CIRM Regenerative Medicine Consortium Roundtable

Best Practices in Clinical Design

Is there a role for Allogeneic Cell-based Therapy in HIV/AIDS?

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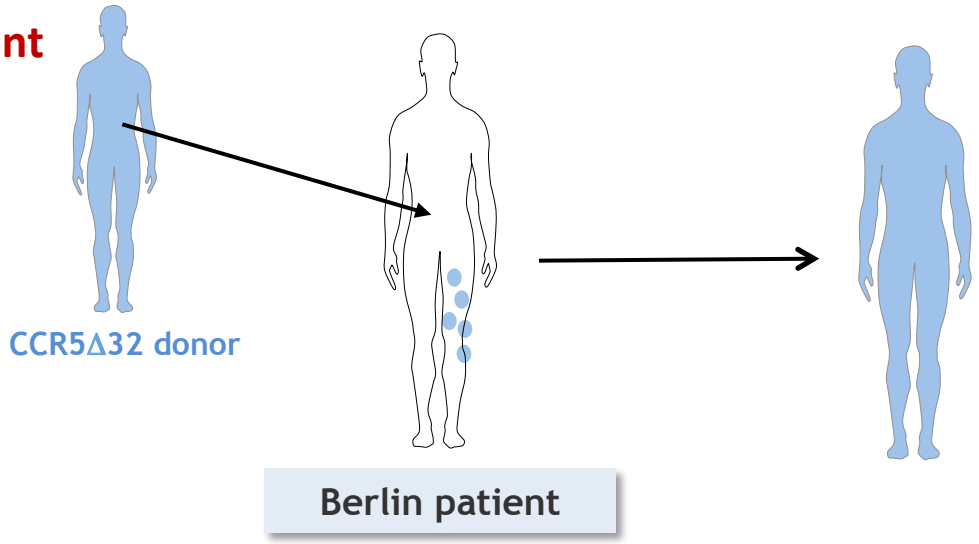
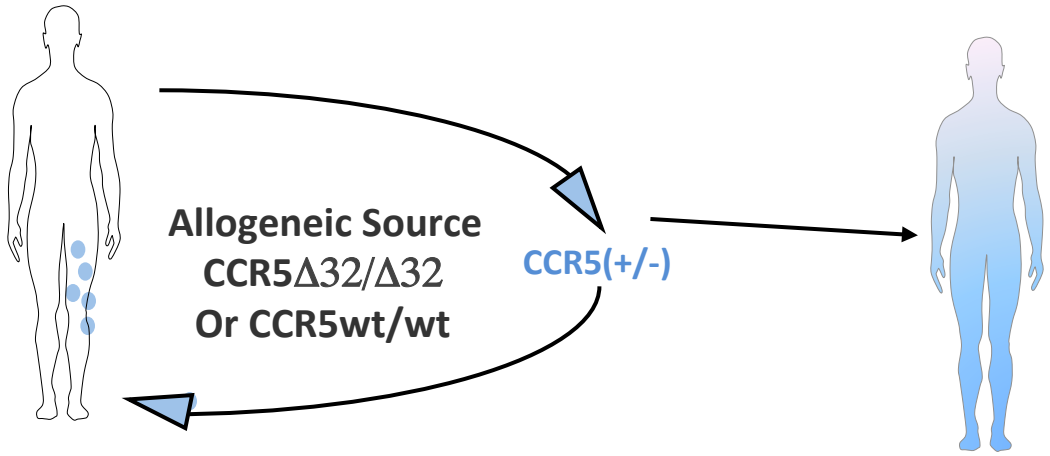
October 16, 2012

HSC transplant



HSC selection/engineering



Effect of HSCT on HIV/AIDS

- AIDS patients can mobilize HSCP cells
- Autologous HSPC transplants in AIDS patients engraft as well as in non-AIDS patients with similar time to engraftment and procedure-related morbidity
- CD4 recovery has been documented post-allogeneic HSCP transplantation
- Concomitant agent use can be altered appropriately
- Controlled phase II studies are feasible

