief, we transplant after reduced intensity conditioning two very different stem cell products: a related haplo-identical graft that is in-vitro CD34 enriched (in effect removing haplo T cells) and an UCB graft.

We conducted a 45 subject prospective study of this procedure. Median age was 50; weight 80 kg and 58% had active disease. Neutrophil engraftment occurred at 11 days (Interquartile range (IQR), 9 -15) and platelet engraftment at 19 days (IQR, 15-33). In the majority of subjects, early haplo-identical engraftment was replaced by durable engraftment of umbilical cord blood by 100 days, with regular persistence of minor cell populations of host and/or haplo-hematopoiesis. Higher haplo chimerism at Day 100 correlated with greater haplo CD34 dose ($p=0.003$). The cumulative incidence of acute GVHD was 25% and chronic GVHD was 5%. Actuarial survival at one year was 55%, profession-free survival was 42%, non-relapse mortality was 28% and relapse was 30%. We concluded that reduced intensity conditioning and haplo-cord transplant result in fast engraftment of neutrophils and platelets, low incidences of acute and chronic GVHD, low frequency of delayed opportunistic infections and promising long term outcomes. Compared to double UCB transplant, transfusion requirements are reduced and length of hospital stay is shortened. UCB cell dose no longer had an impact on time to hematopoietic recovery as opposed to studies of UCB studies not augmented by a haplo graft. A group at the National Institute of Health has reported similar encouraging data.[13]

2.3 Umbilical Cord Blood Transplant and Graft versus Leukemia (GVL) Effect

In our series, haplo cord stem cell transplant was associated with a quantitative reduction in rate of recurrence compared to adult unrelated or related donor transplant (unpublished data), though the difference has not reached statistical significance in this small study. More compelling data on the effects of UCB transplant on rates of recurrence have been reported by others.[14] The reasons for the reduced rate of disease recurrence after UCB transplant has until recently

remained elusive, but may be explained by the presence in the umbilical cord graft of a substantial number of lymphocytes of maternal origin that are primed against the paternal HLA-haplotype of the fetus (the inherited paternal antigen or IPA).

It has long been known that cord blood contains between 0.1% and 0.5% lymphocytes of maternal origin.[15] These lymphocytes are protected from immune mediated destruction by the presence of a very high number of fetal T-regulatory cells. At the same time, the maternal cells residing and surviving within the umbilical cord are exposed to the IPA antigens expressed on the child's cells. In the large majority of cases, the IPA HLA haplotype is not present in these maternal cells; they are foreign antigens and the maternal cells experience them as foreign and are primed to them. Van Rood et al speculated that the IPA-primed maternal cells were responsible for the graft versus leukemia (GVL) activity of the cord and that a similar mechanism explained why haplo-identical transplant from a mother to her child is associated with less relapse than that from a father. In an elegant study, they analyzed for a large number of UCB transplants, the HLA type of both mother and UCB and deduced the IPA of the UCB.[16] By comparing those to the HLA antigens of the recipient patients, they identified transplant cases with IPA-targeting UCB (i.e. cases in which the maternal lymphocytes would be primed against the IPA of the UCB and also against the recipient.) They compared their outcome with that of the rare cases where there was no IPA reactivity. (These are cases where father and mother have a common HLA-haplotype, and the IPA is not foreign to the maternal cells). They found a much increased rate of disease recurrence in the latter. This phenomenon was mostly observed in recipients of well-matched transplants (5/6 matched). Importantly the decreased recurrence rate after IPA targeted UCB SCT was not associated with increased GVHD.

2.4 NIMA (Non-inherited Maternal Antigens) and Tolerance Induction

A similar reasoning underpins the observations of reduced GVHD when umbilical cords are selected that match the recipient for NIMA (the non-inherited maternal antigen). Umbilical cord blood cells, in utero have been exposed to NIMA antigens, which are, in the majority of cases foreign to them. This prolonged exposure leads to tolerance to these NIMA antigens.
Most umbilical cord blood transplants are conducted using HLA mismatched cords. Under usual circumstances, when the UCB cells are infused in the host, they recognize the host HLA as foreign and can cause GVHD (though at a lower frequency and intensity than adult grafts).
But if the host HLA mismatch happens to be an antigen that was also present in the UCB's mother (i.e. NIMA antigen), then the UCB cells have been rendered tolerant to that antigen, will not recognize it as foreign and they will not cause GVHD. This is called a NIMA matched transplant (but HLA mismatched). This principle again was investigated by van Rood et al in a study comparing the outcomes of NIMA matched UCB transplant with that of NIMA mismatches.[17] In principle, it is possible to find NIMA matched UCB grafts in a substantial fraction of donor recipient combinations.

2.5 Novel Determinants of Graft Failure after UCB SCT: HLA Antibodies and Graft Viability

Graft failure has frequently been observed after cord blood transplant and until recently the mechanism was not understood. An increasing percentage of graft failures can however be

attributed to the presence of donor specific anti- HLA antibodies present in a substantial minority of patients. Avoidance of UCB units that are targeted by anti-HLA antibodies should decrease the risk for graft failure.[18;19]

Viability of the umbilical cord graft as determined upon thawing is also emerging as a potentially important predictor of engraftment. Cords with <75% viability tend to engraft poorly and account for up to 20% of grafts in some studies. [20]

2.6 Rationale for the Current Study

Our pilot study of haplo-cord SCT established that early hematopoietic recovery is extremely rapid and appears independent of the UCB cell dose. We also observed encouraging long term outcomes. Van Rood et al, provided preliminary evidence that this GVL effect is mediated by IPA targeting of the graft, which is particularly operative in patients with at least 5/6 grafts. We speculate that identification of a graft that is at least 5/6 matched and IPA targeted (i.e., CB grafts share one or more IPA antigens with the prospective recipient) is more important to the outcome of haplo cord transplant than the nucleated cell dose. The identification of such a graft for a large proportion of the patients may necessitate accepting a lower UCB graft dose.

Data provided to us by the National Marrow Donor Program (Courtesy Martin Maiers) clearly indicate the increased likelihood for identification of a 5/6 match with decreasing cord blood cell dose.

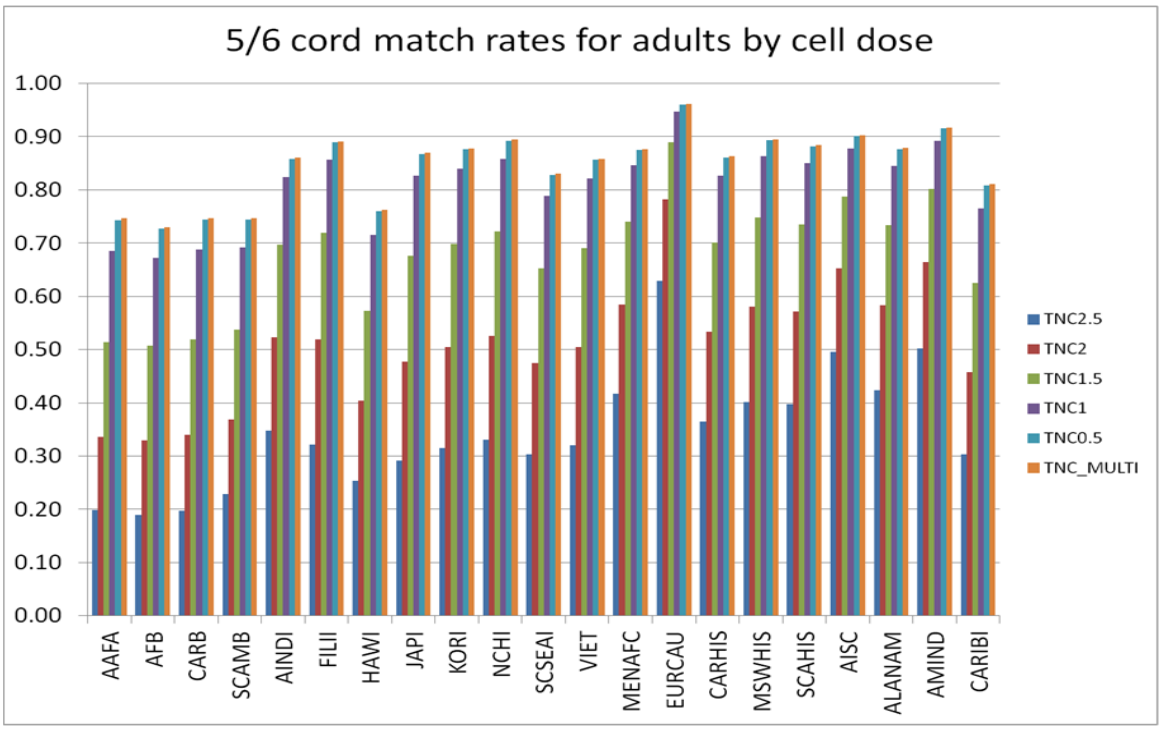


Figure 1: Shows the likelihood of identifying a 5/6 matched donor in various ethnic groups. A cell dose of 2.5 TNC x 10^7 per kg (the current standard) allows the identification of a 5/6 matched UCB in only 20% of African Americans and about 60% of Caucasians. A dose of

0.5x10^7 TNC allows finding a unit for 70% of African Americans and 90% of Caucasians. Similar findings apply to other ethnic groups. The purpose of this study is to establish in a prospective fashion the minimally acceptable UCB graft dose for successful haplo cord transplant and to obtain preliminary data on outcome of haplo cord SCT with optimally selected UCB units.

