Experience in non – Malignant Diseases

- 13 Pediatric patients receive RIC between 2000-2004
- **Dx.**
  - SCA (n=3) , beta Thalassemia (n=1), X linked hyper IgM syndrome (n=2), Inborn Errors on Metabolism (n=3), CGD (n=1), X linked Lymphoprolipherative disease (n=1) Immune- deficiencies (n=2)
- **Source of Stem Cells**
  - MS/PBSC (n=4), MUD/PBSC (n=6), UCB (n=2), MM/PBSC (n=1)

Jacobsohn et al Lancet 2004

Experience with non-Malignant Diseases Results

- Median age 5.2 years
- The PBSC receive median Nucleated cell dose $6.0x10^8$/Kg (5.5-8.7). Cd34+ cell dose 0.97 $x10^6$/Kg (0.7-5.4)
- 11 were eligible for chimerism, 8 of them achieved >95% donor by VNTRs. 2 other patients have achieved a partial chimerism (29 and 44% respectively)
- Median time to full donor chimerism 58 days (24-172)

Jacobsohn et al Lancet 2004

Experience with non-Malignant Diseases Results

- AGVHD 1 patient developed Grade II (8%)
- CGVHD 3 patients developed extensive(37%)
- Patients with SCA 2 had autologous recovery and 1 developed cGVHD
- The patient with thalassemia had a late rejection.
- One patient died from Measles encephalitis

Jacobsohn et al Lancet 2004

Experience with RIC
update

- 55 pts.
- Mean age 8.1 years (.2-22.6)
- 38 malignancies (ALL n=16, AML/MDS n= 3/4, CML n=5, NHLn=4 and 6 solid tumors).
- 17 non malignant (Immune def. n=6, metabolic diseases n=5, Hemoglobinophaties n=4, Aplastic anemia n=2)
- 12 patients had prior HSCT (7 auto and 5 allo)
- Caucasian n=30, Hispanic n=15, African American n=7 and Asian n=3
- Alternative n=33, MR n=22

Duerst et al ASH 2004

RIC cell support.

- Median cell dose infused 5.8 x 10^8 MNC/Kg, CD34+ 2 x 10^6 cells /Kg
- No growth factors were used
- Chimerism was evaluated by VNTRs weekly.

RIC
Results Graft Failure

- 3/55 died too early and are not evaluable for engraftment (toxicity n=2, relapse n=1)
- 8/52 fail to engraft
- 4/16 with non-malignant (all were Hemoglobinopathies)
- 3/30 with malignancies NBL (n=1), Leukemia (n=2)

Engraftment with RIC Results

- Patients who failed to engraft
  - Were younger 6.3 vs. 8.8 years
  - Were lighter 18 vs. 27 Kg
  - Cell doses were smaller 3.9 vs. 5.9 $x10^8$ MNC/Kg ($p=0.05$)
- Patients who engrafted
  - Engraftment was faster on those patients who developed significant GVHD (Grade I-IV) or extensive cGVHD.

Reduced-Intensity Conditioning with Hematopoietic Stem Cell Transplant Offers an Optimal Approach in the Treatment of Severe Primary Immune Deficiency

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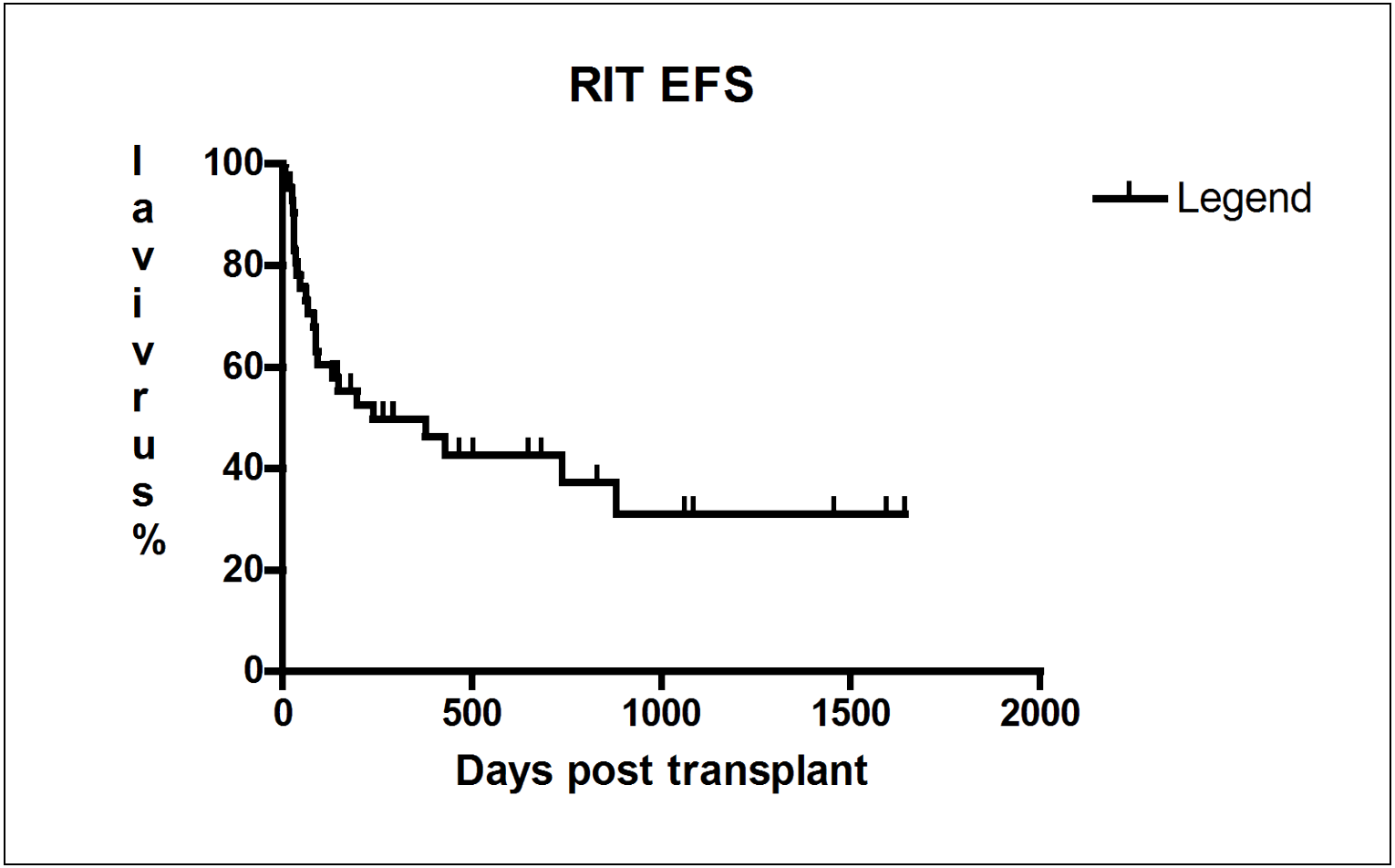
9/2012

Pediatric Experience



Objectives

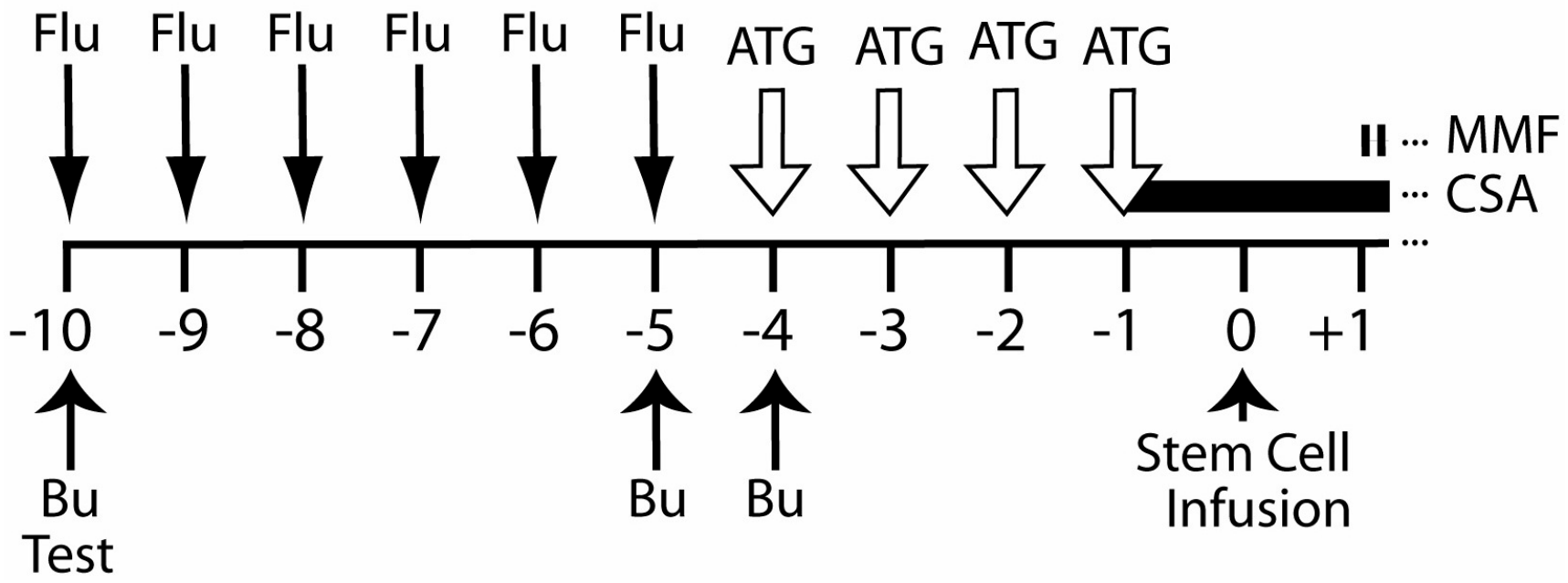
- To test a reduced intensity conditioning regimen for patients with severe congenital immune-deficiencies
- To build in our RIC experience with a using a test dose and targeted busulfan AUC to decrease toxicity and maximize efficacy
- To reduce acute and chronic toxicities
- To assess immune reconstitution post RIC
- To evaluate Overall survival and disease free survival.

