MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2018-0674
Protocol Title	A Phase I/II Study of Recombinant Human Interleukin-7 to Promote T-Cell Recovery after Haploidentical and Cord Blood Stem Cell Transplantation
Protocol Version	14.0
Version Date	09 September 2022
Protocol PI	Gheath Al-Atrash, DO
Department	Stem Cell Transplantation and Cellular Therapy
IND Sponsor	MD Anderson Cancer Center
IND #	143744

A Phase I/II Study of Recombinant Human Interleukin-7 to Promote T-Cell Recovery after Haploidentical and Cord Blood Stem Cell Transplantation

Institution Study Number: **2018-0674**

Study Drug Supplier: Revimmune

IND Sponsor: The University of Texas MD Anderson Cancer Center

IND Number: 143744

Principal Investigator: Gheath Al-Atrash, DO, PhD
The University of Texas MD Anderson Cancer Center
Stem Cell Transplantation and Cellular Therapy Department
1515 Holcombe Blvd, Unit 0423
Houston, TX 77030
Telephone: 713.563.3324
Fax: 713.563.3364
galatras@mdanderson.org

Co-Chairs: Elizabeth Shpall, MD[1]
Katy Rezvani, MD, PhD[1]

Collaborators: Roland L. Bassett, Jr., MS[2]
Chitra M. Hosing, MD[1]
Partow Kebriaei, MD[1]
Rohtesh Mehta, MD[1]
Yago Nieto, MD, PhD[1]
Amanda L. Olson, MD[1]
Betul Oran, MD[1]
Uday Popat, MD[1]
Peter F. Thall, PhD[2]

[1] The University of Texas MD Anderson Cancer Center, Stem Cell Transplantation and Cellular Therapy Department
[2] The University of Texas MD Anderson Cancer Center, Biostatistics Department

Table of Contents

Protocol Body

1.0 Objectives

Primary Objective:

- To determine the safety and establish the optimal biologic dose of CYT107.

Secondary objectives:

- To determine the rate of cytomegalovirus (CMV), Epstein-Barr virus (EBV) and BK viral infections in umbilical cord blood stem cell transplantation (CBT) and haploidentical stem cell transplantation (haplo-SCT) patients who receive three doses of IL-7 following engraftment.

- To calculate the OS, PFS and, cumulative incidence of GVHD and cumulative incidence of relapse

- To evaluate the effects of CYT107 on the recovery of T, NK and B cell populations and their functions in vitro; these data will be used to identify the optimal dose to move to a phase II trial.

2.0 Background

2.1 Haploidentical and Cord blood transplantation

Haploidentical stem cell transplantation (haplo-SCT) and umbilical cord blood stem cell transplantation (CBT) are being increasingly used as a source of hematopoietic stem and progenitor cells (HSPCs) for allogeneic stem cell transplant candidates lacking suitable matched donors. Although haplo-SCT and CBT are successful in many patients, their efficacy have been restricted by slow hematopoietic and immunologic reconstitution due to the quantitative and qualitative differences in the composition of the stem cell grafts.[1-5] While the frequency of HSPCs is greater in CB units, CB grafts contain an average of 1-2 logs fewer total cells compared to peripheral blood (PB) or bone marrow (BM) allografts. Moreover, the vast majority of T, B and dendritic cells in CB grafts are immature,[6;7] which likely explains the low rates of graft-versus-host disease (GVHD) seen after CBT given the degree of HLA-mismatches typically used.[8;9] The use of double unrelated CBT (DUCBT) represents an important advance by allowing larger children and adult patients to be transplanted with an acceptable cell dose. In this setting, although two CB units are initially transplanted, only one provides prolonged engraftment and becomes the “dominant” engrafted unit. Yet, even following DUCBT, severe complications related to infections remain a major cause of morbidity and mortality.[15-20] Similarly, immune recovery after haplo-SCT also tends to be less roubust in comparison with matched grafts, and affects B cells, T cells and their subsets.[1-3]

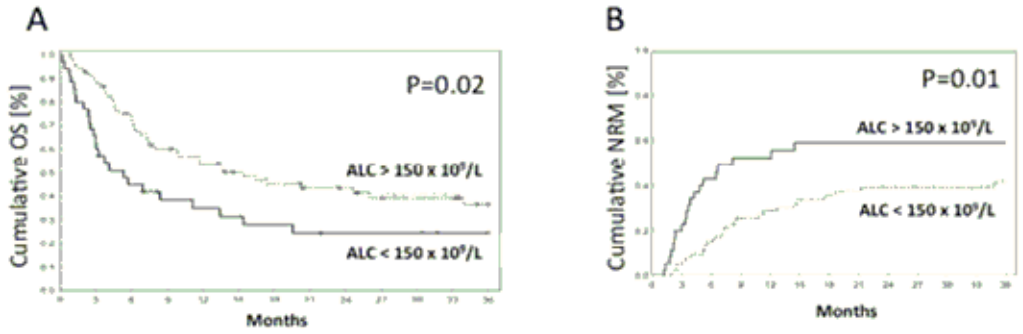
2.2 Strategies to enhance T-cell reconstitution

Interleukin-(IL-7) has a central role in T-cell development and survival; it enhances thymopoiesis, peripheral T-cell survival and expansion in murine models of allogeneic hematopoietic stem cell transplantation (allo-HSCT).[2-5] Initial trials with recombinant human IL-7 (r-hIL-7) demonstrated an expansion of CD4+ and CD8+ T cells in patients with solid tumors or HIV infection.[21-25] A potential concern with IL-7 in allo-HSCT patients is the stimulation of GVHD. In preclinical mouse models, short courses of IL-7 did not induce GVHD in T-cell depleted bone marrow transplant (TCD-BMT) nor did it aggravate the development of GVHD after adding donor T cells.[3] However, IL-7 when given longer and at higher dose to mice after TCD-BMT, did lower the threshold dose of T cells required to induce lethal GVHD.[26] In a recent Phase I clinical study of r-hIL-7 in recipients of a T-cell depleted allo-HSCT, investigators at Memorial Sloan Kettering treated 12 patients with escalating doses of IL-7 administered weekly for 3 weeks after the patients had engrafted. They reported that the study drug was well tolerated with only one patient developing acute skin GVHD. At baseline, patients were profoundly lymphopenic. IL-7 induced a doubling in CD4+ and CD8+ T cells with no significant effect on CD4+CD25+FoxP3+ T cells, NK, or B cells. Importantly, they also demonstrated an increase in functional T cell recovery, including viral-specific T cells that recognize CMV. Enhanced T-cell receptor (TCR) diversity was also observed after treatment. The authors concluded that IL-7 can enhance immune recovery after a T cell–depleted allo-HSCT without causing significant GVHD or other serious toxicity.