In addition to establishing the minimal UCB cell dose, we will take into account the avoidance of donor specific HLA antibodies (DSA) and insist on a high UCB post-thaw viability.

2.7 Conflict with Other Studies

In parallel to this study, WCMC is conducting a randomized study of haplo-cord transplant vs. double umbilical cord blood transplant. The latter study takes precedent. There are many subjects who are not eligible for the randomized study due to disease or subject characteristics, lack of an adequate cord blood dose, or because some subjects refuse participation in randomized studies. Such subjects will be offered enrollment in this study.

Addendum: This study was closed in 2016 and no longer presents a conflict. A BMT CTN randomized study comparing haplo-transplant with cord blood transplant opened to enrollment at WCMC in 2016, but has since closed to accrual and no longer presents a conflict.

2.8 Adjustment of dose of ATG for older patients and use of Low Dose TBI for patients at high risk of CNS recurrence:

Post-transplant lymphoproliferative disorder (PTLD) is a life threatening complication of allogeneic transplantation. It is often caused by EBV reactivation. Three risk factors have been well defined: (1) T-cell depletion with narrow spectrum antibodies such as thymoglobulin. (2) recipient age >50 and (3) mismatched transplant including umbilical cord blood transplant. Some data suggest that the risk increases with increasing levels (~dose) of thymoglobulin. We have observed several cases of PTLD in our ongoing protocol, all occurring in patients over age 50. I order to reduce the risk for PTLD in this subgroup, we are decreasing the dose of ATG by 25%. For patient at high risk of CNS recurrence, particularly those with acute lymphoblastic leukemia (ALL), we will add low dose TBI (200 cGy x2) to the conditioning regimen.

2.9 Protocol Amendments:

2.9.1 Adjustment of Dose of ATG for All Patients and Inclusion of Mismatched Unrelated Donors as Alternative to Haplo-Related Donors

Reduction in the dose of ATG (three instead of four doses) for older patients has been associated with a decrease in the incidence of PTLD. We now will implement this reduced dose for all patients regardless of age.

We continue to regularly face patients who lack haplo-identical related donors or who have high levels of HLA antibodies directed against all haplo-identical related donors. For such patients we

now propose to utilize HLA mismatched unrelated donors, so chosen as not to be targeted by Donor specific antibodies.

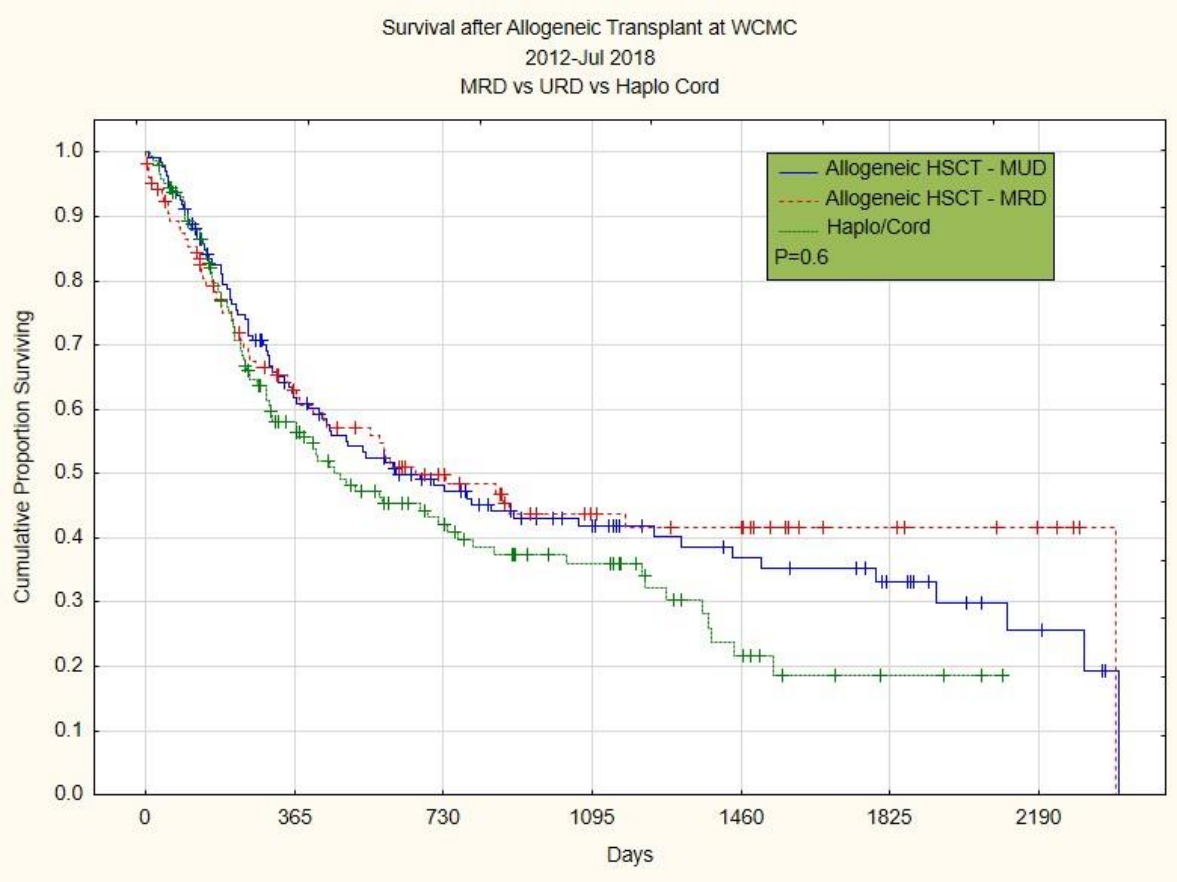
2.9.2 Extension of indications for use of TBI; Establishment of minimal acceptable CBU dose and increasing cohort size:

We have used low dose TBI (200 cGy x 2) in patients at high risk for CNS recurrence. This has been generally well-tolerated. We now plan to also use this in patients at high risk for graft rejection - for example: those with benign hematologic disorders such as aplastic anemia and hemoglobinophathies and those with Donor Specific Antibodies.

As we have systematically studied the use of ever lower CBU doses we have identified a lower CBU threshold dose. When analyzed by CBU cell dose, the incidence of UCB failure increased with decreasing UCB cell dose (P<0.001 U test). For example, there were 2 (6%) UCB failures for 30 evaluable pts with UCB cell dose >1.5 vs 5 (35%) UCB failures for 14 evaluable pts with UCB cell dose <1.5. Though the formal threshold for closing any cohort was not reached, the investigators concluded that a UCB cell dose of 1.2 x10^6 NC/kg was the minimum acceptable. We will continue accrual to this protocol to increase the number of patients and have robust estimates of secondary endpoints for all hematologic malignancies included.

2.9.3 Changes in Primary Objective

We have over the past years continued to accrue experience with the haplo-cord procedure and have identified short term outcomes and its predictors. Many aspects of our experience have been reported including determinants of engraftment and outcome (21-23), effects of variations in conditioning regimens(24), outcomes in specific disease entities(25), comparisons with other approaches(26) and aspects of supportive care(27). As shown in Figure 2, long-term outcomes parallel those of matched unrelated or HLA-identical sibling transplantation.



But allogeneic transplantation is a procedure with long-term consequences and side-effects. Late complications and even late mortality can adversely affect outcomes beyond the initial years, particularly in patients with chronic GVHD.(28, 29) Furthermore, allogeneic transplantation is used across hematological malignancies and even for hemoglobinopathies and autoimmune disorders, some of which are quite rare. It is also used across age groups and -particularly in older patients- individual of various levels of frailty, with potentially major impacts on long-term outcome. Much therefore remains to be learned of this procedure; ongoing data collection of additional patients as well as long-term follow up is warranted.

Additional concerns are the semi-investigational nature of both CD34 collection device and many umbilical cord blood products that are utilized under IND.

Weill Cornell and University of Chicago are the leading centers for haplo-cord transplantation and our experience can be extremely useful to the transplant community.

For all these reasons, we have modified the protocol to allow ongoing accrual of additional patients for the following three years at a rate of approximately 70 patients per year

2.9.4 Various changes

Acceptable Deviations: To avoid frequent request for exemptions or waivers, the eligibility criteria are relaxed. Minor variations in conditioning regimens, GVHD prophylaxis, donor management and supportive care are allowed. This addresses the complexities of transplant care.