A Novel Approach

- Use of a "Reduced Intensity Conditioning" regimen before allogeneic hematopoietic stem cell transplantation
- A treatment that selectively targets immune cells instead of all blood cells
- One that is associated with less acute toxicity and fewer long term effects
- One that is well-tolerated and can be given in the out-patient clinic

Reduced-Intensity Conditioning Regimen

Flu: Fludarabine IV 30 mg/m2/day x 6 days
Bu: Individualized single daily IV dose x 2 days
ATG: Rabbit Thymoglobulin 2 mg/kg/day x 4 days



Busulfan Level & Clinical Outcome

- In a first cohort (n=17), busulfan AUC targeted at 4000 µicroM-min/day.
- 4 patients had primary graft failure and 3 died from complications.
- Inadequate level of busulfan exposure might have contributed to graft failure.
- In a subsequent cohort (n=12), busulfan AUC targeted at 5000 µicroM-min/day.
- No patients had primary graft failure or death.

Risk of Graft Failure

- 3 patients transplanted prior to 2007 did not engraft and died of complications
- Risk appeared to be related to the use of umbilical cord blood and having low AUC busulfan drug levels
- Not seen in subsequent patients after modification of the therapeutic protocol in 2007 (Increased target BU AUC to 5000 and add Thio-Tepa 5mg/kg)

Our Patients

- Between 2000 and 2010, 29 patients with severe immuno-deficiencies were transplanted using the RIC regimen
- Age at transplant: 0-8 months (40%), 6-12 months (35%), >12 months (25%)
- Sex: male (75%), female (25%)
- Ethnicity: Caucasian (35%), Hispanic (35%), Asian-Pacific Islanders (30%)

Patient Characteristics

Age	Median	7.4 months
	Range	1 month to 17 years
Sex	Male	21
	Female	8
Disease	SCID	15
	Wiskott-Aldrich Syndrome	4
	Hyper-IgM Syndrome	2
	X-Linked LPD	2
	IPEX Syndrome	2
	NEMO Syndrome	2
	Omenn Syndrome	1
	Chediak-Higashi Syndrome	1
Donor	Related	10
	Unrelated	19
Stem Cells	Peripheral Blood Stem Cells	19
	Umbilical Cord Blood	10

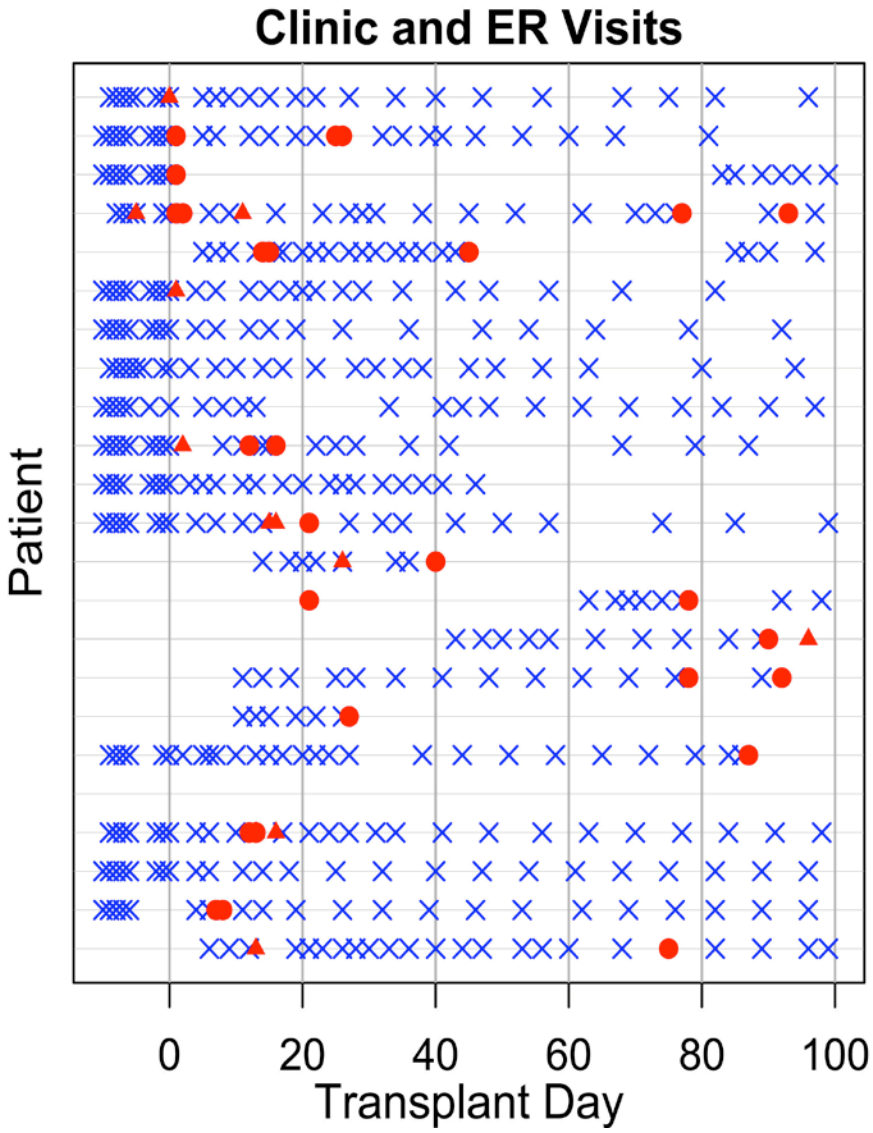
Decreased acute toxicities

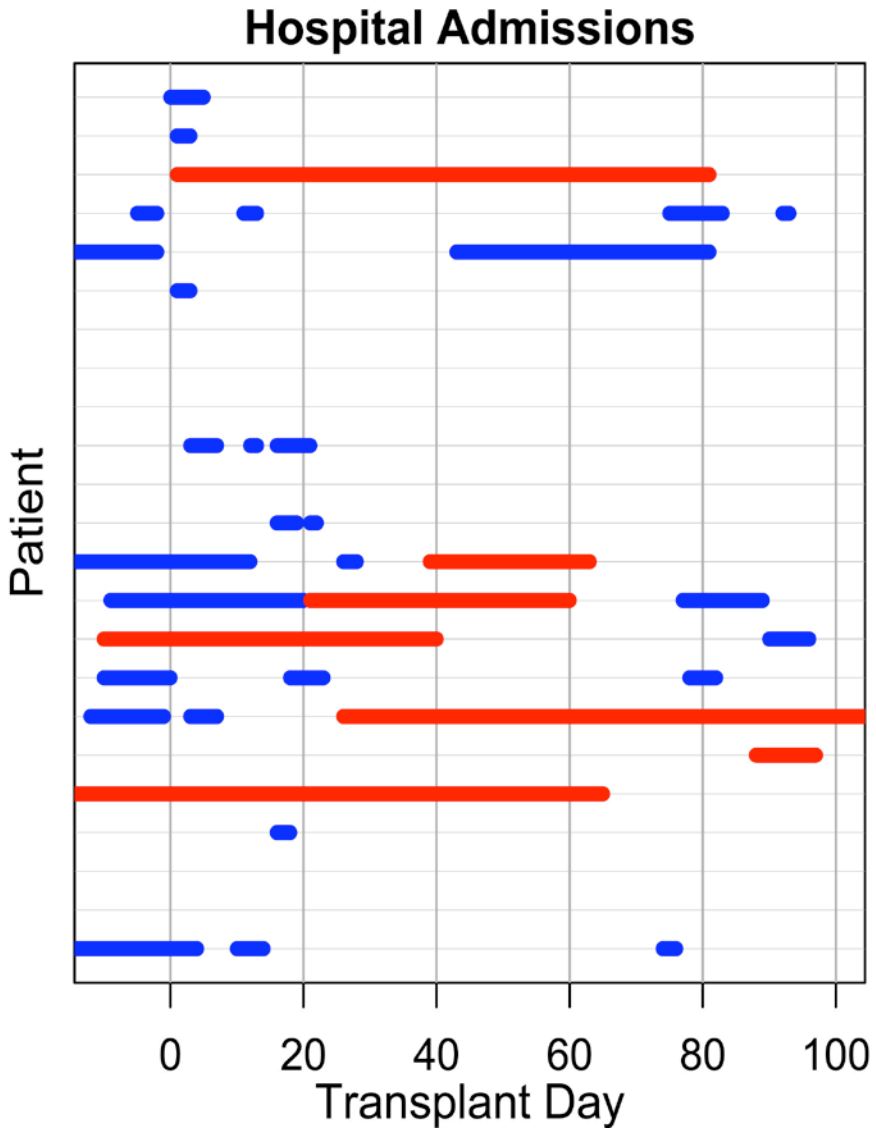
- Mild nausea and vomiting
- Minimal pain and discomfort
- No serious and life-threatening infections
- No mucositis
- No serious organ damage
- No grade II/IV GVHD
- No sinusoidal obstructive syndrome of the liver (VOD)
- No seizures
- Mild suppression of blood counts
- One patient had post-transplant immune-associated blood cell destruction, improving after appropriate therapy
- Most patients went through the procedure as out-patients