2.3 Preliminary Studies

Predictors of Non-Relapse Mortality and Overall Survival after CBT. We analyzed the outcome of 108 patients who underwent a DUCBT at our center for predictors of 3-year non-relapse mortality (NRM).[28] In univariate analysis, the day 30 absolute lymphocyte counts (ALC30) were treated as dichotomous variables above or below 150 x 10^6 /L (upper limit of first quartile) and significantly affected NRM. The median (range) of ALC30 was 240 (10-2420) x 10^6/L. There was no significant impact of age, sex, disease stage at the time of DUCBT, CMV serostatus, the occurrence of grade II-IV acute GVHD before day 30, total nucleated cell dose (TNC) dose, total CD34 dose, preparative regimen or CB manipulation on NRM. In multivariate analysis, ALC30 (HR = 2.3, *P* = 0.01) emerged as an independent factor strongly associated with NRM. **Figure 1** shows the impact of ALC30 on NRM and OS in all patients. For patients with ALC30 > 150 x 10^6/L, overall survival at 3 years was 37% (95% CI 25-49) compared with 25% (95% CI 11-40) for those with counts ≤ 150 x 10^6/L (*P* = 0.02). Similarly, ALC30 > 150 x 10^6 /L was related to a lower risk of NRM, 42% (95% CI 31-56%) vs 59% (95% CI 44-78%) (*P* = 0.01) in patients with ALC30 £ 150 x 10^6/L. The leading causes of NRM in both the groups (ALC30 £ 150 vs. ALC30 >150) included infections (50% vs. 52%, *P*=0.9) and GVHD (40% vs 30%, *P* = 0.5). Further, there was no significant impact of ALC30 on the rate of grade II-IV aGVHD (*P* = 0.4), disease progression (*P* = 0.7) or progression-free survival (*P* = 0.07) at 2 years.

Figure 1



CBT outcome based on ALC30. Impact of ALC30 £ or > 150 x 10^6/L on (**A**) OS; (**B**) NRM.

Figure 2

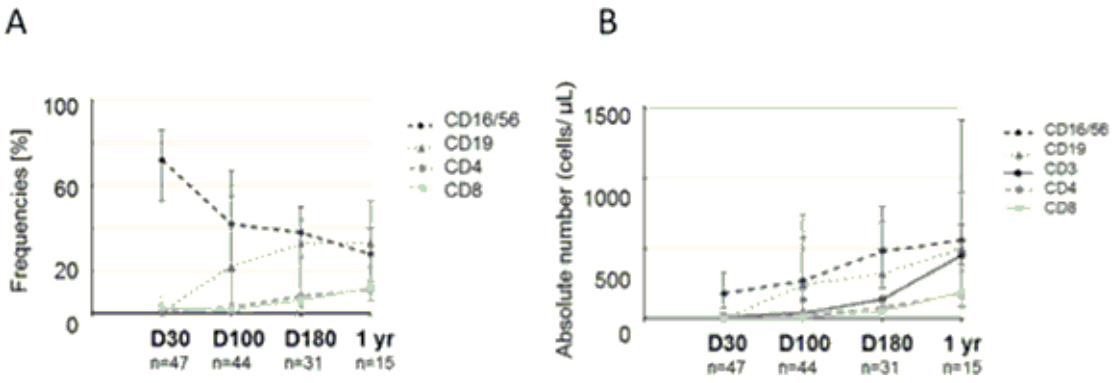


Figure 2. Prolonged T lymphopenia and relative expansion of NK cells and B cells following DUCBT. T (CD3+CD4+ and CD3+CD8+), B (CD19+), and NK (CD56+) cells were prospectively measured by multiparameter flow cytometry on fresh samples; (**A**) frequencies; (**B**) absolute numbers (x 10^6/L) for each immune subset are presented. At baseline and after DUCBT, CD4+ and CD8+ T cells were relatively reduced, whereas early B-cell and NK-cell recovery was evident. Surviving CB transplant recipients demonstrated rebound of CD4+ and CD8+ T cells at later intervals after transplantation. Error bars represent interquartile range.

Lymphocyte subset analysis. In 65 patients for whom peripheral blood (PB) samples had been collected at days +30, +100, +180 or 1 year post-DUCBT, we further characterized immune subset recovery by measuring the frequencies and absolute numbers of CD4+ T cells, CD8+ T cells, CD56+CD3- NK cells, and CD19+ B cells (**Figure 2**). The absolute number of each cell subset was calculated by multiplying their frequencies as determined by flow cytometry by the absolute lymphocyte number (cells/µl) obtained from a diagnostic complete blood count performed on the same day. Lymphocyte reconstitution following DUCBT began with a rapid increase in both the absolute number and frequencies of NK cells over baseline norms, and remained increased at the different study intervals, though the percentage of NK cells declined as T-cell counts recovered. T cell reconstitution on the other hand was significantly delayed. CD4+ and CD8+ T cells declined after conditioning and were significantly

reduced by day 30 post-DUCBT. The median absolute number of CD8+ cytotoxic T cells was 6 x 10^6/L (range 0-170) at 30 days and 11 x 10^6/L (range 0-1900) at 100 days post-transplant. The corresponding numbers of CD4+ helper T cells were 4 x 10^6/L (range 0-100) and 22 x 10^6/L (range 0-390), respectively. These results confirm that quantitative T cell recovery is delayed after DUCBT, with an inverted CD4/CD8 T cell ratio, and that this delay in T cell immunity is associated with a preferential rapid reconstitution of non-T lymphoid cells (e.g., NK cells and B cells). Patients who developed acute GVHD had a slower T and B cell recovery (data not shown)[29], in keeping with previous reports following allogeneic stem cell transplantation.[29]

To assess the tempo of functional virus-specific T cell recovery after DUCBT, we stimulated PBMC from 46 transplant recipients with 15-mer overlapping peptides spanning T cell immunogenic antigens from a range of both latent (CMV, EBV, BKV) and community (AdV, Influenza and RSV) viruses as well as to SEB, which was used as a positive control. Prior to transplant the frequency of T cells reactive against SEB was highest (mean 424.5 SFC/2 x 10^5 PBMCs), followed by CMV (mean 258 SFC in 39 seropositive donors), EBV (mean 33 SFC), AdV (mean 17 SFC), BKV (mean 13 SFC), Influenza (mean 8 SFC), and RSV (mean 10 SFC) (**Figure 3**).