Survival post auto-HSPC transplant: HIV vs non-HIV with complete ablation of immune function

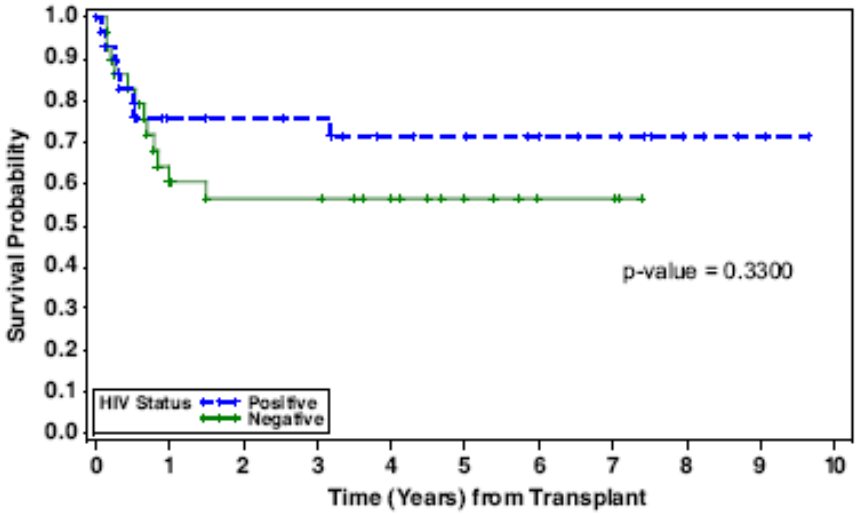


Figure 2. Probability of disease-free survival by HIV status.