Outpatient Care & Management

- Dedicated apartment complex next to hospital.
- Conditioning, transplant and follow-up care primarily in outpatient clinic.
- Urgent visits in clinic or emergency room for acute medical symptoms.
- Inpatient care for those with specific medical or psychosocial needs.
- No anti-bacterial prophylaxis or colony stimulating factors.

Clinic Visits & Hospital Admissions

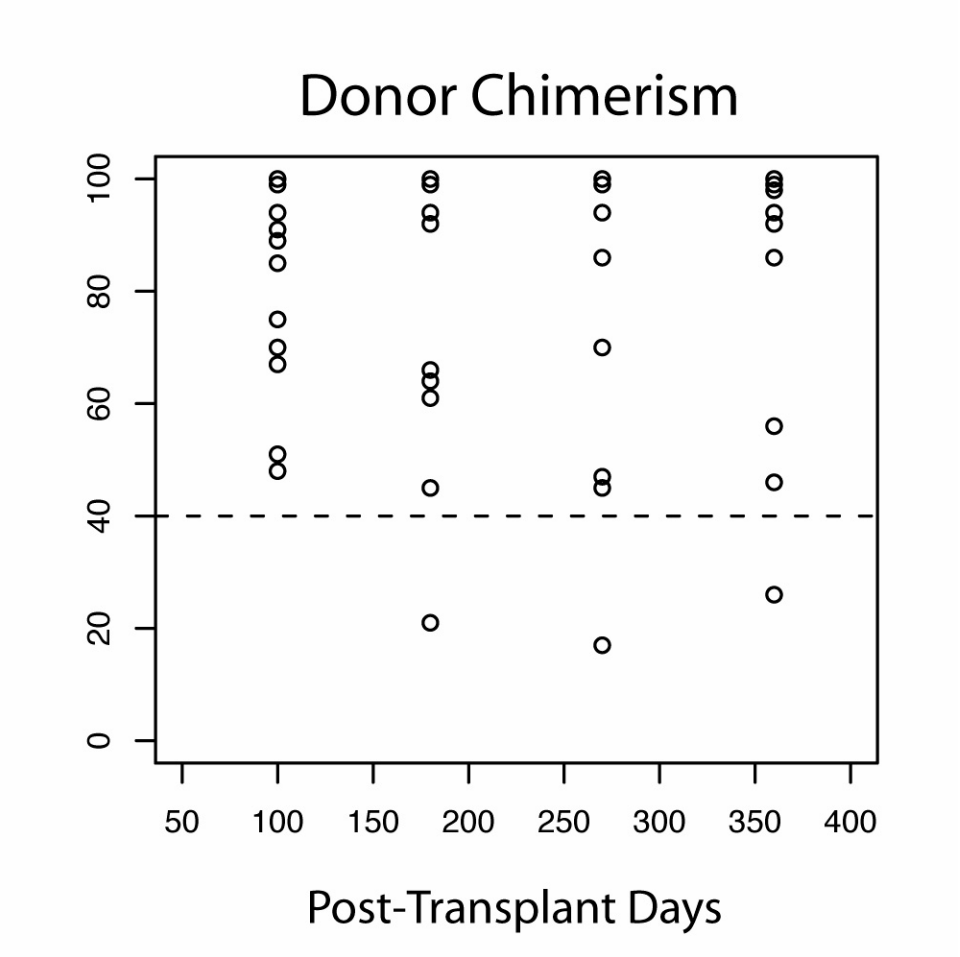




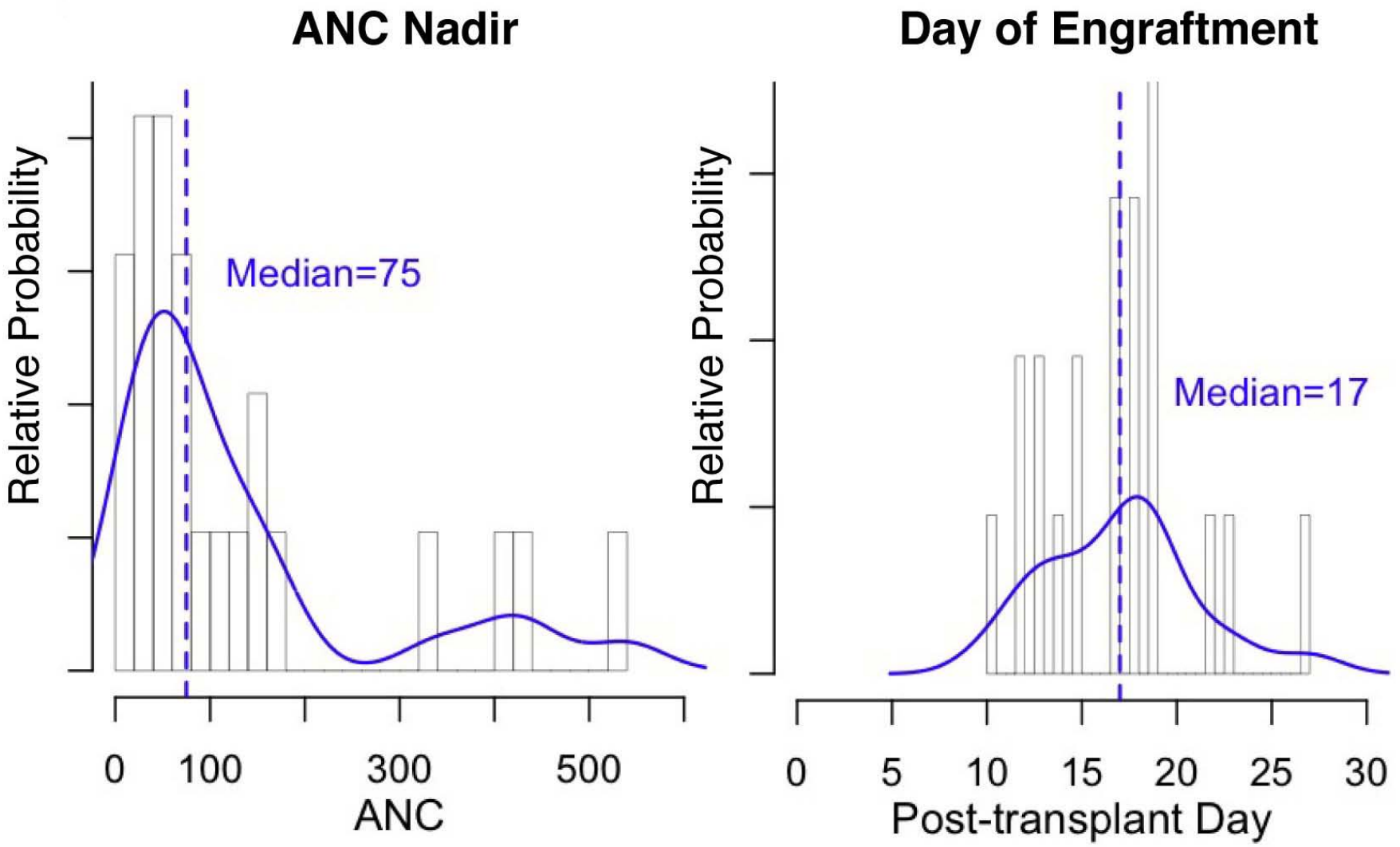
Acute Care Visits & Admissions

	Acute Care Visits	Admissions
Fever	23	14
Bacteremia	2	8
Dehydration	6	4
Bronchiolitis	1	1
Hemolysis	1	1
GI Bleeding	1	1
Pseudotumor cerebri	2	1
Bandemia	1	1
CMV	-	1
Conditioning	-	8
	37	40