Figure 3

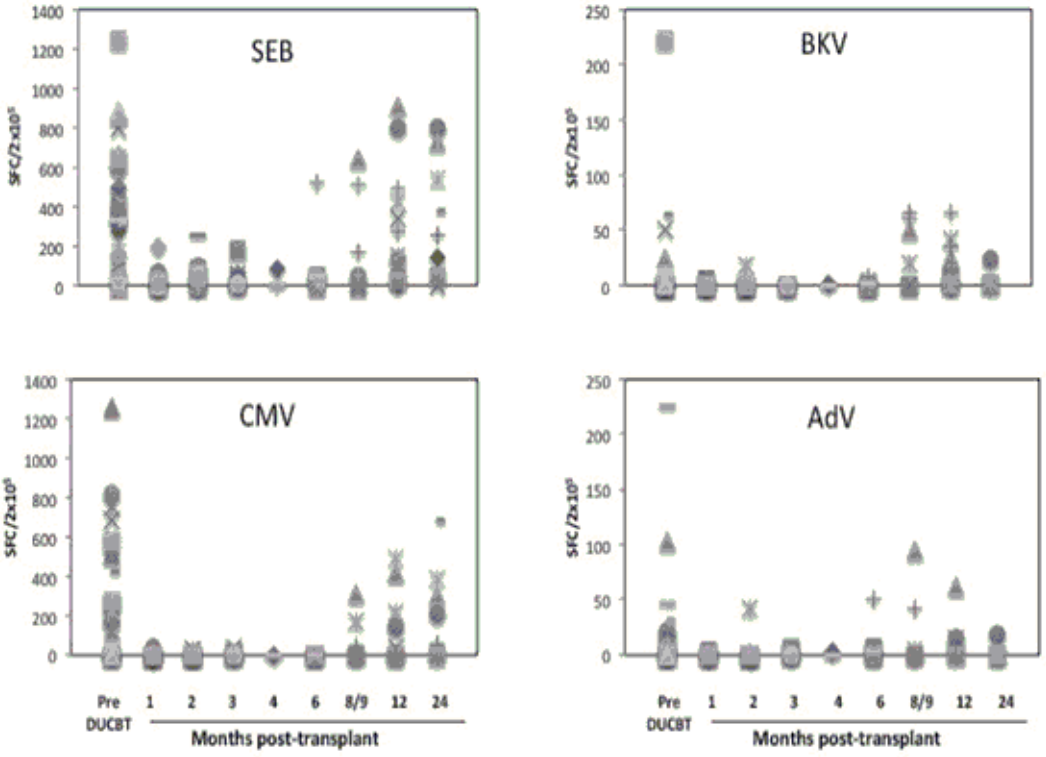


Figure 3. Virus-specific T cell activity following DUCBT. (A) Frequencies of SEB, BKV (Large T and VP1), AdV (Hexon and Penton) AND CMV (IE1 and pp65)-specific T cells in seropositive and seronegative donors in PB samples collected from patients prior to and post-DUCBT using IFN ELIspot as readout. Each symbol represents individual patient and results represent the SFC/2 x 10 input cells.

As shown in **Figure 3**, T cell activity against SEB, CMV, EBV, and AdV was delayed for at least 8-9 months following DUCBT (mean 200, 89, 28 and 24 SFC/2 x 10^5, respectively). All patients developed viral infections/ reactivations post-DUCBT. The most common causes of viral infection included CMV (59%), BKV (20%) and AdV (11%). The majority of these infections occurred within the first 100 days post DUCBT and nearly 50% of patients had infections with multiple viruses.

Haplo-SCT

Immune recovery following haplo-SCT also has been reported to be suboptimal for at least 1 year after stem cell transplantation in comparison with the immune recovery observed following fully matched transplants. [35-37] Furthermore, the absolute numbers of lymphocyte subsets were much lower after haplo-SCT in comparison with lymphocyte counts seen in normal individuls.[35-37] Sluggish recovery was reported for $CD19^+$ B cells, which according to some studies remained under 100 cells/μL until 180 days after transplantation.[37] Poor recovery was also reported in the T cell subsets.[35-37] In one study, $CD4^+$ helper T cells were shown to recover slowly after haplo-SCT and did not reach 400/μL until 12 months after transplantation.[37] Although $CD8^+$ cytotoxic T cells recovered rapidly after haplo-SCT according to some studies, there was a significant inversion of the CD4:CD8 ratio, which was observed up to 12 months after transplantation.[35-37] $CD4^-CD8^-$ T cells recovered slowly and did not reach the normal value until 180 days after transplantation. Slow recovery was also demonstrated in regulatory T cells ($CD4^+CD25^+$).[37] Unlike conventional T and B cells, regulatory T cells never reached normal levels at 12 months following haplo-SCT. In addition to absolute numbers and frequencies, immune cell function may be altered following haplo-SCT. For example, one study demonstrated lower numbers of CD28-expressing T cells 1 year following haplo-SCT.[37] Moreover, a number of studies have shown that successful immune reconstitution after allo-HSCT significantly correlates with better post-transplant outcomes, including lower infection, relapse and less secondary malignancy rates.[38,39] Moreover, rapid immune reconstitution specifically following haplo-SCT prognosticated for superior outcomes, suggesting that measures that could “normalize” immune recovery may improve the outcomes for patients following haplo-SCT.[40]

IL-7 and GVHD

Previous studies with infusion of exogenous IL-7 have shown variable effects on GVHD. Whereas Alpdogan et al, using an allogeneic murine model with full MHC class I and II disparity, reported that IL-7 improves immune reconstitution without aggravating GVHD,[29] Sinha et al reported increased GVHD in a murine parent into an F1 model.[31] More recently, a small phase I study, the administration of IL-7 in the setting of T-depleted bone marrow allogeneic transplant appeared to be safe and associated with an increase in functional T cell recovery, including virus-specific T cells that recognize CMV.[27] Thus, we propose that treatment with IL-7 after CBT and haplo-SCTwill be safe and will not increase the risk of graft-versus-host disease (GVHD) for several reasons: i) the number of infused T cells after CBT is one-log lower than that infused after a bone marrow transplant and two-logs lower than a peripheral blood stem cell transplant (akin to a T-depleted graft); ii) all patients will receive serotherapy with ATG as part of their CBT conditioning and will therefore undergo in vivo T cell depletion; iii) in our CBT population, the median time to acute GVHD grade I-IV is 34 days (manuscript submitted). Administration of CYT107 can be initiated between day 60-180, and all patients with a prior history of aGVHD will be excluded from the study.