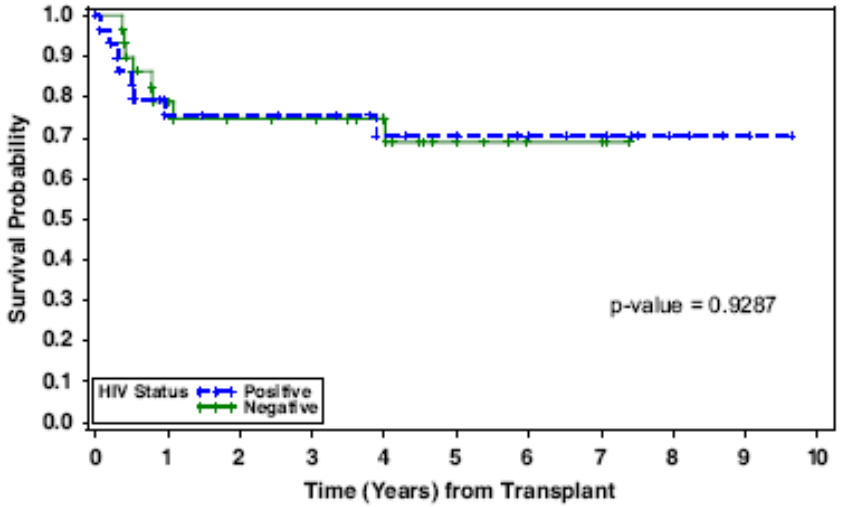
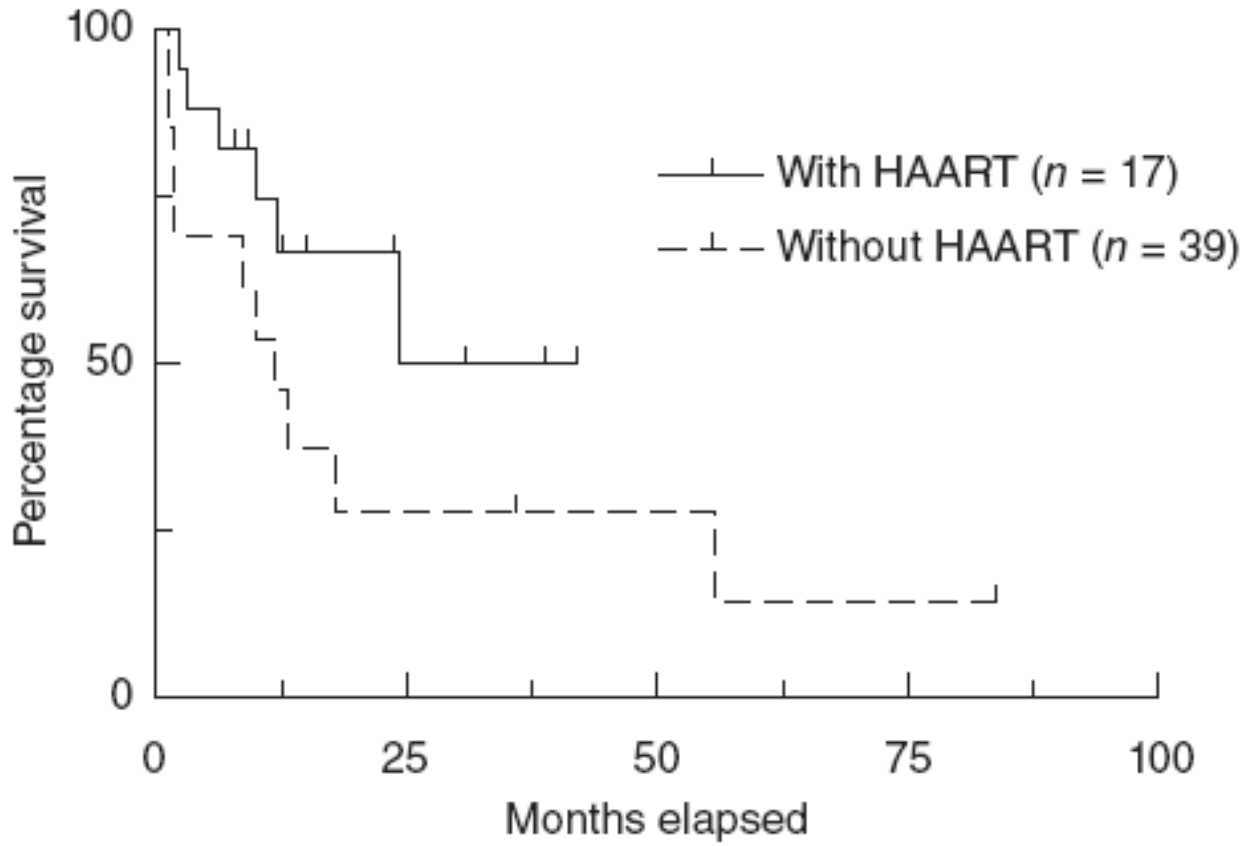


Figure 3. Probability of overall survival by HIV status.

From Krishnan et al. BBMT 2010; 16: 1302-08

Survival of HIV/AIDS recipients post allo-HSPC transplant for treatment of malignancy



From Hutter & Zaia Clin Exper Immunol 2011; 163: 284-295.