Examples include:

a) Adjustments in doses of melphalan and fludarabine may be necessitated by age or renal function. (30-32)
b) Sirolmus may substitute for tacrolimus when serious tacrolimus toxicity occurs or is likely. (33)
c) Mycophenolate dose may be reduced or discontinued for early toxicity.
d) Pre-emptive Rituximab will be administered to patients not previously exposed. This should reduce risks of EBV reactivation and PTLD. (34)
e) We have also eliminated several redundancies in post-transplant monitoring, including frequent thyroid function checks.

3.0 SUBJECT SELECTION

3.1 Inclusion Criteria

Subjects will be eligible for this study if they have any one of the diseases that are known to be cured after allogeneic stem cell transplantation.

All subjects have to fulfill the criteria listed below:

1. Subject must have a confirmed diagnosis of one of the following:
    a. Relapsed or refractory acute leukemia (myeloid or lymphoid)
    b. Acute leukemia in first remission at high-risk for recurrence
    c. Chronic myelogenous leukemia in chronic, accelerated phase or blast-crisis
    d. Recurrent, refractory or high risk malignant lymphoma or Hodgkin's lymphoma
    e. Chronic lymphocytic leukemia, relapsed or with poor prognostic features
    f. Multiple myeloma
    g. Myelodysplastic syndromes
    h. Chronic myeloproliferative disease
    i. Hemoglobinopathies
    j. Aplastic anemia
    k. Other hematological disorder in need of allogeneic transplant (e.g. blastoid dendritic cell neoplasm)
2. Age $\geq$ 18 years
3. Likely to benefit from allogeneic transplant in the opinion of the transplant physician
4. An HLA-identical related or unrelated donor cannot be identified within an appropriate time frame
5. Karnofsky (KPS) Performance status of $\geq$ 70%

6. Acceptable organ function as defined below:
   - Serum bilirubin: < 2.0 mg/dL
   - ALT(SGPT): < 3 X upper limit of normal
   - Creatinine Clearance: > 50 mL/min/1.73m^2 (eGFR as estimated by the modified MDRD equation)
   - Patients whose organ function or KPS do not fulfill these criteria, may still be enrolled if considered appropriate transplant candidates and after discussion in transplant conference.
7. Ability to understand and the willingness to sign a written informed consent document

3.2 Exclusion Criteria

1. Life expectancy is severely limited by concomitant illness or uncontrolled infection
2. Severely decreased Left Ventricular Ejection Fraction (LVEF) or severely impaired pulmonary function tests (PFT's)
3. Evidence of chronic active hepatitis or cirrhosis
4. Uncontrolled HIV disease
5. Pregnant or lactating

4.0 ENROLLMENT AND REGISTRATION PROCEDURES

Subjects at Weill Cornell Medical College and at the University of Chicago will be enrolled simultaneously to reach the end goal of 300 total subjects across both sites.

At University of Chicago, subjects will be screened for eligibility utilizing identical guidelines. A baseline eligibility form will be faxed to the transplant office at WCMC (212-746-6678) and the PI will be contacted (by WCMC). Subjects will then be assigned to the cohort in sequential order by the WCMC team and the treatment assignment emailed and by telephone to Dr. Liu or her delegate. Researchers at Chicago shall not proceed with study procedures until they receive a confirmation of registration from WCMC, which will include the cohort assignment.

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All potential recipients will have complete human leukocyte antigen (HLA) typing at HLA A, B, C, DR, DP and DQ and determination of HLA class I and II antibodies An appropriate donor source for haplo-cord transplant will have been identified. (See section 5.1 for definitions of donor source.)

4.1 Central Patient Registration

Subjects will be centrally registered with the Weill Cornell Medical College (WCMC), Division of Hematology and Medical Oncology Clinical Research Office. To register a subject, fax the following documents to the Clinical Research Office at (646) 962-1610:

- WCMC Patient registration form
- First and last page of the fully executed informed consent form, plus additional pages if checkboxes for correlative studies are required.
- Fully executed HIPAA research authorization form
- Eligibility checklist signed and dated by investigator and research nurse
- Documentation of any eligibility waivers granted
- For inpatients at WCMC, signed consent documentation template

Central registration information is reviewed and entered into the HemOnc centralized research database.

5.0 STEM CELL SOURCE AND CELL DOSE

5.1 UCB UNIT

The UCB unit must supply a minimum number of nucleated cells – this number depends on the study cohort to which the subject is assigned. Three cohorts are anticipated.

Cohort #	Minimal Cell Dose	Number of Evaluable Subjects
1	2 x 10^7 TNC/kg	10
2	1 x 10^7 TNC/kg	10
3	0.5 x 10^7 TNC/kg	10

In cohort 1, the minimum required cell dose is 2.0x10^7 TNC/kg. In cohort 2, the minimum required cell dose is 1.0x10^7 TNC/kg. In cohort 3, the minimum required cell dose is 0.5 x10^7 TNC/kg. The unit must match at a minimum of 4 of 6 at HLA-A, -B, -DRB1 loci with the recipient. This may include 0-2 antigen mismatches at each A or B (at the antigen level) or DRB1 (at the allele level) loci. The best matched unit fulfilling the cell dose requirements should be utilized.

All typing will be done using molecular typing. Though molecular level typing will be available, a match is defined at intermediate resolution for HLA-A and –B and at high resolution for –DRB1. All recipients should have been tested for class I and class II HLA antibodies. If antibodies are present UCB should be chosen that are not targeted. This may require DQ and DP testing of the umbilical cord blood.[19;21;22] The testing for HLA antibodies should be done within 100 days from the planned transplant.

When available, the cord blood and maternal HLA typings will be reviewed by WCMC or the

Cord Blood Bank to identify units with IPA shared targets with the recipient, or HLA-mismatched but NIMA matched units. These cord blood units will be preferred as grafts for the present study assuming a similar HLA match.

HLA-C matching at the antigen level will also be considered after the above selection criteria. Thus, for units equal on all other accounts, an HLA-C match will be considered.

One back-up unit will also be identified per subject following similar selection criteria.

5.2 Third Party Donor

The preferred 3rd party donor will be a young HLA haplo-identical relative. After appropriate evaluation as per transplant program criteria, the donor will receive G-CSF (filgrastim) 5 mcg/kg SQ BID or 10 mcg/kg SQ daily for four consecutive days (doses rounded to the nearest vial size). Apheresis will start on the morning of the fifth day and proceed until sufficient cells have been collected. If a second day of collection is required, G-CSF will be administered day 5 after collection.

The apheresis procedure will be conducted as per transplant program policy. Typically four total blood volumes (TBV) will be collected or less if a high CD34 yield is expected based on high number of circulated CD34+ cells in the blood sample drawn immediately prior to apheresis. The use of pediatric donors is restricted to donors who are over the age of 14 and weigh more than 50 kg. After collection and prior to cryopreservation, cells will be T-cell depleted using the Miltenyi Clinimax® depletion device. The target will be to obtain a product containing less than $1x10^4$CD3+ cells per kg of recipient body weight and approximately $3x10^6$/kg CD34 positive cells. The CD34 selection procedure will be performed if possible in the stem cell laboratory of the transplant center. We also have obtained FDA approval to use contract services provided by progenitor cell tech. (Hackensack, NJ)

If donor specific HLA-antibodies are present in the recipient an effort should be made to choose a third party donor who is not targeted. This may require DQ and DP testing of the third party donor. **Occasionally the use of a mismatched unrelated CD34 selected PBSC graft will be permissible, for cases where no haplo-identical relative can be identified, or when the recipient has donor specific antibodies directed against all haplo-identical relatives.**

5.3 Infusion of Cells

The infusion of UCB and the haplo-identical units will be separated by at least 2 hours and preferably they will occur on successive days (Day 0 and Day 1). The order of infusion is not specified.

Several lines of evidence indicate that post-thaw cord viability affects engraftment. If an umbilical cord blood product turns out to have less than 70% CD34 cell viability upon thawing, a second UCB product will be rapidly ordered and infused as soon as possible.

6.0 TREATMENT PLAN

6.1 Conditioning Regimen:

	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1 or day 0
Fludarabine	30 mg/ m^2	30 mg/m^2	30 mg/m^2	30 mg/m^2	30mg/m^2			Haplo Stem Cell	UCB stem cell
Melphalan						140 mg/m^2			
rATG			1.5 mg/kg		1.5 mg/kg		1.5 mg/kg		
TBI*				2 Gray	2 Gray				

Fludarabine: Administer 30 mg/m2 /day intravenously x 5 days (Day -7 to Day -3) of a total dose of 150 mg/m2. Fludarabine will be dosed according to actual body weight.