3.0 Patient Eligibility

3.1 Patient Inclusion Criteria

1. Patient 18 years old or older.
2. English and non-English speaking patients are eligible.
3. Patient post a cord blood transplant (CBT) or haplo-SCT, mismatched unrelated donors (mMUDmatched), unrelated donors (MUDs), matched related donors (MRDs), both PB and marrow sources with documented absolute neutrophil engraftment.
4. Patients with documented engraftment but require G-CSF to treat myelosuppression induced by drugs used to treat or prevent infection are eligible.
5. Karnofsky performance status (KPS) > 60%.
6. Adequate organ function:
   - Pulmonary: Absence of dyspnea or hypoxia (< 90% of saturation by pulse oximetry on room air).
   - Hepatic: Bilirubin </= 1.5 X ULN, AST (SGOT) and /or ALT (SGPT) </= 2.5 X ULN. PT/PTT < 1.5 X ULN.
   - Renal: Calculated Creatinine clearance > 50 mL/min/1.73 m2.
7. Diagnosis of acute myeloid leukemia; myelodysplastic syndrome; chronic myeloid leukemia; myelofibrosis or myeloproliferative disease.
8. Patients are allowed to enroll on this study if they are enrolled on another IND trial.

3.2 Patient Exclusion Criteria

1. Pregnant or nursing.
2. History of lymphoid malignancy (including Hodgkin disease, non-Hodgkin lymphoma, Acute Lymphoblastic Leukemia and Chronic Lymphocytic Leukemia) or acute biphenotypic leukemia.
3. Patients with acute GVHD > grade 2 at any time during the post-transplant course.
4. Ongoing immunosuppressive therapy for the treatment of GVHD. Patients receiving GVHD prophylaxis will be allowed on this study.
5. History of EBV associated lymphoproliferation.
6. Active uncontrolled viral, bacterial or fungal infection.
7. History of autoimmune disease.
8. Receiving systemic corticosteroid therapy at </=5 mg, budesonide is allowed.
9. Uncontrolled hypertension.
10. QTc prolongation (QTc > 470 ms) or prior history of significant arrhythmia or ECG abnormalities.
11. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements.
12. Patients with cognitive impairments and/or any past or current psychiatric illness that, in the opinion of the investigator, would interfere with adherence to study requirements or the ability and willingness to give written informed consent.

4.0 Treatment Plan and Study Design

CYT107 will not be administered before Day 60 but could be started as late as Day 180 post-CBT or haplo-SCT.

The active treatment period will be from the first injection of CYT107 and for 30 days after the last injection. The follow-up period will be for three years after the last injection.

Patients will be treated with CYT107 by intramuscular route (I.M.)* post CBT or haplo-SCT (from 60 to 180 days), with 1 of 3 doses below:

- 5 mcg/kg/dose for 3 doses, one week apart
- 10 mcg/kg/dose for 3 doses, one week apart
- 20 mcg/kg/dose for 3 doses, one week apart

Enrollment of the first 3 participants will be staggered by 14 days. Accrual in between cohorts will be halted for 30 days after the last patient in each cohort has received the last dose of CYT107.
* If the patient's platelet count is below 35,000, the product may be administered by subcutaneous route.

All patients will receive foscarnet for the management of CMV infection as per Stem Cell Transplantation and Cellular Therapy Department's standard of care.

Dose modifications

Treatment will be permanently discontinued for patients developing grade 3 or 4 GVHD, secondary graft failure, disease relapse, PTLD, PML, grade 2-4 skin rash, or grade 3-4 non-hematological toxicity attributable to CYT107.

Patients who develop grade 2 non-hematological toxicity attributable to the CYT107 will have the next dose withheld until the toxicity resolves to grade 1. If the toxicity resolves within 2 weeks the drug will be administered at the same dose, however if the toxicity takes more than 2 weeks to resolve the drug will be administered at the next lower level, or permanently discontinued if the patient was already at the lowest level. If the toxicity takes more than 4 weeks to improve to grade I, the CYT107 will be permanently discontinued

For patients who at study entry have grade 0, 1 or 2 hematological toxicity and develop grade IV hematological toxicity attributable to the CYT107 will have the next dose withheld until the toxicity resolves to grade 2. If the toxicity resolves within 2 weeks the drug will be administer at the same dose, however if the toxicity takes more than 2 weeks to resolve the drug will be administered at the next lower level, or permanently discontinued if the patient was already at the lowest level. If the toxicity takes more than 4 weeks to improve to grade 2, the CYT107 will be permanently discontinued

There are no planned dose modifications for patients who already have grade 3-4 hematological toxicity at study entry

5.0 Background Drug Information

5.1 CYT107 (IL-7)

Description

CYT107 is a recombinant protein belonging to the class of growth factors and more specifically to the class of cytokines. CYT107 is a heavily glycosylated and sialylated form of recombinant human interleukin-7 expressed from a CHO cell line, composed of 152 amino acids, with an average molecular mass as determined by mass spectrometry of 22 kDa and a mean pI of 7. The molecular formula of the peptidic sequence only (non glycosylated) is C762H1241N213O228S11. The protein contains 3 disulfide bridges (Cys2- Cys 92, Cys 34- Cys 129, and Cys 47- Cys 141) and 4 glycosylation sites (3N, 1O).

Source

CYT107 used in this clinical trial was manufactured under good manufacturing practice (GMP) criteria at a 600 L fermentation and purification scale by PATHEON (Princeton, NJ), for REVIMMUNE Inc. At clinical site, the product will be made available to the hospital pharmacy by CSM, Fargo, ND 58103.