HIV agent and Transplant Agent: Pharmacology

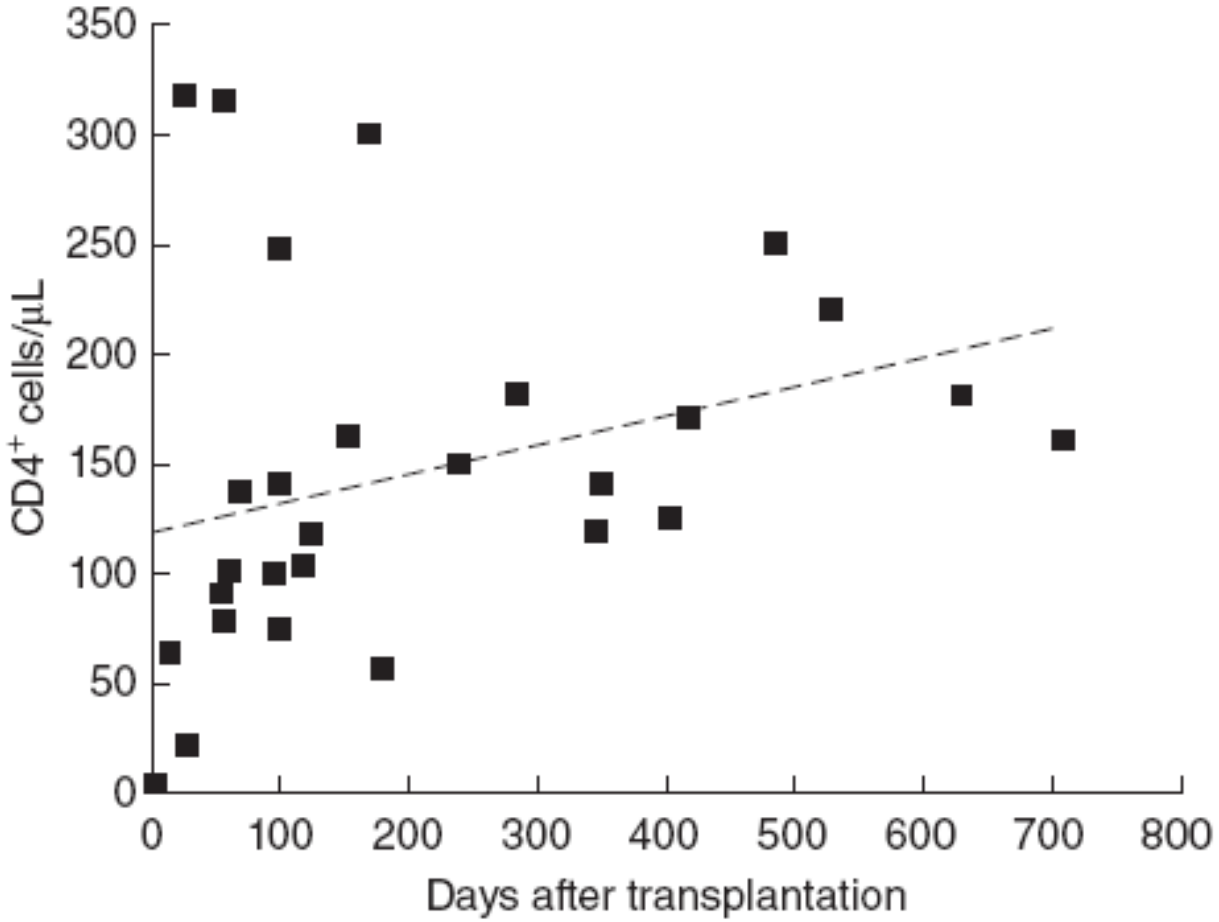
Table 4. Interactions of agents commonly used during allogeneic haemopoietic stem cell transplantation and anti-retroviral medications.

Agent	Anti-retroviral drug	Interaction on agent
Cyclophosphamide	Indinavir	Indinavir AUC: increased 38%
Cyclosporine	Darunavir Lopinavir/ritonavir Nelfinavir Saquinavir	Increased cyclosporine effects (increased immunosuppression, renal toxicity)
Mycophenolate mofetil	Nevirapine	Nevirapine clearance: increased 27%
Tacrolimus	Nelfinavir Lopinavir/ritonavir	Increased tacrolimus levels (e.g. increased bone marrow suppression)

AUC, area under the curve.

From Hutter & Zaia Clin Exper Immunol 2011; 163: 284-295.

CD4 Recovery after Allogeneic HSPC transplant



From Hutter & Zaia Clin Exper Immunol 2011; 163: 284-295.

Allogeneic HSCT in HIV/AIDS: Boston Cases

- Two subjects, CCR5wt/Δ32, had HIV infection and Hodgkin lymphoma
- Matched unrelated donor HSCT after reduced intensity conditioning; both donors were CCR5wt/wt
- GVHD treated with methotrexate, tacrolimus/sirolimus, prednisone
- Continued on ART with undetectable HIV levels by standard assay
- CD4 levels ~500 in patient #1 at ~700d post-HSCT; >1000 in pt #2 at ~1200d post-HSCT
- HIV outgrowth assay negative at +d652 (pt #1) and +d1266 (pt#2)
- Likely conclusion is that the allogeneic effect has altered the pool of circulating CD4 cells latently infected with HIV
- Only the absence of HIV outgrowth during cessation of ART will demonstrate whether this effect has eliminated the latent HIV