Melphalan: Administer 140mg/m2/day intravenously on day -2. Melphalan will be dosed according to actual body weight. Cryotherapy with ice chips will be administered to prevent mucositis.[23]

Rabbit ATG (rATG)-thymoglobulin: 1.5 mg/kg/day IV x3 days total for all patients. ATG will be dosed according to actual body weight. The first dose will be infused over at least six hours, and subsequent doses over at least 4 hours. Pre-medications include acetaminophen 650 mg by mouth, diphenhydramine 25-50 mg by mouth or intravenously, and methylprednisolone 2 mg/kg (1 mg/ kg at the initiation and 1 mg/kg half-way through anti-thymocyte globulin administration). Circumstances may require minor changes in scheduling of chemotherapy. Variations of up to 24 hours in scheduling will be acceptable.

Rituximab for prevention of PTLD: All patients not previously exposed to rituximab or who have not received rituximab in the six months prior to transplant, will receive one dose of rituximab 375 mg/m^2 prior to or upon admission.

TBI*: Because of occasional cases of graft failure, conditioning has been intensified for certain groups of patients. Patients at high risk for CNS relapse (e.g ALL or Burkitt's) or patients at high risk for graft rejection (i.e., donor-specific HLA antibodies, patients with severe aplastic anemia, or hemoglobinopathies) may receive 2 doses of TBI as part of the conditioning

6.2 Post-Transplant Course (GVHD Prophylaxis)

Subjects will receive the drug tacrolimus (Prograf ®) and another immunosuppressant, mycophenolate mofetil (Cellcept ®), starting before transplant also to reduce the risks of graft versus host disease and to promote the growth of the graft.

Tacrolimus: 0.03 mg/kg/day using continuous intravenous infusion over 24 hour time period from Day -2 until engraftment or when subject is able to take by mouth, then tacrolimus approximately

0.09 mg/kg by mouth in 2 divided doses. Tacrolimus should be given at full dose to maintain levels of 5-15 ng/mL through approximately Day 180, tapered by 20% every week thereafter. Infection ,toxicity or other clinical circumstances may prompt earlier discontinuation. In the presence of GVHD, a clinical decision by the attending physician will determine if tacrolimus can be tapered or should be continued. PO tacrolimus can be used in the pre-engraftment period when IV access for tacrolimus is not available.

Mycophenolate mofetil (MMF): will be started on Day -2 and given at a dose of 1000 mg every 8 hours until Day 28. Earlier discontinuation, dose adjustments or more prolonged administration may be required for clinical reasons. MMF may be given PO or IV. . Infection, toxicity, very low patient weight (<50kg) may prompt earlier discontinuation or adjustment of doses

Note: Patient-specific circumstances may mandate minor variations in conditioning regimen and/or GVHD prophylaxis, such as reduction of some of the doses of medications, changes in schedule or-rarely- substitution of a particular drug. These changes will be noted and justified, but will not require IRB approval. Refer to section 2.9.4 for further details.

6.3 Supportive care

If successful, transplantations will result in production of normal blood and cure of the underlying disorder. In some cases, a drug called filgrastim (G-CSF) may be administered to hasten the recovery of counts. Filgrastim administration will follow institutional guidelines. Generic formulations of filgrastim may be utilized as required by insurance or pharmacy.

In case of cytomegalovirus (CMV) seropositivity of donor and/or recipient, CMV prophylaxis will use high dose ganciclovir and (val) Acyclovir as outlined below. All doses should be adjusted for renal function. [24;25] Adjustment for renal dysfunction should follow institutional guidelines.

Supportive Care Schedule

Admission to Day -2	Day -1 until engraftment	Engraftment until Day 210	Day 210
Ganciclovir 5mg/kg IV every 1hr	Acyclovir 500mg/m^2 IV every 8hrs (or equivalent PO)	Valcyclovir 2gm by mouth four times per day	Acyclovir 400 mg by mouth three times per day(or equivalent IV)

Changes and incorporation of alternative medications, unless dictated by clinical circumstances (side-effect, intolerance, failure, contra-indication), require discussion with the Principal Investigator.

CMV seronegative donor and recipients: Acyclovir 400 mg po TID or IV equivalent.

- A prophylactic broad-spectrum antifungal with anti-mold activity is strongly recommended.
- Other infection prophylaxis and supportive care will be as per institutional unit policy.

- In some cases, a drug called filgrastim (G-CSF) may be administered to hasten the recovery of blood counts. Filgrastim administration will follow institutional guidelines. Generic formulations of filgrastim may be utilized as required by insurance or pharmacy.
- Blood transfusion policy should follow institutional policy.
- Cytomegalovirus (CMV) monitoring at least weekly until Day 100 and at least monthly until Day 210, regardless of donor/recipient CMV status.
- Epstein-Barr virus (EBV) monitoring:
  - EBV viral load monitoring at least weekly until Day 100 and at least monthly until Day 365 is strongly recommended.
  - Rising EBV titers should warrant investigation for an EBV post-transplant lymphoproliferative disorder (PTLD) including CT imaging and PET scanning for positive CT findings. A bone marrow evaluation is recommended if any evidence of PTLD by imaging or on peripheral blood findings.
  - Evidence of PTLD or consecutive increases in EBV polymerase chain reaction should lead to treatment with rituximab at a dose and schedule per institutional policy.

7.0 PRE-TRANSPLANT EVALUATION (See also TABLE 2)

Subjects will be admitted to the hospital for a period of four to six weeks, sometimes more. In the first six days, subjects will receive the conditioning regimen.

The following observations are **considered standard evaluations** for transplant eligibility and should be determined as close to conditioning as possible and at a reasonable interval from transplant usually < 12 weeks before initiation of conditioning therapy. More remote tests may be utilized upon approval of the patient's physician.
These tests may be adjusted as warranted by clinical circumstances and evolving transplant policy. Please also refer to institutional transplant work up guidelines.

1. Medical history, physical examination, vital signs, height and weight.
2. KPS (Karnofsky Performance Score)
3. Complete blood count (CBC) with differential and platelet count, serum creatinine, bilirubin, alkaline phosphatase, ALT, and AST.
4. Infectious disease titers, as per institutional guidelines.
5. Immunoglobulin levels
6. High resolution HLA typing, if not already performed.
7. Left ventricular ejection fraction or shortening fraction.,
8. Diffusing capacity the lung for carbon monoxide (DLCO), Forced Expiratory Volume in One Second (FEVI) and Forced Vital Capacity (FVC) or O_2 saturation.
9. Bone marrow evaluation with aspirate and/or biopsy. Cytogenetic analysis as clinically indicated.
10. Beta -HCG serum pregnancy test for females of childbearing potential within 4 weeks of conditioning.
11. Chest CT as clinically indicated.
12. Pre-transplant chimerism testing.
13. Diagnostic Lumbar Puncture as clinically indicated (particularly ALL and High grade lymphoma)

8.0 POST-TRANSPLANT EVALUATION

The follow-up schedule for scheduled study visits is outlined in **Table 1** below.

Study Visit	**Target Day Post-Transplant**
1 week	7 ± 2 days
2 week	14 ± 5 days
3 week	21 ± 5 days
4 week	28 ± 5 days
7 weeks	49 ± 7 days
10 weeks	70 ± 7 days
100 day	100 ± 7 days
6 month	180 ± 28 days
12 month	365 ± 28 days

Table 1: The follow-up schedule for scheduled study visits is outlined in Table2. These tests may be adjusted as warranted by clinical circumstances and evolving transplant policy. Please also refer to institutional transplant work up guidelines.

	Baseline**	7	14	21	28	49	70	100	180	365
Physical exam, height, weight, and KPS performance status	X				X			X	X	X
GVHD and other morbidity assessments[5]					X			X	X	X
Toxicity assessments	X				X			X	X	X
Infectious disease titers[3]	X									
Chest CT or x-ray	X									
LVEF, or shortening fraction	X									
DLCO, FEV I and FVC and 02-saturation	X									
HLA typing[7]	X									
B-HCG serum pregnancy test (pre-menopausal females only) within 4 week of conditioning	X									
CBC[1] , differential, platelet count, and blood chemistries[2]	X	X	X	X	X			X	X	X
Disease restaging	X							X	X	X
Bone marrow biopsy and aspirate for pathology	X				X[6]			X[6]	X[6]	X[6]
Chimerism	X	X	X		X	X	X	X	X	X
Lymphocyte Subsets and Ig Levels	X				X			X	X	X
Pneumococcal antibody levels[5]	X								X	X
HLA Antibodies	X				X[5]			X[5]		X[5]
Sample for correlative assays[5]	X				X	X	X	X		X

Table 2: Table of study visit time points and assessments.