Formulation

CYT107 is supplied in a 2 mL vial as 0.5 mL of CYT107 (1 mg) in 10 mM Sodium Acetate, 100 mM NaCl, 50 mM glutamic acid. The pH of the solution is 5 and the osmolality is 320 40 mOsm. The concentration of CYT107 in solution is 2 mg/ml.

Stability

Stability studies will continue throughout the clinical study. Updated stability information will be periodically communicated to the hospital pharmacy.

Special Handling

There are no specific guidelines for safe handling of CYT107. Institutional guidelines for safe handling of proteins in general should be followed.

CYT107 Preparation

Syringes containing the CYT107 dose will be prepared by the hospital pharmacy. The product should be defrosted at least 1 hour before administration. Defrosted product (and possibly put in syringe) should be kept refrigerated at +4°C/+8°C until use and for no more than 8 hours.

CYT107 flip-top vials will only be used if the solution is clear (following visual inspection), the vial is undamaged and the use by (expiration) date (if marked on the vial) has not been passed. Based on patient's body weight on day of study entry, the appropriate number of vials of CYT107 drug product will be prepared and administered. (See Body Weight (BW) Calculation below.) CYT107 will be kept refrigerated until time of immediate administration to the patient.

To minimize the chance for contamination, sterile or septic technique should be carefully observed during CYT107 solution preparation (filling of the syringe) and administration.

A flip-top vial is restricted for use by a single patient. Take no more than 0.5 mL into the syringe. The dose to be injected will be divided as necessary into intramuscular injections so that each injection will not exceed 0.5 ml in volume. (Dosing guidelines for ideal body weight make the requirement for multiple injections highly unlikely).

Body Weight (BW) Calculation

If patient is </= 20% of ideal body weight (IBW), use actual weight.

In obese patients, a corrected weight will be used to calculate the final dose the patient will receive. The corrected dose will be calculated and used if the patient's actual weight give a Body Mass Index (BMI) at the upper limit of normal (i.e. BMI >30).

BMI=weight (Kg)/[height(m)]^2

A BMI calculator is provided by www.cdc.gov:

https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html

If BMI >30 proceed with the following steps to determine the adjusted body weight for the dose calculation:

- Determins Ideal weight (1 kg=2.2 lbs):
    - Males: 50 kg + (2.3kg/inch over 5 ft)
    - Females 45.5 kg + (2.3kg/inch over 5 ft)
- Determine Adjusted Body weight:
    - Ideal Weight + 0.25 (actual weight - ideal weight)= Adjusted Body Weight

CYT107 Presentation and Packaging

CYT107 is supplied as a sterile colorless liquid in 2 cc glass vials that are packed individually in cardboard box. Labels are stuck on vial and box.

The labeling is following local and GMP rules. The detailed description of labeling is provided in the Pharmacy Manual.

CYT107 Storage Accountability and Return of Unused Product

Study product will be stored frozen at -25°C to -10°C until used.

The Investigational Pharmacy will maintain complete records of all study products received, stored and subsequently dispensed.

Per MDACC standard, empty, partially used, and expired vials will not be retained. These vials will be discarded immediately upon use in accordance with waste stream policy.

MD Anderson's Investigational Pharmacy Services will use its electronic accountability system in lieu of sponsor-provided accountability forms.

The detailed procedures to be followed are provided in the Pharmacy Manual.

Study Drug Administration

Each dose of CYT107 will be administered by a registered nurse. CYT107 will be administered by intramuscular route at the dose of 5, 10 or 20 mcg/kg based on the patient's body weight and the dose escalation cohort. (See Body Weight (BW) Calculation above.)

The detailed procedures to be followed are provided in the Pharmacy Manual including a table of volumes to be administered per patient total body weight.

6.0 Evaluation During Study

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule and occasional missed required research samples. Missed samples for correlative studies will not constitute protocol deviations.

For patients who have discharged to their home clinics, and are not being followed weekly at MD Anderson, labs and assessments will be collected as feasible in their home clinics or upon patient's return to MDACC clinic. Any missed time points will not be counted as protocol deviations.

6.1 Pre-Treatment Evaluations

Within 2 weeks of first dose:

1. BK, CMV, and EBV blood level by PCR
2. EKG
3. Oxygen saturation by pulse oximetry
4. Creatinine
5. AST, ALT, bilirubin
6. PT/PTT
7. Electrolytes
8. Physical exam
9. Medical history

6.2 Evaluation after CYT107 administered:

Weekly until day +42 following CYT107:

1. CBC, differential, platelets
2. SGPT, calcium, glucose, uric acid, magnesium, serum bilirubin, BUN and creatinine, serum protein, albumin, ALT, alkaline phosphatase, electrolytes, tacrolimus levels.
3. Physical examination
4. Adverse event assessment

6.3 Viral Infections. Patients will be monitored for viral infections after the CYT107.

1. CMV by PCR will be assayed in the blood weekly from the start of IL-7 therapy until day 180 from the start of IL-7 therapy.
2. EBV PCR will be assayed in the blood every two weeks from day 60 until day 100 and then monthly until day 180 from the start of IL-7 therapy.
3. BKV PCR will be assayed in the urine and blood if patients become symptomatic, as clinically indicated.

6.4 Correlative Studies

Circulating lymphocyte subsets will be measured, using immune reconstitution lab, prior to administration of each dose of CYT107 and approximately days 21 and 28, and 100 days after the first injection in the MD Anderson CLIA-approved clinical flow cytometry laboratory. The lymphocytes subsets analyzed will be CD4 and CD8 subsets including naïve and memory T-cells based on expression CD45RO, CD62L and CCR7. T-regulatory cells, B-cells and NK cells will also be evaluated. This studies will be used to help identify the optimal IL-7 dose for a subsequent phase-II trial.

Correlative study samples will be obtained via MD Anderson laboratory protocol LAB99-062 if patient consents.

6.5 Plasma Samples

Plasma samples will be drawn to test for anti-CYT107 antibodies on approximately Days 0 (prior to IL-7 administration), 42, and 100 from the start of IL-7 therapy. The samples will be batched and sent to Revimmune for immunogenicity assays.

6.6 Outside Physician Participation During Treatment

a) MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record
b) A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care.
c) Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
d) Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
e) A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
f) Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
g) The home physician would only be alerting the Principal Investigator to a subject’s life-threatening event (much as a family member would) and the Principal Investigator would be assessing the event per the protocol.
h) Patients will be evaluated either in person or remotely via telemedicine.