Henrich et al. IAS 2012

Rationale for use of Cord Blood Donors

- It is a statistical improbability that a matched unrelated donor is both an adequate HLA match and CCR5Δ32/Δ32

- A collaboration among investigators from COH and StemCyte Inc have joined with other cord blood banks to screen >15,000 CB units for CCR5Δ32/Δ32 gene status

- A CCR5Δ32/Δ32 CB Bank now exits containing ~120 units; if all the currently available CB banks were screened, there would be ~4000 CCR5Δ32/Δ32 available

- CB transplant technology is undergoing significant study to improve the outcome, including in vitro stem cell expansion methods, use of CXCR4 agonist therapy to increase CB engraftment efficiency, and use of combined haploID-CB donors

Screening for CCR5Δ32/Δ32 CB

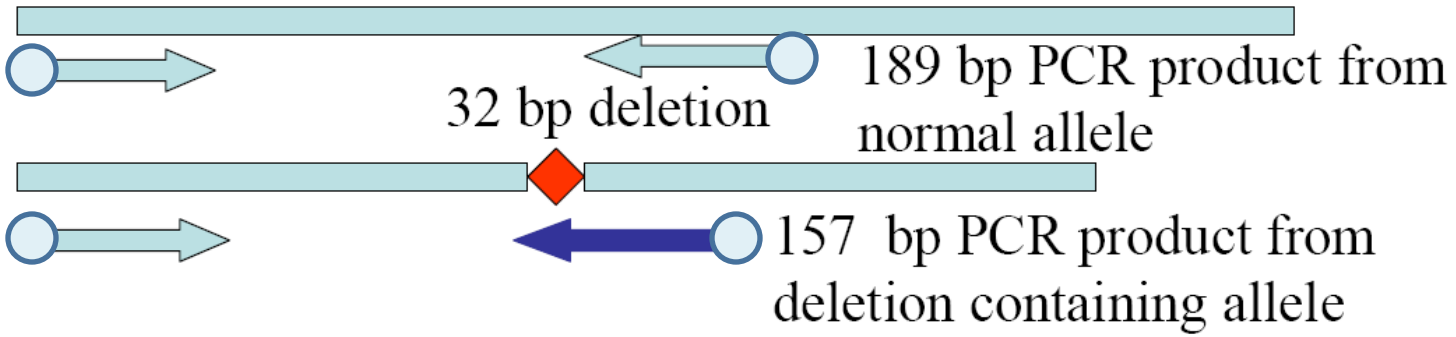


Figure 1. PCR scheme for detection of 23 bp deletion in CCR5 gene. The deletion specific primer will only amplify DNA from homozygous or heterozygous deletion containing DNA. Thus a positive Real Time PCR signal represents either a heterozygous or homozygous sample.

Primer 1 TTCATTACACCTGCAGCTCTC
Primer2 CCTGTTAGAGCTACTGCAATTAT
Primer 3 TGCAGCTCTCATTTTCCATACATTA

From Petz et al. BBMT 2012 in press

Likelihood of HLA matched CB Unit

PROJECTED HLA MATCH RATE WITH 300 UNIT INVENTORY OF *CCR5*-Δ32 CB UNITS

INCLUDES NEED FOR TNC OF 2.5 X 10(7) CELLS/KG:

ADULT PATIENTS	PEDIATRIC PATIENTS
6 OF 6 MATCHES: 0.01%	6 OF 6 MATCHES: 0.01%
5 OF 6 MATCHES: 4.49%	5 OF 6 MATCHES: 10.58%
4 OF 6 MATCHES: 27.92%	4 OF 6 MATCHES: 73.61%

INCLUDES NEED FOR TNC OF 1 X 10(7) CELLS/KG:

ADULT PATIENTS	PEDIATRIC PATIENTS
6 OF 6 MATCHES: 0.09%	6 OF 6 MATCHES: 1.01%
5 OF 6 MATCHES: 10.7%	5 OF 6 MATCHES: 10.8%
4 OF 6 MATCHES: 82.1%	4 OF 6 MATCHES: 85.6%

From Petz et al. BBMT 2012 in press

Engraftment potential of CCR5Δ32/Δ32 CB

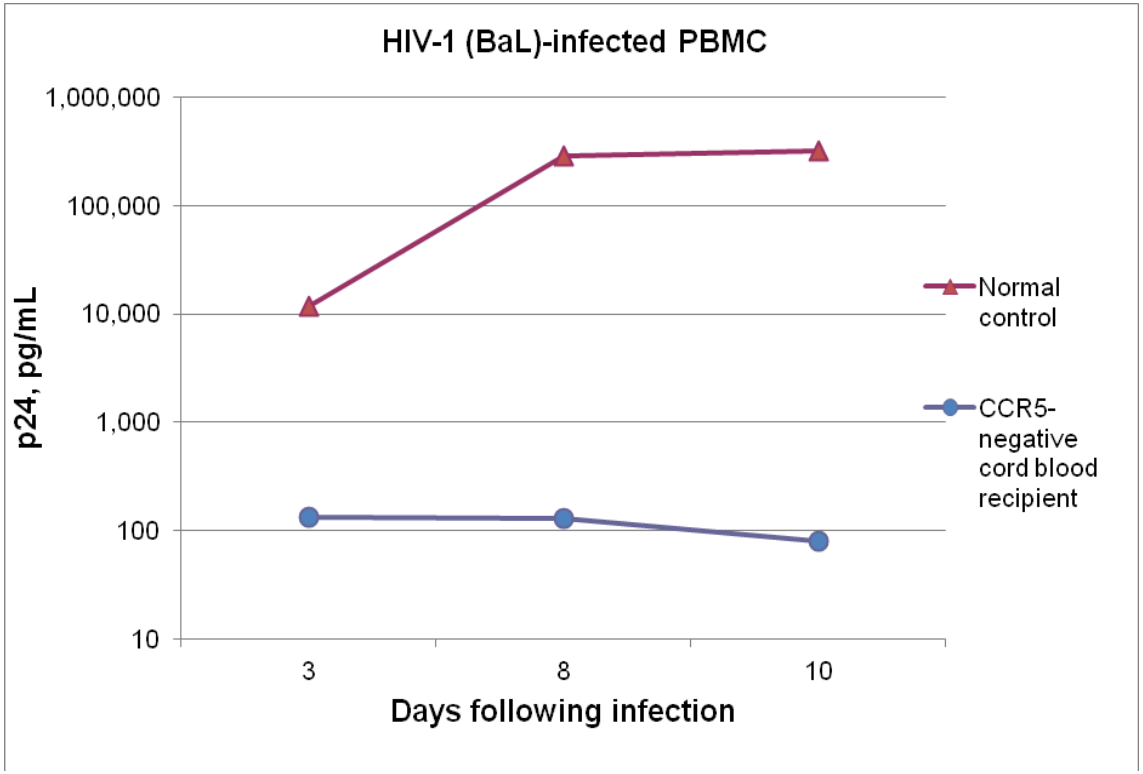


Figure 1A ***In vitro*** **study of HIV-1 PBMCs in posttransplant period from an HIV uninfected patient transplanted with CCR5Δ32/Δ32 cord blood. The recipient's PBMCs showed no significant infection with either lab strains of HIV-1, BAL (CCR tropic) and NL4-3 (CXCR4) compared to a normal adult control. From L. Petz et al. BBMT in press 2012**

Proposed Study for CCR5Δ32/Δ32 CB in HIV/AIDS

CITY OF HOPE NATIONAL MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC STEM CELL TRANSPLANTATION

TITLE: Hematopoietic cell transplantation with unrelated cord blood unit selected for Δ32CCR5 /Δ32CCR5 combined with facilitator haploidentical hematopoietic cells for HIV+ patients nonresponsive or intolerant to highly active antiretroviral therapy (HAART).