Note:
**The exact day of the tests is approximate. Tests can be scheduled several days before or after. The window is up to five days before and after in the first three weeks. Up to seven days before and after in the first 100 days and up to one month before and after at subsequent time points.*
***Baseline tests: see also section 7.0*

1. CBC performed at least three times a week from Day 0 until ANC >500 mcL for three days after nadir. CBC performed twice weekly until Day 28.CBC performed approximately weekly after Day 28 until 12 weeks post-transplant.
2. Blood chemistries include: serum creatinine, bilirubin, alkaline phosphatase, AST, and ALT, LDH, sodium, magnesium, potassium, chloride, and thyroid function tests (where standard of care should be according to institutional guidelines). Blood chemistries performed twice weekly if possible until Day 28. Blood chemistries performed weekly if possible after Day 28 until day 100 post-transplant.
3. Infectious disease titers to be done as per institutional guidelines.
4. Correlative Assays may include lymphocyte subset enumeration, spectratyping and TREC assays.
5. Recommended, not required.
6. Bone Marrow Biopsy and Aspirate for Pathology post-transplant will be performed as per the treating physician's medical-related recommendation.
7. If not already performed.

9.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, and electrocardiographs.

9.1 Investigational Risks

See consent form. There are no known side-effects related to the use of the Miltenyi CliniMacs device to select cells.

9.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

9.3 Recording and reporting of Adverse Events and SAE

- Stem Cell transplant is a complex procedure with prolonged initial admission and numerous immediate and delayed complications as well as frequent readmissions.

- Expected adverse events are those listed in the consent form and include regimen-related toxicities, myelosuppression, opportunistic infections and GVHD. Most expected adverse events of grade III and higher CTC severity will be captured in the transplant database and reported to the IRB upon request.

- **Adverse events that are judged to be unexpected and possibly related to the investigational procedure, will be reported to the study chairman within 48 hours. Such events will be reported to the local IRB within the institution's prescribed time period.**

- **All fatal Adverse Events will also be reported to the study chairman within 48 hours and reported to the local IRB within the institution's prescribed time period.**

	Immediate Reporting	**Report quarterly**
Hematopoietic Toxicity	**Graft failure and death**	**Time to Hematopoietic recovery**
Extramedullary Toxicity	**Fatal toxicity. Grade III-IV Toxicity deemed unexpected and possibly related to the investigational procedure**	**Grade III-IV toxicities not deemed expected/unrelated**
Infections	**Fatal**	**Grade II-IV**
Acute GVHD	**Fatal or Grade IV**	**Grade II-III**
Chronic GVHD	Fatal	Limited and extensive

9.4 Reporting of Adverse Events to FDA

If a reportable AE occurs on this study, the event will be filed on a MedWatch form with the FDA. Adverse drug reactions that are Serious, Unlisted/Unexpected, and at least possibly associated, and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) in writing by the PI (the principal sponsor-investigator). A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The principal sponsor-investigator shall notify the FDA by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drug or device as

soon as possible but no later than 7 calendar days after the sponsors initial receipt of the information. Each phone call or fax shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.

The principal investigator must also call the FDA as soon as an unexpected and possibly related adverse reaction occurs. The phone number is (301) 796-8240. A recorder is available after hours. Report these reactions to the FDA within ten (10) working days both verbal and written.

The address for Center for Biologics Evaluation & Research (CBER) FDA is:

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

The phone number of the CBER is: 800-835-4709

10.0 CRITERIA FOR STUDY EVALUATION

- **Event Free Survival**
- Relapse will be recorded by the day of initial detection of malignant cells if these cells were on subsequent testing confirmed to be increasing in number or by unequivocal radiological progression. The molecular detection of matched related donor will not be taken into account for the definition of clinical recurrence. The diagnosis of disease recurrence will be based on clinical and pathological criteria.
- **Treatment Related Mortality**
  Treatment related mortality is considered any death that cannot be explained by persistence, relapse or progression of the underlying malignancy once the preparative regimen starts.

- **Acute GVHD**
  Acute GVHD will be scored according to the criteria proposed by Przepiorka et al. [23]

- **Chronic GVHD**
  Chronic GVHD will be scored according to the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Report.[24]

- **Neutrophil engraftment**
  Neutrophil engraftment will be defined as the first day in which the ANC is > 500/mm^3 for three consecutive days.

- **Platelet engraftment**
  Platelet engraftment will be defined as the first day the platelet count is > 20,000/mm^3 without transfusion support for seven consecutive days. Chimerism studies will be used to

determine the percentage cord vs. haplo-identical donor engraftment.

11.0 STATISTICAL CONSIDERATIONS

Statistical Design and Analysis Plan:

The primary end point of the study is percentage of cord engraftment defined as the presence of at least 40% cord chimerism in peripheral blood of unfractionated cells by Day 100 or earlier. Cord blood cells are required to invoke cord versus leukemia effects and therefore an essential ingredient to success is to establish a minimum degree of cord blood cells at day 100. In our initial experience, cord blood levels often increased over time once a minimum proportion of cord blood cells are present

We will define the lowest tolerated dose of UCB as the lowest dose which assures cord blood engraftment (as defined above) in at least 80% of subjects.

Cohort #	Minimal Cell Dose	Number of Evaluable Subjects
1	2 x 10^7 TNC/kg	10
2	1 x 10^7 TNC/kg	10
3	0.5 x 10^7 TNC/kg	10

We will enroll 10 evaluable subjects in each cohort consecutively. However, accrual will continue at the same cell dose level until at least 10 subjects are evaluable. Because of the day 100 endpoint of chimerism, cohorts may enroll more than 10 subjects. With 10 subjects per dose cohort (the first 10 subjects evaluable), a two-sided 95% confidence interval for the proportion of subjects with successful engraftment in any dose group can be constructed to be within +/- 24.8% of the observed proportion of subjects with successful engraftment. This calculation assumes an expected engraftment proportion of 80%.

We will then calculate the rate of engraftment for each cohort using all the subjects accrued at each dose level. If the confidence interval of rate of engraftment includes 80% within the 95% confidence interval in all groups, then further accrual will continue using the minimum cell dose limits set in the lowest cohort for a total of 30 subjects (thus around 20 more subjects or slightly less if the cohort overaccrued).

With 30 subjects treated at lowest cell dose cohort, a two-sided 95% confidence interval for the proportion of subjects with successful engraftment can be constructed to be within +/- 14.3% of the observed proportion of subjects with successful engraftment (binomial distribution). This calculation assumes an expected engraftment proportion of 80%.

Subjects who die or relapse before chimerism can be assessed, will be considered not evaluable, and will be replaced. We predict that up to 16 subjects will fall into this category. Some cohorts that are not expanded will have more than 10 evaluable subjects as above. We estimate this will be four subjects. Thus, we are stating our accrual number as 150 total subjects.

Increase in Sample Size and New Primary Endpoints – September 2018

Accrual to this protocol has occurred more rapidly than initially anticipated and primary objective has been revised to provide access to haplo-cord transplants for patients in need of alternative donor transplant and to determine long-term outcomes. We currently accrue approximately 40 patients per year at Weill Cornell and another 30 at the University of Chicago. Close to 300 patients have been accrued over the past six years and we now propose to increase this number to an overall number of 500 patients and utilize this study to provide access to this procedure, report results and collect correlative samples.

This will also allow us to obtain data on long-term outcomes including late complications and cure rates on patients in various disease and age categories. We will continue to monitor secondary endpoints as described below.

Secondary endpoints

The proportion of subjects where desirable IPA or NIMA targeting from the cord blood unit occurred will be determined. We expect that by using lower cord blood doses and having more units available, we can perform IPA or NIMA targeting in 33% of units.

At the conclusion of the study, 95% confidence intervals will be generated for PFS, the incidence of graft failure, and the cumulative incidence of acute and chronicGVHD. Kaplan-Meier estimates of progression-free and overall survival rates will be calculated, and the median progression-free and overall survival times and their associated 95% confidence intervals derived. Cumulative incidence of neutrophil recovery, platelet recovery, and acute and chronic GVHD, will be calculated using relapse or death as a competing outcome. The cumulative incidence of 1) relapse using transplant-related mortality (TRM) as a competing outcome and 2) TRM using relapse as a competing outcome, will also be calculated using the cumulative incidence method.

We will conduct preliminary analysis to assess the impact of IPA targeting and NIMA matching on outcome of transplant, though we realize that subject numbers in this pilot trial may not allow definitive conclusions.

Guidelines for Early Stopping of the Trial

The study could be stopped early for subject safety, particularly if in one of the cohorts time to hematopoietic recovery is delayed in an excessive fraction of subjects (i.e. >40% of subjects in a cohort require more than 18 days to recovery ANC> 100/uL). We do not expect other unusual toxicities. In particular we do not expect an excess GVHD, given our previous encouraging experience at the University of Chicago with low GVHD and the fact that better HLA- matching as we expect to occur in this study should further minimize GVHD.