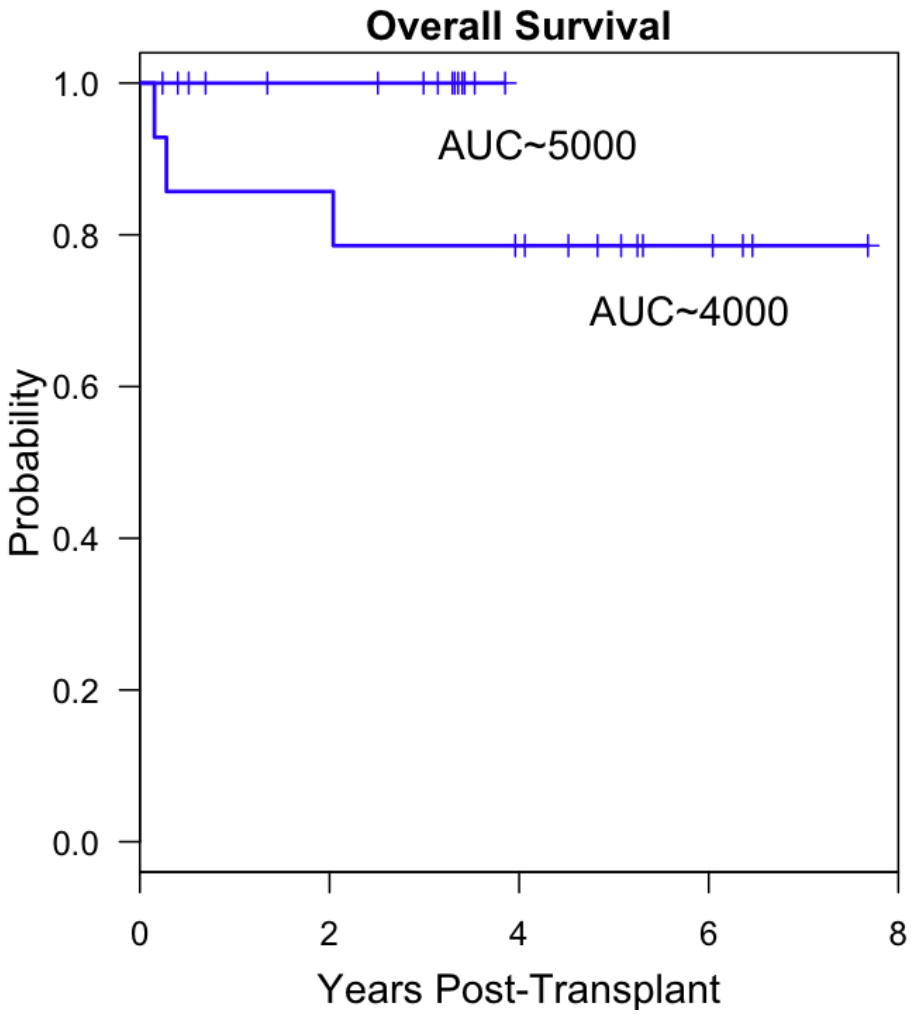
Good Donor Cell Engraftment

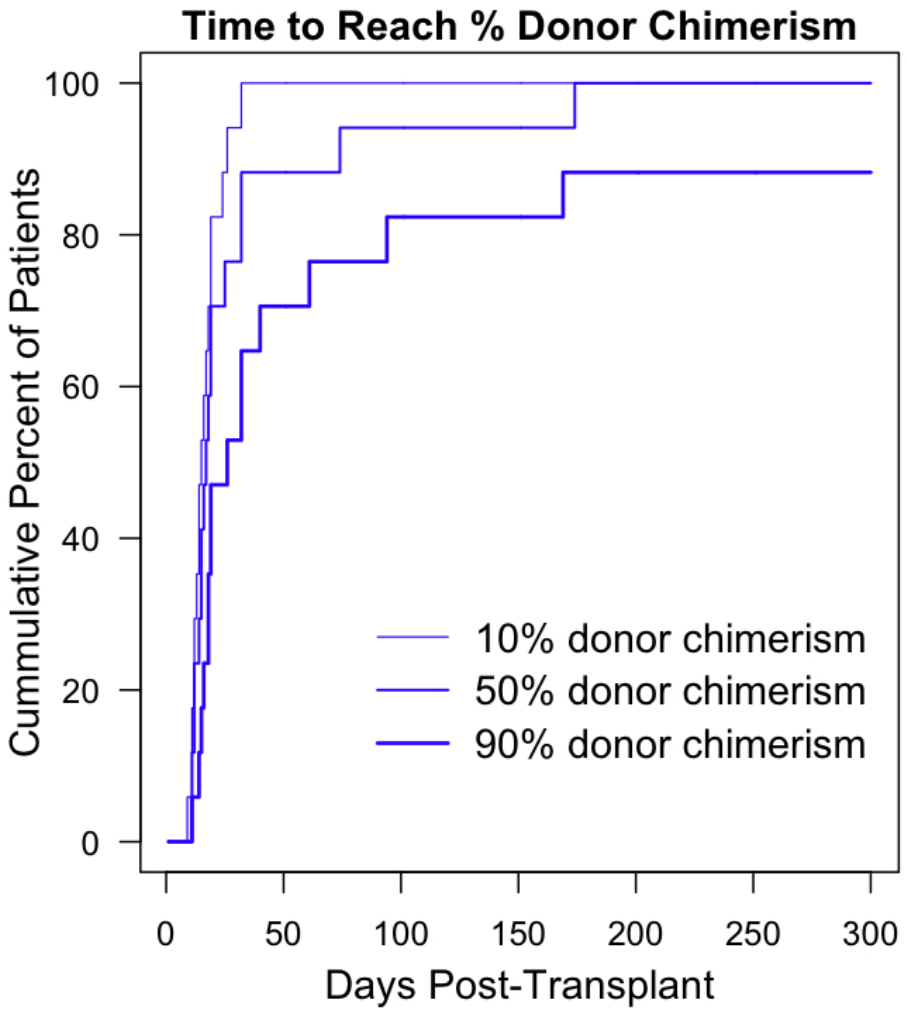


Neutropenia & Engraftment

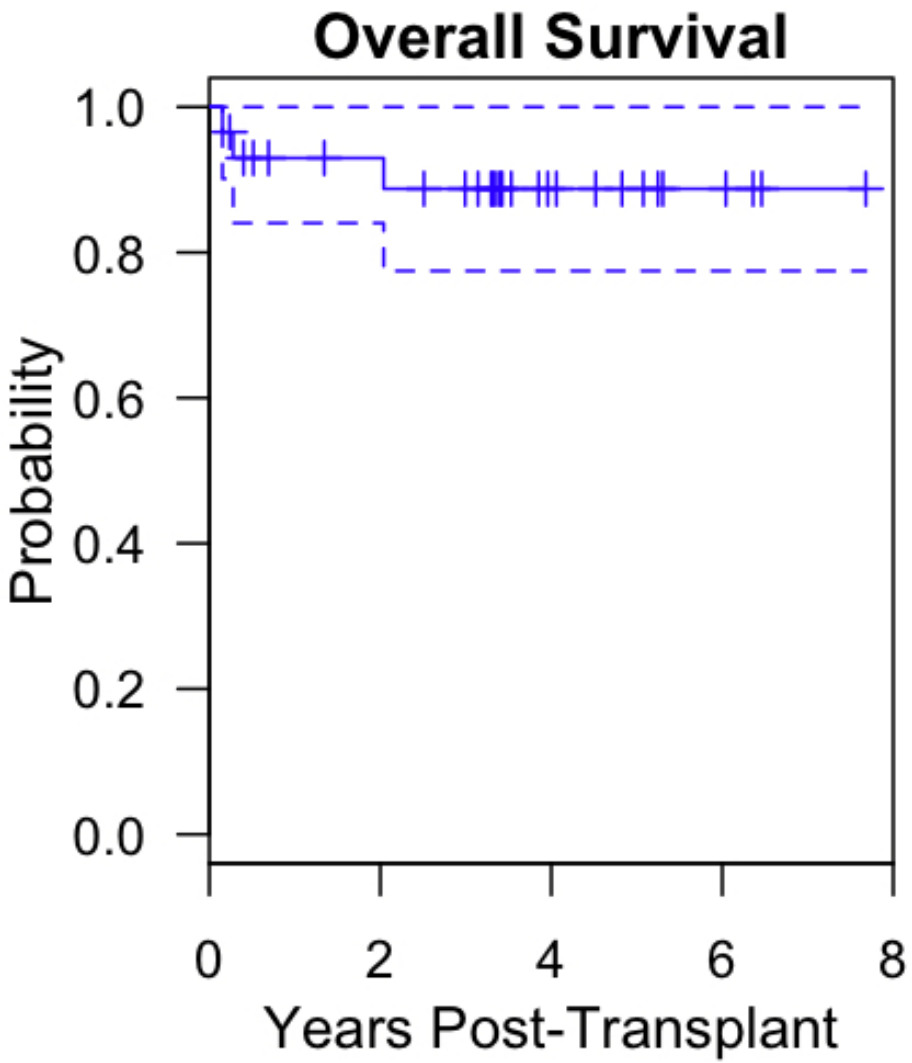


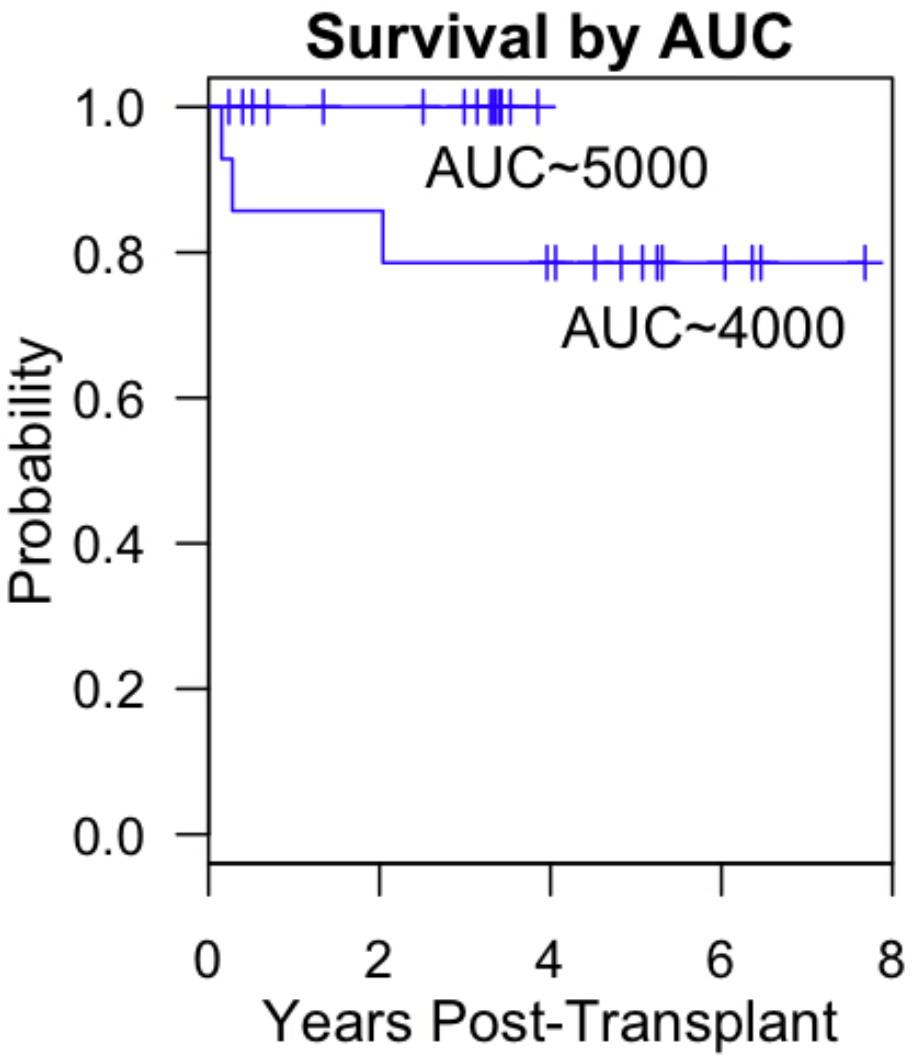
Overall Clinical Outcome





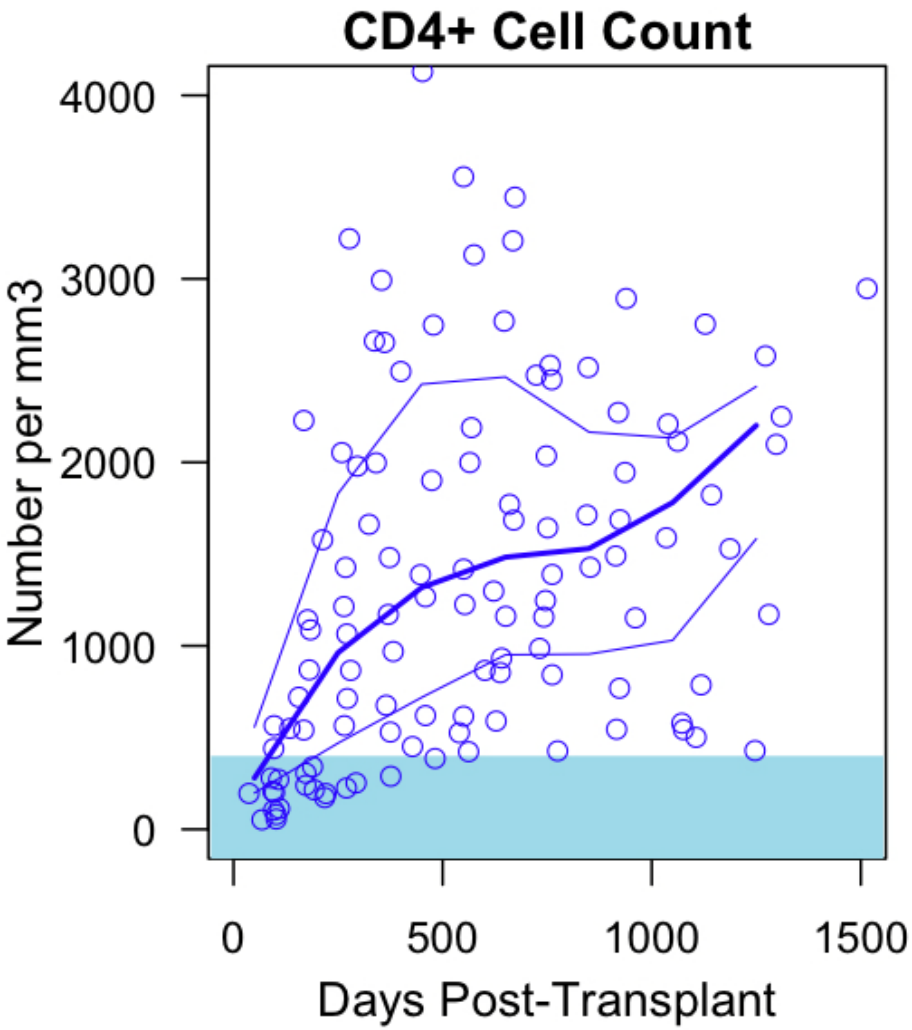
Overall Clinical Outcome

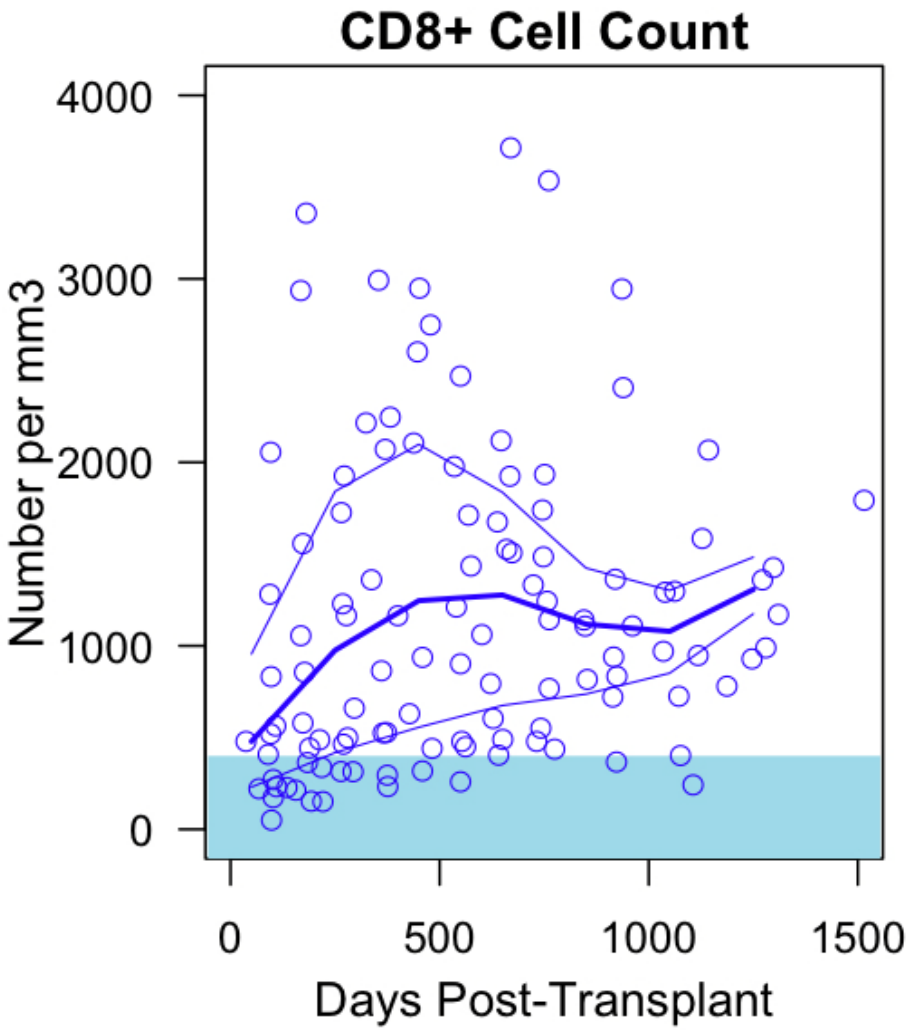