7.0 Statistical Considerations

7.1 Outcomes and Covariates

7.1.1 Primary Outcomes

Toxicity. Dose limiting toxicity (DLT) is defined as any of the following events: grade 3 or 4 GVHD, secondary graft failure, disease relapse, development of PTLD, development of PML, grade 2 organ failure or grade 2-4 skin rash, fatigue, AST and ALT elevations, allergic anaphylaxis, or hemolytic anemia, attributable to CYT107, or death, occurring within 42 days of the first CYT107 injection.

Biological Responses. The absolute number and percentage of total White Blood Cells (WBCs) consisting of T-cells and of B-cells will be observed at 1, 3, 6, 9 and 12 months.

7.1.2 Secondary Outcomes

Progression-free survival time, Overall survival time, Cytomegalovirus occurrence and severity , Epstein-Barr virus occurrence and severity, BK virus occurrence and severity

All time-to-event outcomes will be measured from the time of CYT107 administration, with a maximum follow up of at least 12 months.

7.2 Baseline covariates

Baseline patient covariates to be recorded at enrollment will include the following variables:

Conditioning regimen received
GVHD prophylaxis
Type of donor
Type of graft
Time to engraftment from cell infusion
Donor age
Acute (grades 2 – 4) GVHD
Patient age
Time to neutrophil engraftment
Time to platelet engraftment
Disease (AML or MDS)

7.3 Trial Conduct

7.3.1 Dose Assignments

Three dose levels of CYT107 will be considered: 5, 10, and 15 mcg/kg, hereafter denoted as dose levels 1, 2, and 3.

Randomization, rather than conventional sequentially adaptive dose selection, is based on the fact that neither Pr(DLT) nor any biological outcomes are necessarily monotone increasing in

dose of the biological agent IL-7, and also the scientific goal to obtain unbiased comparisons between doses.

A maximum of 21 patients will be randomized among the three IL-7 3 doses, with the randomization constrained to have exactly 7 patients per dose. Since 2 patients previously have been enrolled and assigned to d=1, a randomization sequence will be provided for assigning doses to the remaining 19 patients, 3 – 21.

7.3.2 Within-Dose Safety Monitoring Rule

For each dose d = 1, 2, 3, denote p(d) = Pr(DLT at dose d). Assume that each p(d) follows a beta(.35, .65) prior. Applying the method of Thall et al.[41], enrollment to dose d will be stopped if Pr[p(d) > .35 | data] > .85. This criterion will be applied continuously starting at n = 3, which implies that accrual to d should be stopped if [number of DLTs] / [number of patients evaluated] is greater than or equal to 3/3 or 4/5. To apply this safety rule for each dose to 2 cohorts of size 3 each may or may not require suspension of accrual. For each dose (a) once 1 or more pats in cohort 1 (pats #1,2,3) have "No toxicity" by day 42 of followup, cohort 2 may begin enrollment, and (b) once 2 or more pats in cohorts 1 and 2 combined (pats #1,2,3,4,5,6) have "No toxicity" by day 42 of follow up, the last patient 7 may be enrolled. This rule has the following operating characteristics.

Operating characteristics of the within-dose safety monitoring rule

True p(DLT | d)	Pr(Stop accrual to d)	Sample Size Quartiles
.35	.163	7, 7, 7
.55	.497	4, 7, 7
.60	.601	4, 6, 7
.65	.607	3, 4, 7

7.4 Enrichment

If enrollment to a dose d is stopped early at n(d) = 3 or 6 before 7 patients are treated, then the remaining 7–n(d) = 1 or 4 patients will be randomized between the remaining two doses. If enrollment to 2 doses is stopped early, then all remaining patients, up to Nmax = 21, will be treated at the one remaining dose. If enrollment to all 3 doses is stopped early, then the trial will be stopped with no dose selected.

7.5 Data Analysis

7.5.1 Tabulation

Each primary and secondary variable will be tabulated by dose using summary statistics, consisting of counts and percentages for categorical variables and the sample median and range for numerical valued variables. Kaplan-Meier plots[34] will be used to estimate the PFS and OS distribution for each dose.

7.5.2 Regression Modeling

Bayesian longitudinal regression models[42] will be fit to the final data on each of the four biological response variables, as defined in section 1, including in each model a parametric function of time and the baseline covariates patient age, type of graft, and disease (AML vs MDS). Preliminary analyses will include a smoothed plot of each longitudinal outcome variable as a function of time.

7.5.3 Optimal Biological Dose Selection

At the completion of the trial, when all patients have been followed up fully and all outcomes evaluated, the optimum biological dose (OBD) will be defined as the dose maximizing the sample mean percentage of WBCs that are T-cells, evaluated at one year of follow up.

7.6 Trial Conduct

The Biostatistics Department Clinical Trial Conduct Website will be used to assign a dose to each patient at enrollment. This will be set up and overseen by a Research Statistician in the Biostat Dept to be designated by Dr. Thall prior to re-starting the trial at patient number 3, using a randomization sequence provided by Dr. Thall. The Principal Investigator and designated personnel in the SCT Dept will be responsible for recording all baseline covariates and outcome variables and implementing the within-dose stopping rule in terms of DLTs.

7.7 Summary Reports

The investigator is responsible for completing a toxicity summary report and submitting it to the IND Office, Medical Affairs and Safety Group, for review and approval. This should be submitted after the first, the first three, and the first five evaluable patients per cohort, have completed 42 days post-first CYT107 injection.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder, under "Sponsor Correspondence".

8.0 Criteria for Removal from the Study

Any patient can be removed from study for the following:

- Patient withdrawal of the informed consent
- Patient not being compliant
- An increasing or unexpected pattern of toxicity is observed deemed unacceptable by the study chairman
- Grade 2-4 skin rash, grade 3 or 4 GVHD, secondary graft failure, disease relapse, PTLD, PML or grade 3-4 non-hematological toxicity attributable to CYT107
- Disease progression
- Investigator judgment when the well-being and best interest of the patient is compromised
- Secondary Graft Failure
- 1 year after last injection.

9.0 Adverse Events and Reporting Requirements

Adverse event definition:

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy and otherwise meet the criteria for a reportable adverse event as defined above. They are to be captured under the signs, symptoms or diagnoses associated with them.