Addendum September 2018: At no point during the trial has there been an incidence of adverse outcomes that would have warranted early closing of the trial. Therefore, the protocol's stopping rules will be abandoned. Instead, we will continue to monitor long-term outcomes on a six month

basis and provide updates to the IRB. If at any moment one year survival drops below 50%, the protocol will be suspended for evaluation.

12.0 CRITERIA FOR REMOVAL OF SUBJECTS FROM PROTOCOL THERAPY

Because this is a one-time treatment, there is no indication for subjects to be taken off protocol for any reason except the ones mentioned below. Even if the subject had near fatal toxicity, it would not harm him/her to stay active on the study.

12.1 Disease Progression or Disease Persistence

Relapsing subjects (i.e. those with pathologically proven disease progression) will be removed from protocol therapy and followed for survival and secondary malignancy.

12.2 Extraordinary Medical Circumstances

If, at any time, the constraints of this protocol are detrimental to the subject's health and/or the subject no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy in subject records.
- Follow the subject for survival, progression, relapse, and secondary malignancies

13.0 DATA, SAMPLE AND PROTOCOL MANAGEMENT

- **Protocol Compliance:** Subjects will be reviewed weekly during admission by the study investigators who will score the subject for standard endpoints. After discharge they will be reviewed at least once a month.
- **Data Entry:** REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA. The data entry will follow formats proposed by CIBMTR.

  Data Collection: *Many endpoints of allogeneic transplant such as acute and chronic GVHD, certain infections and/or viral reactivations can occur at any moment after transplant and can go through many different phases. (evolution to different stage, improvement, recurrence, resolution, in case of infections: viremia to disease etc). The*

assignment of stage and extent often requires the input of various investigators and clinicians. All outcomes of allogeneic transplant patients including GVHD status, infections, graft function, disease outcomes etc are discussed at a biweekly conference and the data collected and discussed there will serve for data entry purposes for this study. This will also include discussion of data from patients enrolled at University of Chicago who will be discussed at biweekly conference for the first one hundred days. Thereafter they will be discussed when there is a change in their status.

- **Accuracy of Data Collection:** The Study Chairman will be the final arbiter of toxicity or assignment of disease related outcome should a difference of opinion exist

- **Management of Research Samples:** Research samples will be cryopreserved after ficolling and isolation of viable cells. The serum will be stored separately. Part of the product may be stored after DNA extraction. The samples will be stored securely. They will coded with the key to identification of the samples kept in a secure location and available only to the PI or his delegate. Samples and appropriate clinical information may be shared with other investigators at WCMC and elsewhere, but will be de-identified. Samples will be kept indefinitely.

14.0 DATA SAFETY MONITORING BOARD

The Weill Cornell Medical College Data Safety Monitoring Board (DSMB) is being requested to review safety data and to make recommendations regarding continuation, termination, or modification to the study.
The research team will report all adverse events to the DSMB after half the patients have been enrolled. The report to the DSMB will include the choice of cell dose for the continuation of the study and the justification for the choice.

15.0 REGULATORY CONSIDERATIONS

15.1 Institutional Review Board/Ethics Committee Approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted for approval by the Investigator to the IRB/EC. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

15.2 Informed Consent Procedures

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedure as per GCP's as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files. At the pre-admission consultation, subjects will be fully informed as to the purposes and potential risks and benefits involved in this study. Subjects will have ample opportunity to ask questions before consenting. Legal guardians will sign informed consent for legally incompetent patients in accordance with hospital policy.

15.3 Protecting Privacy and Confidentiality

Confidentiality will be maintained within the limits of the law. Subject names or any other identifying information will not be used in reports or publications resulting from this study. Only qualified staff from New York Presbyterian Hospital, Weill Medical College of Cornell University, the Food and Drug Administration, or other study support such as the National Cancer Institute will be able to review subject medical records.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

15.4 Study Records Requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

15.5 Protection of Human Rights

Participation in this trial is voluntary. All subjects will be required to sign a statement of informed consent, which must conform to Weill Cornell Medical College IRB guidelines.

Subjects will be eligible for this trial regardless of gender or racial/ethnic background.

APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

WCMC IRB SAE Reporting Forms

http://researchintegrity.weill.cornell.edu/institutional_review_board/irb_adv.html

APPENDIX C

BACKGROUND DRUG INFORMATION

FILGRASTIM (G-CSF: Granulocyte Colony Stimulating Factor, Neupogen®)

AVAILABILITY
G-CSF is commercially available in 1.0 and 1.6 mL vials containing 300 mcg and 480 mcg G-CSF, and in prefilled syringes containing 300 mcg/0.5 mL and 480 mcg/0.8 mL.

STORAGE & STABILITY
Intact vials and prefilled syringes should be stored under refrigeration. Do not allow the drug to freeze.

ADMINISTRATION
The daily dose of G-CSF should be injected subcutaneously in one or two sites. The dose following peripheral blood stem cell infusion is 5 mcg/kg/day. The dose of G-CSF may be rounded up to the nearest vial size.

TOXICITY
The most common side effect associated with G-CSF is bone pain. Bone pain is usually reported as mild or moderate and, if necessary, may be treated with non-opiod or opiod analgesics.

FLUDARABINE(Fludara®)

AVAILABILITY
Fludarabine is commercially available as a white, lyophilized powder. Each vial contains 50 mg of fludarabine, 50 mg of mannitol and sodium hydroxide to adjust pH.

STORAGE & STABILITY
Intact vials should be stored under refrigeration. Reconstituted vials are stable for 16 days at room temperature or under refrigeration. Solutions diluted in D_5W or NS are stable for 48 hours at room temperature or under refrigeration.

PREPARATION
Fludarabine should be reconstituted with Sterile Water for Injection, USP or normal saline per institutional pharmacy guidelines.

ADMINISTRATION
Fludarabine will be administered as an IV infusion over 30 minutes.

TOXICITY
Myelosuppression, (dose-limiting toxicity), fever, mild nausea and/or vomiting, diarrhea, stomatitis, skin rashes, myalgia, headache, agitation, hearing loss, transient episodes of somnolence and fatigue, autoimmune hemolytic anemia (may be life-threatening), peripheral neuropathy, and pulmonary toxicity. (Both pneumonia and hypersensitivity reactions have been reported. Fatal pulmonary toxicity has been described, especially when fludarabine was used in combination with pentostatin. Severe, fatal CNS toxicity presenting with loss of vision and progressive deterioration of mental status was encountered

almost exclusively after very high doses of fludarabine. Such toxicity has only been rarely demonstrated at the 25-30 mg /m^2 dosage of fludarabine. Very rarely described complications include transfusion-associated graft versus host disease. Tumorlysis syndrome has been observed, especially in patients with advanced bulky disease. Opportunistic infections (protozoan, viral, fungal, and bacterial) have been observed.

MELPHALAN(Alkeran®)

AVAILABILITY
Melphalan for IV use is commercially available in sterile 50 mg vials. The product is a lyophilized powder with 20 mg povidone per vial. Also provided is 10 mL of special diluent for use in reconstituting the product. The special diluent has 0.20 g sodium citrate, 6 mL propylene glycol, 0.5 mL 95% ethanol, and sterile water.

STORAGE & STABILITY
Intact vials should be stored at room temperature (15ºC-30ºC) and protected from light. Reconstituted solutions are chemically and physically stable for at least 90 minutes at room temperature. Solutions further diluted in 0.9% sodium chloride to a concentration of 0.1 mg/mL to 0.45 mg/mL are stable for at least 60 minutes. Solutions diluted to 1 mg/mL are reported to be physically stable for at least 4 hours at room temperature-chemical stability of this dilution is not known. Because of the relative instability of melphalan solutions, it is recommended that administration of the diluted solution be completed within 60 minutes of reconstitution. Reconstituted solutions should not be refrigerated.

PREPARATION
Melphalan should be prepared immediately before intended use. Each vial is reconstituted with 10 mL of the special diluent to yield a concentration of 5 mg/mL. The reconstituted solution may be diluted with 0.9% sodium chloride to a concentration of 0.1 mg/mL to 0.45 mg/mL.

ADMINISTRATION
The total dose of melphalan will be administered by short IV infusion over 30-60 minutes, as per institutional pharmacy guidelines.

TOXICITY
The major toxicity of melphalan is bone marrow suppression, usually lasting four to eight weeks. Other toxicities include nausea, vomiting, diarrhea, and mucositis. Less common toxicities include pulmonary fibrosis, interstitial pneumonitis, vasculitis, alopecia, hemolytic anemia, and allergic reactions. Transient rises in BUN and creatinine have occurred with high dose melphalan and also acute renal failure. Tissue necrosis may result if infiltration occurs.