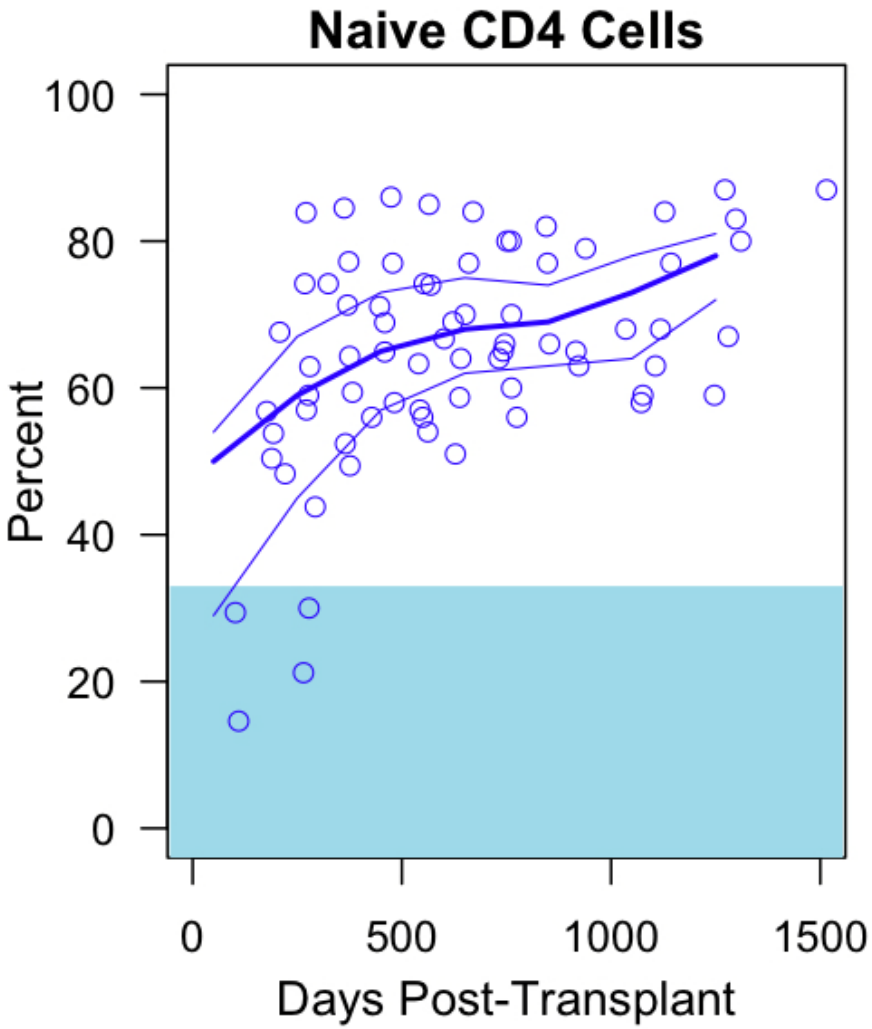
Immune Reconstitution

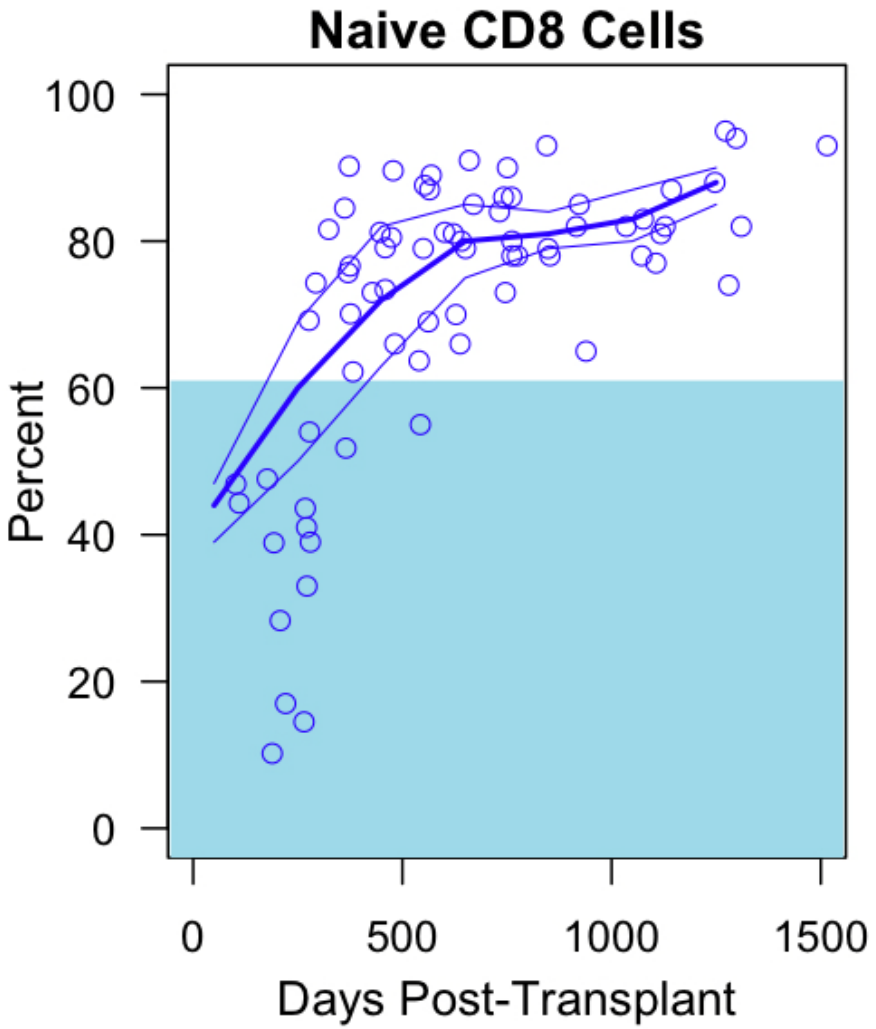
Recovery of CD4 & CD8 Cells



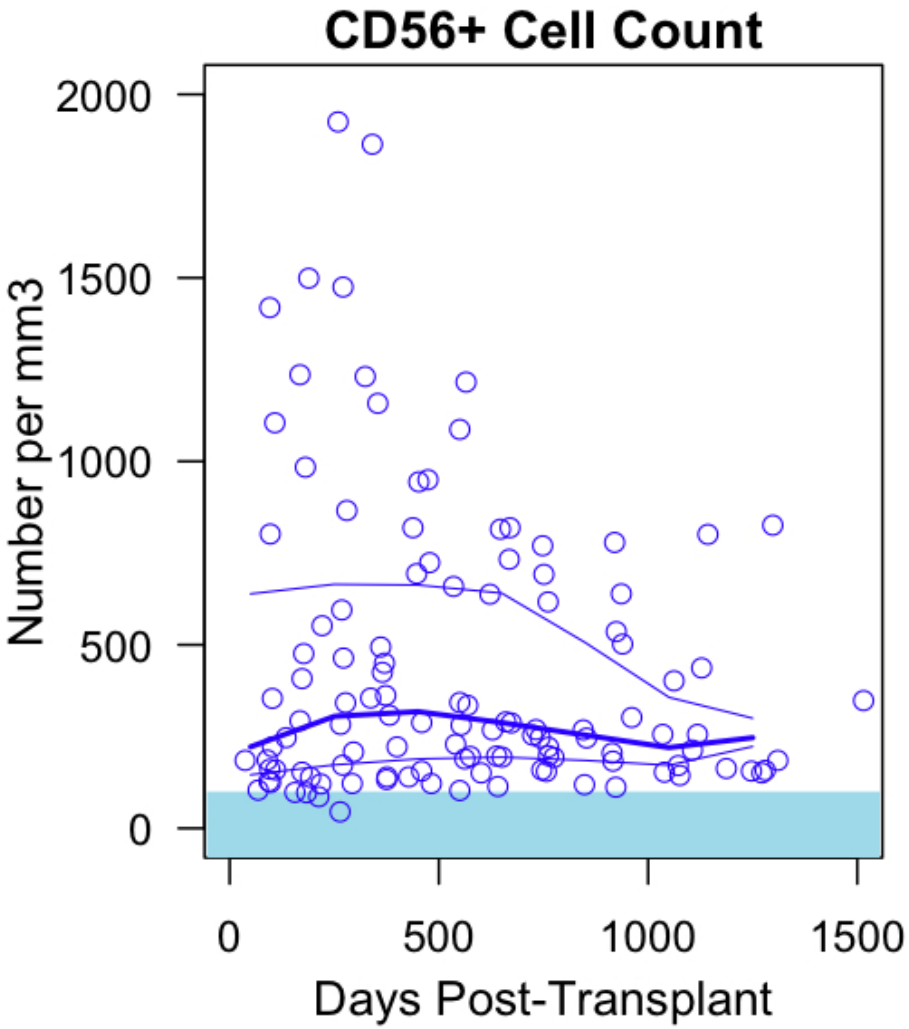


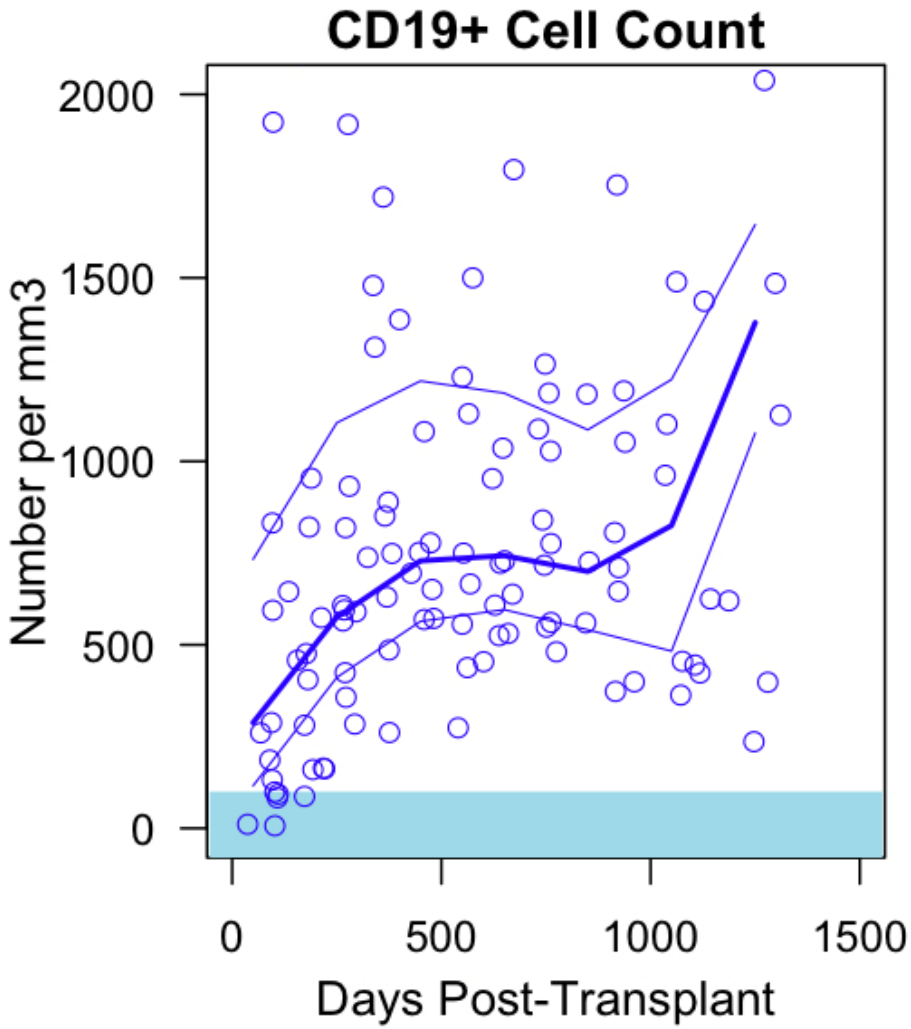
Recovery of Naive T Cells



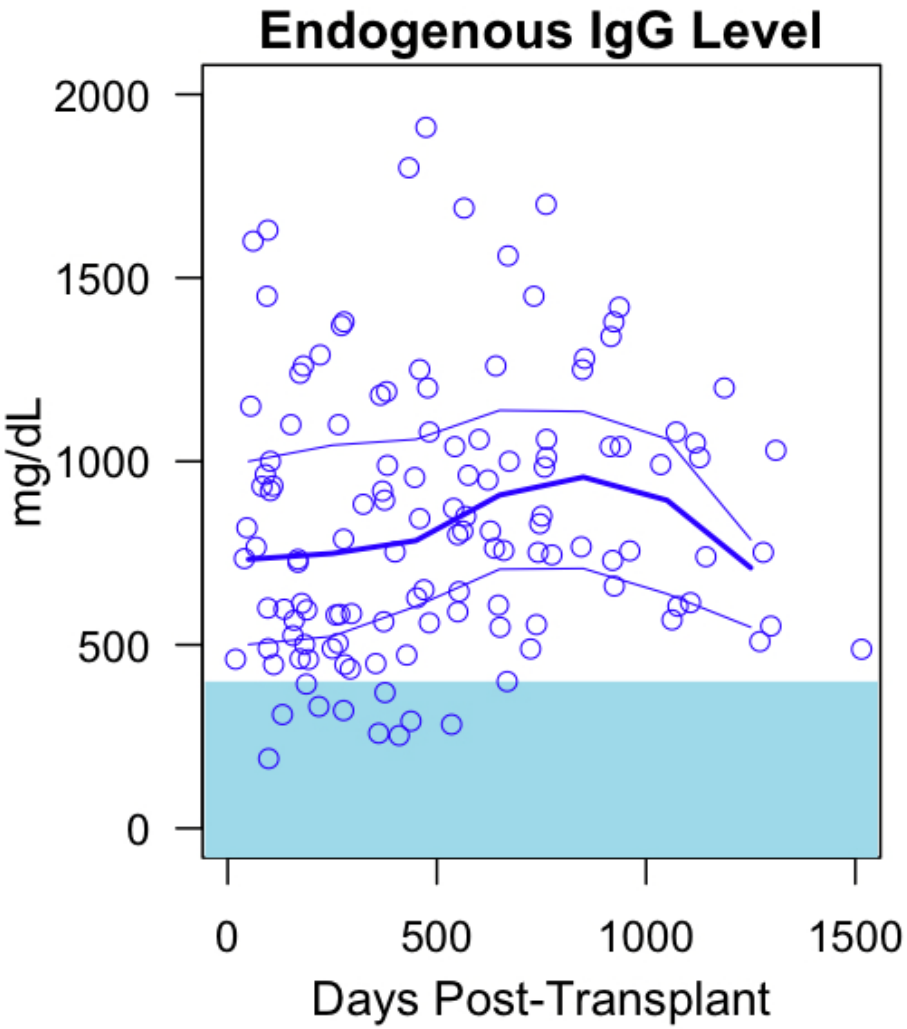


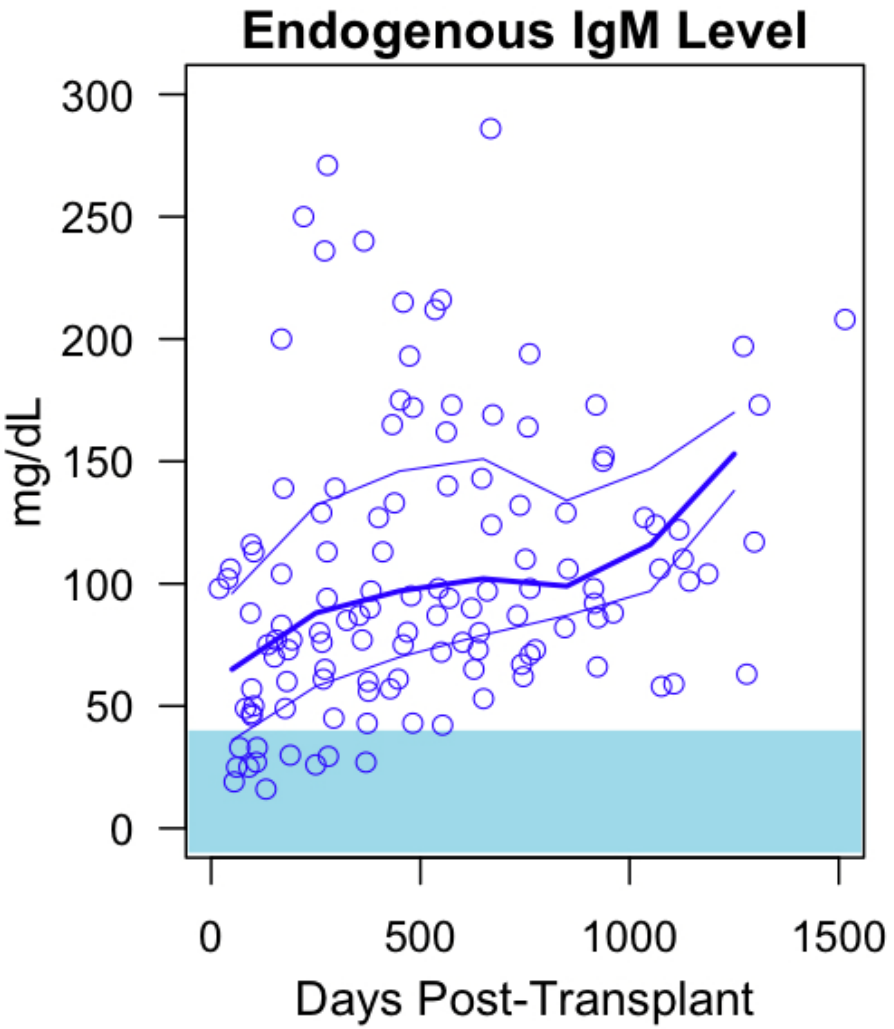