It is common for HCT recipients to experience multiple complications as part of the transplant itself that are unrelated to exposure to investigational agents. Symptoms of the original or targeted disease are not to be considered adverse events for this study except for hematological toxicities as defined below. From start of study treatment through 30 days from last dose of CYT107, symptoms related to the conditioning regimen will not be reported unless the event is both serious and considered by the investigator to also be possibly, probably, or definitely related to CYT107. After 30 days from the last dose of CYT107, adverse events should only be reported if they are both serious and probably or definitely related to CYT107. Events that are unlikely or unrelated to CYT107 are not required to be reported. Reporting of such events should include the investigator's assessment as to whether the event should be attributed to any of the HCT procedure itself, CYT107, GVHD, or exposure to immunosuppressive agents. An event may be attributable to all, some, or one of these categories.

Assessment of the Adverse Events Severity:
The severity of the adverse events (AEs) will be graded according to the Common Terminology Criteria v4.0 (CTCAE).

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

Treatment period:
Active treatment period (ATP) is defined from the first injection of CYT107 through 30 days from

the last injection.

Time for Adverse Event (AE) Collection:
Adverse events will be collected from the first injection of CYT107 through 30 days from the last injection. AEs that occur up to 30 days from the last injection of CYT107 will be followed until resolution.

The collection of adverse events will reflect the onset and resolution date and maximum grade. If a patient is taken off study while an event is still ongoing, this will be followed until resolution or the event has stabilized. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the active treatment period. Co-morbid events will not be scored separately.

Adverse Event Reporting:
The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events, and assigning attribution for each event on all subjects enrolled on this study.

Adverse events will be documented and entered into the electronic case report form (REDCap/CORe). All protocol specific data will be entered into REDCap/CORe.

Events not to be considered adverse events in this study are those related to original disease or expected in the post-allogeneic transplant period.

Isolated changes in laboratory parameters such as electrolyte, magnesium and metabolic imbalances, uric acid changes, elevations of GPT, GOT, LDH and alkaline phosphatase will not be captured.

Concomitant medications
Patients treated on this protocol will require supportive care treatment (concomitant medications). These medications are considered standard of care and have no scientific contribution to the protocol; therefore no data will be captured on various medications needed or their side effects. All concomitant medications will be captured in the medical record.

Causality Assessment.
The principal investigator will be the final arbiter in determining the casualty assessment.

List of most common expected adverse events:
1. GVHD
2. Secondary graft failure

Serious Adverse Event Reporting (SAE) for MD Anderson-Sponsored IND Protocols

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an 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 (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- A copy of the eSAE report will also be sent to Michel Morre (michel.morre@revimmune.com) and to Revlimid (pv-revimmune@anticipsante.com), the supporter of CTY-107.

- Serious adverse events will be captured from the time of the first injection of CYT107 through 30 days from the last injection. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

AEs Attribution Assessment

Events assessed as to be caused by the administration of CYT107 and its direct consequences will be assessed as definite related.

When the relationship of the adverse event cannot be ruled out between the CYT107 and the drugs used as part of the treatment plan, as well as for GVHD, infections and supportive treatment, the event will be scored as probably or possible related.

The principal investigator will be the final arbiter in determining the causality assessment.

AEs Severity Assessment

AEs will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Events not included in the CTCAE version 4.0 will be scored as follows:

General grading:

Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.
Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
Grade 4: Life Threatening: discomfort that represents immediate risk of death.

AEs Data Collection

Redcap/Core will be used as the electronic database/case report form (CRF) for this protocol.

During the active treatment period, expected and unrelated adverse events considered unexpected and related to CYT107 will be collected in electronic medical record (EPIC). SAEs and AEs that require dose modifications will be captured in REDCap. The data will reflect the onset and resolution date and maximum grade. Intermittent events should be labeled as such and followed until resolution. If a patient is taken off study while an event still ongoing, this will be followed until resolution or the event has stabilized. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the ATP. Co-morbid events will not be scored and collected separately.

Medical events not considered adverse events will not be documented in the CRF. They will be captured in the medical record.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
  A copy of the eSAE will also be sent to RevImmune, the supporter of CYT-107.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.
- Patients who withdraw consent due to toxicities will be evaluable and considered treatment failures.

10.0 References

1. Goldberg GL, Zakrzewski JL, Perales MA, van den Brink MR. Clinical strategies to enhance T cell reconstitution. Semin.Immunol. 2007;19:289-296.

2. Mackall CL, Fry TJ, Bare C et al. IL-7 increases both thymic-dependent and thymic-independent T-cell regeneration after bone marrow transplantation. Blood 2001;97:1491-1497.

3. Alpdogan O, Muriglan SJ, Eng JM et al. IL-7 enhances peripheral T cell reconstitution after allogeneic hematopoietic stem cell transplantation. J.Clin.Invest 2003;112:1095-1107.

4. Schluns KS, Kieper WC, Jameson SC, Lefrancois L. Interleukin-7 mediates the homeostasis of naive and memory CD8 T cells in vivo. Nat.Immunol. 2000;1:426-432.

5. Heufler C, Topar G, Grasseger A et al. Interleukin 7 is produced by murine and human keratinocytes. J.Exp.Med. 1993;178:1109-1114.

6. Gluckman E, Rocha V, Boyer-Chammard A et al. Outcome of cord-blood transplantation from related and unrelated donors. Eurocord Transplant Group and the European Blood and Marrow Transplantation Group. N.Engl.J.Med. 1997;337:373-381.

7. Escalon MP, Komanduri KV. Cord blood transplantation: evolving strategies to improve engraftment and immune reconstitution. Curr.Opin.Oncol. 2010;22:122-129.

8. Kanda J, Chiou LW, Szabolcs P et al. Immune recovery in adult patients after myeloablative dual umbilical cord blood, matched sibling, and matched unrelated donor hematopoietic cell transplantation. Biol.Blood Marrow Transplant. 2012;18:1664-1676.

9. Sanz J, Sanz MA FAU - Saavedra S, Saavedra S FAU - Lorenzo I et al. Cord blood transplantation from unrelated donors in adults with high-risk acute myeloid leukemia. Biol.Blood Marrow Transplant. 2010;16:86-94.

10. Kurtzberg J, Laughlin M, Graham ML et al. Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. N.Engl.J.Med. 1996;335:157-166.

11. Kim YJ, Broxmeyer HE. Immune regulatory cells in umbilical cord blood and their potential roles in transplantation tolerance. Crit Rev.Oncol.Hematol. 2011;79:112-126.