MYCOPHENOLATE MOFETIL (Cellcept®; Myfortic®; MMF)

AVAILABILITY
Mycophenolatemofetil is available as a **Capsule**, as mofetil: CellCept®: 250 mg;
as **Injection**, powder for reconstitution, as mofetil hydrochloride: CellCept®: 500 mg [contains polysorbate 80]; as **Powder** for oral suspension, as mofetil: CellCept®: 200 mg/mL (225 mL) [provides 175 mL suspension following reconstitution; contains phenylalanine 0.56 mg/mL; mixed fruit flavor]; as a **Tablet**, as mofetil: CellCept®: 500 mg [may contain ethyl alcohol]; and as a **Tablet, delayed release**, as mycophenolic acid: Myfortic®: 180 mg, 360 mg [formulated as a sodium salt].

STORAGE & STABILITY
Intact vials should be stored at room temperature 15ºC to 30ºC (59ºF to 86ºF). Store solutions at 15ºC to 30ºC (59ºF to 86ºF) and begin infusion within 4 hours of reconstitution. Store capsules at room temperature of 15ºC to 39ºC (59ºF to 86ºF). Tablets should be stored at room temperature of 15ºC to 39ºC (59ºF to 86ºF) and protected from light. Store powder for oral suspension at room temperature of 15ºC to 39ºC (59ºF to 86ºF). Once reconstituted, the oral solution may be stored at room temperature or under refrigeration. Do not freeze. The mixed suspension is stable for 60 days.

PREPARATION
Mycophenolatemofetil is stable in D5W should be reconstituted per institutional pharmacy guidelines.

ADMINISTRATION
Intravenous solutions of mycophenolatemofetil should be administered over at least 2 hours (either peripheral or central vein); do not administer intravenous solution by rapid or bolus injection. Oral dosage formulations (tablet, capsule, suspension) should be administered on an empty stomach to avoid variability in MPA absorption. The oral solution may be administered via a nasogastric tube (minimum 8 French, 1.7 mm interior diameter); oral suspension should not be mixed with other medications. Delayed release tablets should not be crushed, cut, or chewed.

TOXICITY
Pain, abdominal pain, fever, headache, infection, sepsis, asthenia, chest pain, back pain, hypertension, tremor, insomnia, dizziness, acne, rash, diarrhea, constipation, mild N/V, oral monoliasis, anemia, leukopenia, thrombocytopenia, hypochromic anemia, leukocytosis, peripheral edema, hypercholesterolemia, hypophosphatemia, edema, hypo or hyperkalemia, hyperglycemia, infection, dyspnea, cough increase, pharyngitis, bronchitis, pneumonia, UTI, hematuria, kidney tubular necrosis, urinary tract disorder.

RABBIT ANTITHYMOCYTE GLOBULIN(Thymoglobulin®**,** rATG)

AVAILABILITY
Antithymocyte globulin is commercially available. Each package contains two vials: the first vial contains 25 mg antithymocyte globulin, and the second vial contains > 5 mL SWFI diluent.

STORAGE & STABILITY
Ampuls must be refrigerated (2ºC-8ºC/ 36ºF-46ºF),). Do not freeze.

PREPARATION
Reconstitute 25 mg vial with diluent provided by manufacturer (SWFI > 5 mL). Roll vial gently to dissolve powder. Use contents of vial within 4 hours of reconstitution. Dilute dosage to a final concentration of 0.5 mg/mL in 0.9% sodium chloride injection or 5% dextrose injection. Gently invert admixture 1-2 times to mix solution. Use admixture solution immediately. Final concentration must be 0.5 mg/mL.

ADMINISTRATION
Infuse the first dose over at least six hours, and subsequent doses over at least 4 hours. Infuse through a 0.22 micron in-line filter into a high-flow vein. Premedications include acetaminophen 650 mg PO, diphenhydramine 25-50 mg PO/IV, and methylprednisolone 1 mg/kg (at the initiation and half-way

through antithymocyte globulin administration).

TOXICITY
Infusion-related toxicities, including fevers, chills, rash, dyspnea, cardiovascular (hypo- or hypertension, tachycardia, edema, chest pain). In rare cases, anaphylaxis has been reported in which case the infusion should be terminated immediately, and emergency treatment with epinephrine and other resuscitative measures should be instituted. rATG should not be administered again to this patient. Immunosuppression is a common feature of rATG and can result in severe infections including sepsis, CMV, and urinary tract infections. Serum sickness, neutropenia (57%), thrombocytopenia (37%), leucopenia (57%), pain (46%), headache (40%), nausea and diarrhea (37%), peripheral edema (34%), systemic infection, malaise, pain, stomatitis, GI bleed, swelling or redness at injection site, myalgia, back pain, development of human anti-rabbit antibodies (HARA).

TACROLIMUS (Prograf®, FK506)

AVAILABILITY
Tacrolimus is commercially available as an injection (5 mg/mL; 1 mL ampuls) and as oral capsules (0.5 mg, 1 mg, and 5 mg).

STORAGE & STABILITY
Store tacrolimus capsules and injection at controlled room temperature, 15ºC-30ºC (59ºF-86ºF).

PREPARATION – FOR IV USE
Tacrolimus injection must be diluted prior to IV infusion with 0.9% sodium chloride or 5% dextrose injection to a concentration of 4-20 mcg/mL. Solutions should be prepared in non-PVC plastic or glass. Tacrolimus injection and diluted solutions of the drug should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

ADMINISTRATION
Oral therapy should be started as soon as possible as per protocol and 8 to 12 hours after stopping intravenous therapy. Oral doses will be administered twice a day. The conversion from IV to oral therapy should take into account concomitant medications (such as voriconazole).

TOXICITY
In patients receiving tacrolimus, 5% to 47% experienced anemia, 8% to 32% experienced leukocytosis, and 14% to 24% experienced thrombocytopenia. Rare cases of microangiopathic hemolytic anemia have been reported. Chest pain was reported in 19%. Mild to moderate hypertension is a common adverse effect associated with tacrolimus therapy. Antihypertensive therapy may be required. The most common adverse effects of tacrolimus have involved the central nervous system, and include headache (37% to 64%), tremors (48% to 56%), insomnia (32% to 64%), paresthesia (17% to 40%), and dizziness (19%). Tremor and headache may respond to dosage reduction. Visual changes, agitation, anxiety, confusion, seizures, depression, hallucinations, myoclonus, neuropathy, psychosis, incoordination, and abnormal dreams have been reported in 3% to 15%. Hyperkalemia (13% to 45%), hypokalemia (13% to 29%) hypophosphatemia (49%) and hypomagnesemia (16% to 48%) have been associated with tacrolimus therapy. Hyperuricemia has been reported in >3%. Gastrointestinal adverse effects included nausea (32% to 46%), vomiting (14% to 29%), anorexia (7% to 34%), constipation (23% to 35%), and diarrhea (37% to 72%). Nephrotoxicity was reported in 38% to 52% of liver and kidney transplant patients, respectively. Hematuria has been reported in greater than 3%. Abnormal liver function tests have been reported in 6% to 36% of patients; ascites in 7% to 27%.

Other effects reported in clinical trials include pain, fever, asthenia, back pain, and peripheral edema. The incidence of hyperglycemia was 17% and may require therapy with insulin. Other less frequently occurring effects include abscess, chills, peritonitis, and photosensitivity reactions. Anaphylaxis has been reported in a few patients receiving intravenous tacrolimus. Tacrolimus injection contains cremophor which in other drugs has been associated with anaphylaxis. Because tacrolimus is an immunosuppressant, the risk of opportunistic infections is increased.

DRUG INTERACTIONS
Tacrolimus is metabolized by cytochrome P450 3A4. Drugs that are inhibitors (e.g. itraconazole) of inducers (e.g. phenytoin) of 3A4 might be expected to increase or decrease tacrolimus concentrations, respectively, possibly resulting in increased or decreased effects.