Recovery of CD56 & CD19 Cells



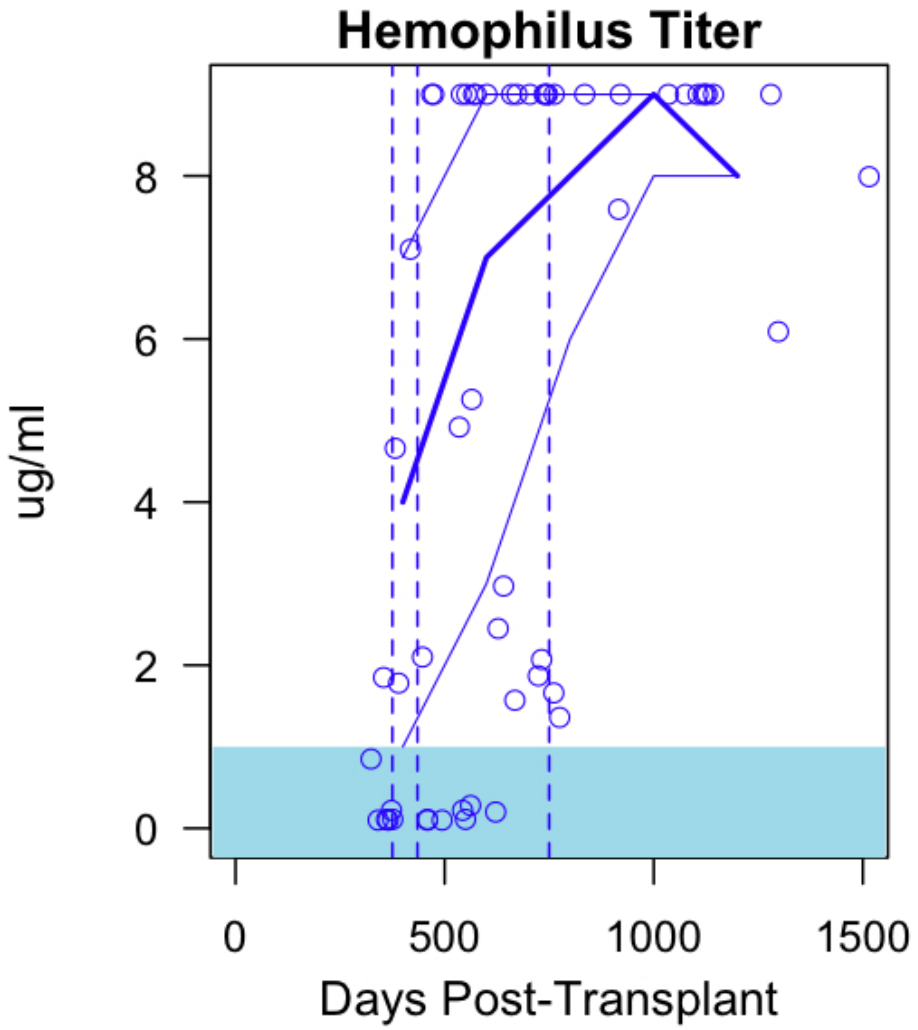


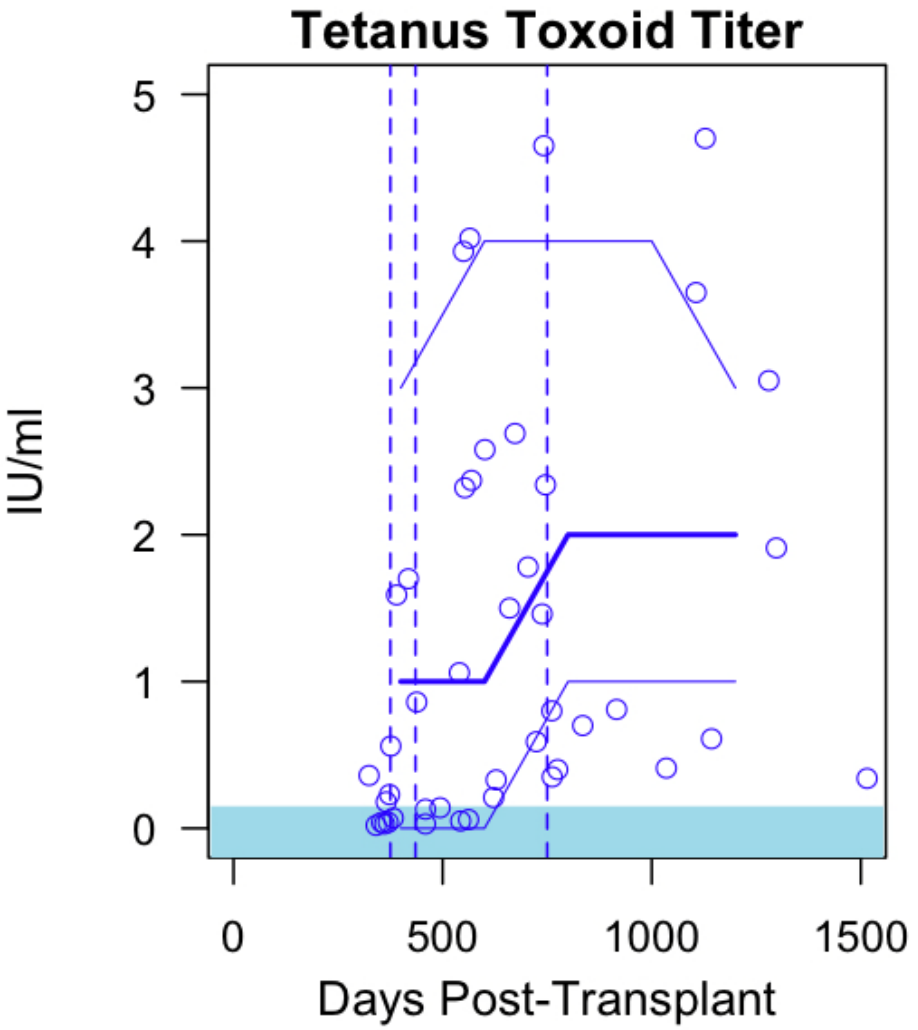
Recovery of Immunoglobulin Levels





Response to Immunization





Conclusions

- Stem cell transplant utilizing RIC is highly effective.
- Ensuring adequate busulfan exposure is essential to minimizing the risk of graft failure.
- The approach was well tolerated and associated with minimal acute and long term complications.
- Robust immune reconstitution post-transplant resulted in correction of both T and B cell defects.
- A multi-center trial is warranted to further validate this approach.

Future directions

- Improve clinical outcomes through refinement of therapy
- Provide longitudinal follow-up care of transplanted patients
- Expand service to benefit more patients
- Initiate outreach and education activities
- Promote early diagnosis and treatment for patients with severe immunodeficiency

Acknowledgment

- Stem Cell Transplant Team
- Patients and Families

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