12. Danby R, Rocha V. Improving Engraftment and Immune Reconstitution in Umbilical Cord Blood Transplantation. Front Immunol. 2014;5:68.

13. Rocha V, Wagner JE, Jr., Sobocinski KA et al. Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling. Eurocord and International Bone Marrow Transplant Registry Working Committee on Alternative Donor and Stem Cell Sources. N.Engl.J.Med. 2000;342:1846-1854.

14. Rocha V, Labopin M, Sanz G et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. N.Engl.J.Med. 2004;351:2276-2285.

15. Brunstein CG. Umbilical cord blood transplantation for the treatment of hematologic malignancies. Cancer Control 2011;18:222-236.

16. Brunstein CG, Fuchs EJ, Carter SL et al. Alternative donor transplantation after reduced intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. Blood 2011;118:282-288.

17. Brunstein CG, Eapen M, Ahn KW et al. Reduced-intensity conditioning transplantation in acute leukemia: the effect of source of unrelated donor stem cells on outcomes. Blood 2012;119:5591-5598.

18. Delaney C, Heimfeld S, Brashem-Stein C et al. Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution. Nat Med 2010;16:232-236.

19. Gutman JA, Leisenring W, Appelbaum FR, Woolfrey AE, Delaney C. Low relapse without excessive transplant-related mortality following myeloablative cord blood transplantation for acute leukemia in complete remission: a matched cohort analysis. Biol.Blood Marrow Transplant. 2009;15:1122-1129.

20. Milano F, Pergam SA, Xie H et al. Intensive strategy to prevent CMV disease in seropositive umbilical cord blood transplant recipients. Blood 2011;118:5689-5696.

21. Levy Y, Sereti I, Tambussi G et al. Effects of recombinant human interleukin 7 on T-cell recovery and thymic output in HIV-infected patients receiving antiretroviral therapy: results of a phase I/IIa randomized, placebo-controlled, multicenter study. Clin.Infect.Dis. 2012;55:291-300.

22. Sportes C, Babb RR, Krumlauf MC et al. Phase I study of recombinant human interleukin-7 administration in subjects with refractory malignancy. Clin.Cancer Res. 2010;16:727-735.

23. Levy Y, Lacabaratz C, Weiss L et al. Enhanced T cell recovery in HIV-1-infected adults through IL-7 treatment. J.Clin.Invest 2009;119:997-1007.

24. Sportes C, Hakim FT, Memon SA et al. Administration of rhIL-7 in humans increases in vivo TCR repertoire diversity by preferential expansion of naive T cell subsets. J.Exp.Med. 2008;205:1701-1714.

25. Rosenberg SA, Sportes C, Ahmadzadeh M et al. IL-7 administration to humans leads to expansion of CD8+ and CD4+ cells but a relative decrease of CD4+ T-regulatory cells. J.Immunother. 2006;29:313-319.

26. Sinha ML, Fry TJ, Fowler DH, Miller G, Mackall CL. Interleukin 7 worsens graft-versus-host disease. Blood 2002;100:2642-2649.

27. Perales MA, Goldberg JD, Yuan J et al. Recombinant human interleukin-7 (CYT107) promotes T-cell recovery after allogeneic stem cell transplantation. Blood 2012;120:4882-4891.

28. Saliba RM, Rezvani K, Leen A et al. General and Virus-Specific Immune Cell Reconstitution

after Double Cord Blood Transplantation. Biol.Blood Marrow Transplant. 2015

29. Sarantopoulos S, Stevenson KE, Kim HT et al. Altered B-cell homeostasis and excess BAFF in human chronic graft-versus-host disease. Blood 2009;113:3865-3874.

30. Alpdogan O, Schmaltz C, Muriglan SJ et al. Administration of interleukin-7 after allogeneic bone marrow transplantation improves immune reconstitution without aggravating graft-versus-host disease. Blood 2001;98:2256-2265.

31. Sinha ML, Fry TJ, Fowler DH, Miller G, Mackall CL. Interleukin 7 worsens graft-versus-host disease. Blood 2002;100:2642-2649.

32. Yin G., Yuan Y. (2009). Bayesian model averaging continual reassessment method in phase I clinical trials. Journal of the American Statistical Association. 104:954-968,2009.

33. Thall PF, Wooten LH, Tannir N. Monitoring event times in early phase clinical trials: some practical issues. Clinical Trials, 2:467-478, 2005.

34. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-81, 1958.

35. Chang YJ, Zhao XY, Huo MR, Xu LP, Liu DH, Liu KY, Huang XJ. Immune reconstitution following unmanipulated HLA-mismatched/ haploidentical transplantation compared with HLA-identical sibling transplantation. J Clin Immunol 2012; 32(2): 268–280

36. Azevedo RI, Soares MVD, Albuquerque AS, Tendeiro R, Soares RS, Martins M, Ligeiro D, Victorino RMM, Lacerda JF, Sousa AE. Long-term immune reconstitution of naive and memory T cell pools after haploidentical hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2013; 19(5): 703–712

37. Xuying Pei, Xiangyu Zhao, Yu Wang, Lanping Xu, Xiaohui Zhang, Kaiyan Liu, Yingjun Chang, Xiaojun Huang. Comparison of reference values for immune recovery between event-free patients receiving haploidentical allografts and those receiving human leukocyte antigen-matched sibling donor allografts. Front. Med. 2018, 12(2): 153–163

38. Seggewiss R, Einsele H. Immune reconstitution after allogeneic transplantation and expanding options for immunomodulation: an update. Blood. 2010;115(19):3861–3868. pmid:20215642

39. Bosch M, Khan FM, Storek J. Immune reconstitution after hematopoietic cell transplantation. Curr Opin Hematol. 2012;19(4):324–335. pmid:22517587

40. Tian DM[1,2], 1, Zhang XH[1], Liu KY[1], Huang XJ[,1,3,4], Chang YJ[1,4]. Rapid Recovery of CD3+CD8+ T Cells on Day 90 Predicts Superior Survival after Unmanipulated haploidentical Blood and Marrow Transplantation. PLoS One. 2016 Jun 8;11(6)

41. Thall PF, Simon R, and Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat in Medicine 14(4):357-79, 1995.

42. Gelman A and Hill J. Data Analysis Using Regression and Multilevel/Hierarchical Models. 2007. Cambridge University Press, New York.