References

1. Confer DL. Unrelated marrow donor registries. Curr Opin Hematol. 1997;4(6):408-12.
2. Beatty PG, Clift RA, Mickelson EM, Nisperos BB, Flournoy N, Martin PJ, et al. Marrow transplantation from related donors other than HLA-identical siblings. N Engl J Med. 1985;313:765.
3. Kurtzberg J, Laughlin M, Graham ML, Smith C, Olson JF, Halperin EC, et al. Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. N Engl J Med. 1996;335:157-66.
4. Barker JN, Davies SM, Defor T, Ramsay NK, Weisdorf DJ, Wagner JE. Survival after transplantation of unrelated donor umbilical cord blood is comparable to that of human leukocyte antigen-matched unrelated donor bone marrow: results of a matched-pair analysis. Blood. 2001;97(10):2957-61.
5. Wagner JE, Barker JN, DeFor TE, Baker KS, Blazar BR, Eide C, et al. Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival. Blood. 2002;100(5):1611-8.
6. Laughlin MJ, Barker J, Bambach B, Koc ON, Rizzieri Da, Wagner JE, et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. The New England journal of medicine. 2001;344(24):1815-22.
7. Offner F, Schoch G, Fisher LD, Torok-Storb B, Martin PJ. Mortality hazard functions as related to neutropenia at different times after marrow transplantation. Blood. 1996;88(10):4058-62.
8. Dahlberg A, Milano F, Gooley TA, Delaney C. The Risk of Day 100 Mortality Following Umbilical Cord Blood Transplantation Is Significantly Higher in Patients Who Do Not Achieve An ANC of 100 by Day +16 Post Transplant. ASH Annual Meeting Abstracts. 2011;118(21):3033.
9. Eapen M, Rubinstein P, Zhang MJ, Stevens C, Kurtzberg J, Scaradavou A, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. Lancet. 2007;369(9577):1947-54.
10. Barker JN, Byam C, Scaradavou A. How I treat: the selection and acquisition of unrelated cord blood grafts. Blood. 2011;117(8):2332-9.
11. Fernandez MN, Regidor C, Cabrera R, Garcia-Marco JA, Fores R, Sanjuan I, et al. Unrelated umbilical cord blood transplants in adults: Early recovery of neutrophils by supportive co-transplantation of a low number of highly purified peripheral blood CD34+ cells from an HLA-haploidentical donor. Exp Hematol. 2003;31(6):535-44.
12. Liu H, Rich ES, Godley L, Odenike O, Joseph L, Marino S, et al. Reduced-intensity conditioning with combined haploidentical and cord blood transplantation results in rapid engraftment, low GVHD, and durable remissions. Blood. 2011;118(24):6438-45.
13. Gormley NJ, Wilder J, Khuu H, Pantin J, Donohue T, Kurlander R, et al. Co-Infusion of Allogeneic Cord Blood with Haploidentical CD34+ Cells Improved Transplant Outcome for Patients with Severe Aplastic Anemia Undergoing Cord Blood Transplantation. ASH Annual Meeting Abstracts. 2011;118(21):654.
14. Brunstein CG, Gutman JA, Weisdorf DJ, Woolfrey AE, DeFor TE, Gooley TA, et al. Allogeneic hematopoietic cell transplantation for hematological malignancy: relative risks and benefits of double umbilical cord blood. Blood. 2010.

15. Mold J, Micaelson J, Burt T, al e. Maternal Alloantigens Promote the Development of Tolerogenic Fetal Regulatory T Cells in Utero. Science. 2008;322:1562-8.
16. van Rood JJ, Scaradavou A, Stevens CE. Indirect evidence that maternal microchimerism in cord blood mediates a graft-versus-leukemia effect in cord blood transplantation. Proceedings of the National Academy of Sciences of the United States of America. 2012:1-6.
17. Van Rood JJ, Stevens CE, Smits J, Carrier C, Carpenter C, Scaradavou A. Reexposure of cord blood tononinherited maternal HLA antigens improves transplant outcome in hematological malignancies. Proceedings of the National Academy of Sciences. 2009;106:19952-7.
18. Cutler C, Kim HT, Sun L, Sese D, Glotzbecker B, Armand P, et al. Donor-specific anti-HLA antibodies predict outcome in double umbilical cord blood transplantation. Blood. 2011.
19. Takanashi M, Atsuta Y, Fujiwara K, Kodo H, Kai S, Sato H, et al. The impact of anti-HLA antibodies on unrelated cord blood transplantations. Blood. 2010;116(15):2839-46.
20. Avery S, Shi W, Lubin M, Gonzales AM, Heller G, Castro-Malaspina H, et al. Influence of infused cell dose and HLA match on engraftment after double-unit cord blood allografts. Blood. 2011;117(12):3277-85; quiz 478.

21. Tsai SB, Liu H, Shore T, Fan Y, Bishop M, Cushing MM, et al. Frequency and Risk Factors Associated with Cord Graft Failure after Transplant with Single-Unit Umbilical Cord Cells Supplemented by Haploidentical Cells with Reduced-Intensity Conditioning. Biol Blood Marrow Transplant. 2016;22(6):1065-72.

22. van Besien K, Koshy N, Gergis U, Mayer S, Cushing M, Rennert H, et al. Cord blood chimerism and relapse after haplo-cord transplantation. Leuk Lymphoma. 2016:1-10.
23. van Besien K, Koshy N, Gergis U, Mayer SA, Cushing M, Rennert H, et al. Haplo-cord transplant: HLA-matching Determines Graft Dominance. Leuk Lymphoma. 2016.
24. Choe HK, Gergis U, Mayer SA, Nagar H, Phillips AA, Shore TB, et al. The Addition of Low-Dose Total Body Irradiation to Fludarabine and Melphalan Conditioning in Haplocord Transplantation for High-Risk Hematological Malignancies. Transplantation. 2017;101(1):e34-e8.
25. Hsu JM, Artz A, Mayer SA, Guarner D, Bishop MR, Reich-Slotky R, et al. Combined Haploidentical and Umbilical Cord Blood Allogeneic Stem Cell Transplantation for High-Risk Lymphoma and Chronic Lymphoblastic Leukemia. Biology of Blood and Marrow Transplantation. 2018;24(2):359-65.
26. van Besien K, Hari P, Zhang MJ, Liu HT, Stock W, Godley L, et al. Reduced intensity haplo plus single cord transplant compared to double cord transplant: improved engraftment and survival free of progression and GVHD (GRFS). Haematologica. 2016.
27. van Besien K, Bachier Rodriguez L, Brown MA, Gergis U. Prophylactic rituxumab eliminates EBV PTLD after haplo cord transplant. 2018.
28. Baker KS, Ness KK, Weisdorf D, Francisco L, Sun CL, Forman S, et al. Late effects in survivors of acute leukemia treated with hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. Leukemia. 2010;24(12):2039-47.
29. Bhatia S, Francisco L, Carter A, Sun CL, Baker KS, Gurney JG, et al. Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. Blood. 2007;110(10):3784-92.
30. Mehta J, Ayers D, Mattox S, Singh J, Singhal S, Siegel D, et al. High-dose melphalan and autotransplantation in myeloma with renal impairment: a matched-pair comparison with

patients without renal failure. Blood. 1997;90(Suppl 1):1863.
31. Kersting S, Verdonck LF. Successful outcome after nonmyeloablative allogeneic hematopoietic stem cell transplantation in patients with renal dysfunction. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2008;14(11):1312-6.
32. van Besien K, Schouten V, Parsad S, Smith S, Odenike O, Artz AS. Allogeneic stem cell transplant in renal failure: engraftment and prolonged survival, but high incidence of neurologic toxicity. Leukemia and Lymphoma. 2012;53(1029-2403 (Electronic)):158-9.
33. Cutler C, Logan B, Nakamura R, Johnston L, Choi S, Porter D, et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. Blood. 2014;124(8):1372-7.
34. Burns DM, Rana S, Martin E, Nagra S, Ward J, Osman H, et al. Greatly reduced risk of EBV reactivation in rituximab-experienced recipients of alemtuzumab-conditioned allogeneic HSCT. Bone Marrow Transplant. 2016;51(6):825-32.
35. Barzaghi F, Amaya Hernandez LC, Neven B, Ricci S, Kucuk ZY, Bleesing JJ, et al. Long-term follow-up of IPEX syndrome patients after different therapeutic strategies: An international multicenter retrospective study. J Allergy Clin Immunol. 2018;141(3):1036-49 e5.
36. Snowden JA, Badoglio M, Labopin M, Giebel S, McGrath E, Marjanovic Z, et al. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. Blood Adv. 2017;1(27):2742-55.
37. Spellman S, Bray R, Rosen-Bronson S, Haagenson M, Klein J, Flesch S, et al. The detection of donor-directed, HLA-specific alloantibodies in recipients of unrelated hematopoietic cell transplantation is predictive of graft failure. Blood. 2010;115(13):2704-8.
38. Cutler C, Stevenson K, Kim HT, Brown J, McDonough S, Herrera M, et al. Double umbilical cord blood transplantation with reduced intensity conditioning and sirolimus-based GVHD prophylaxis. Bone Marrow Transplant. 2011;46(5):659-67.
39. Lilleby K, Garcia P, Gooley T, McDonnnell P, Taber R, Holmberg L, et al. A prospective, randomized study of cryotherapy during administration of high-dose melphalan to decrease the severity and duration of oral mucositis in patients with multiple myeloma undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 2006;37(11):1031-5.
40. Ljungman P, Larsson K, Kumlien G, Aschan J, Barkholt L, Gustafsson-Jernberg A, et al. Leukocyte depleted, unscreened blood products give a low risk for CMV infection and disease in CMV seronegative allogeneic stem cell transplant recipients with seronegative stem cell donors. Scand J Infect Dis. 2002;34(5):347-50.
41. Milano F, Pergam SA, Xie H, Leisenring WM, Gutman JA, Riffkin I, et al. Intensive strategy to prevent CMV disease in seropositive umbilical cord blood transplant recipients. Blood. 2011;118(20):5689-96.