CITY OF HOPE PROTOCOL NUMBER/VERSION: **IRB #** **VERSION: 01**

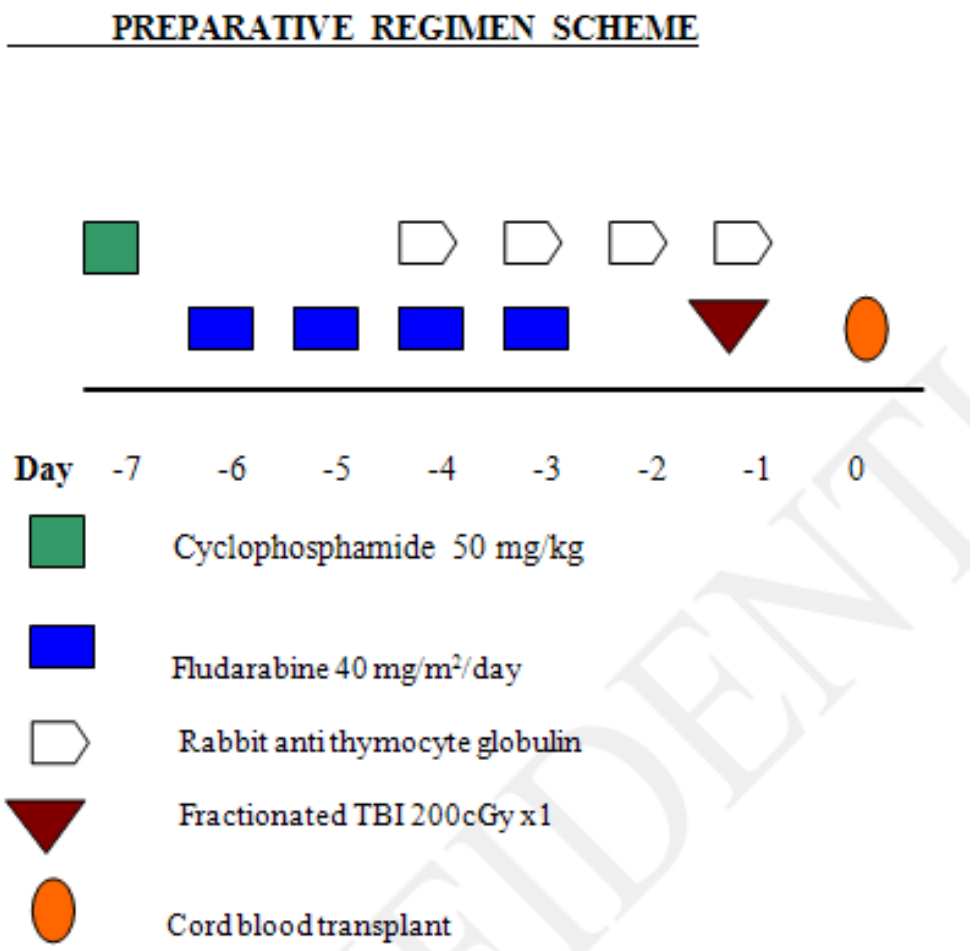
DATE(S)/ OF AMENDMENT(S)/REVISION(S):

MODALITY: Transplant

TYPE: Feasibility

PRINCIPAL INVESTIGATORS: Joseph Rosenthal, MD[1,2]

Conditioning Regimen



Summary of Issues with Autologous Cell Rx for HIV/AIDS

- Selection of donor requires HLA compatibility which currently limits its use
- Risk of the procedure linked to requirement for cytoreductive "space making" pre-infusional therapy
- Risk of the procedure linked to graft vs host disease that can require immunosuppressive therapy lasting years
- Progeny cells derived from a stochastic selection of multipotent progenitor cells
- Selection of such progenitor cells might require additional cyto-toxic therapy, e.g. MGMT/BCNU
- Complexity of the procedures required for allogeneic HSCT currently limits its use to tertiary/quartiary medical centers
- Any commercial business plan for allo HSCT will be novel