Long-term Results of T cell Depleted HLA haploidentical Marrow Allografts for SCID Administered With or Without Myeloablation

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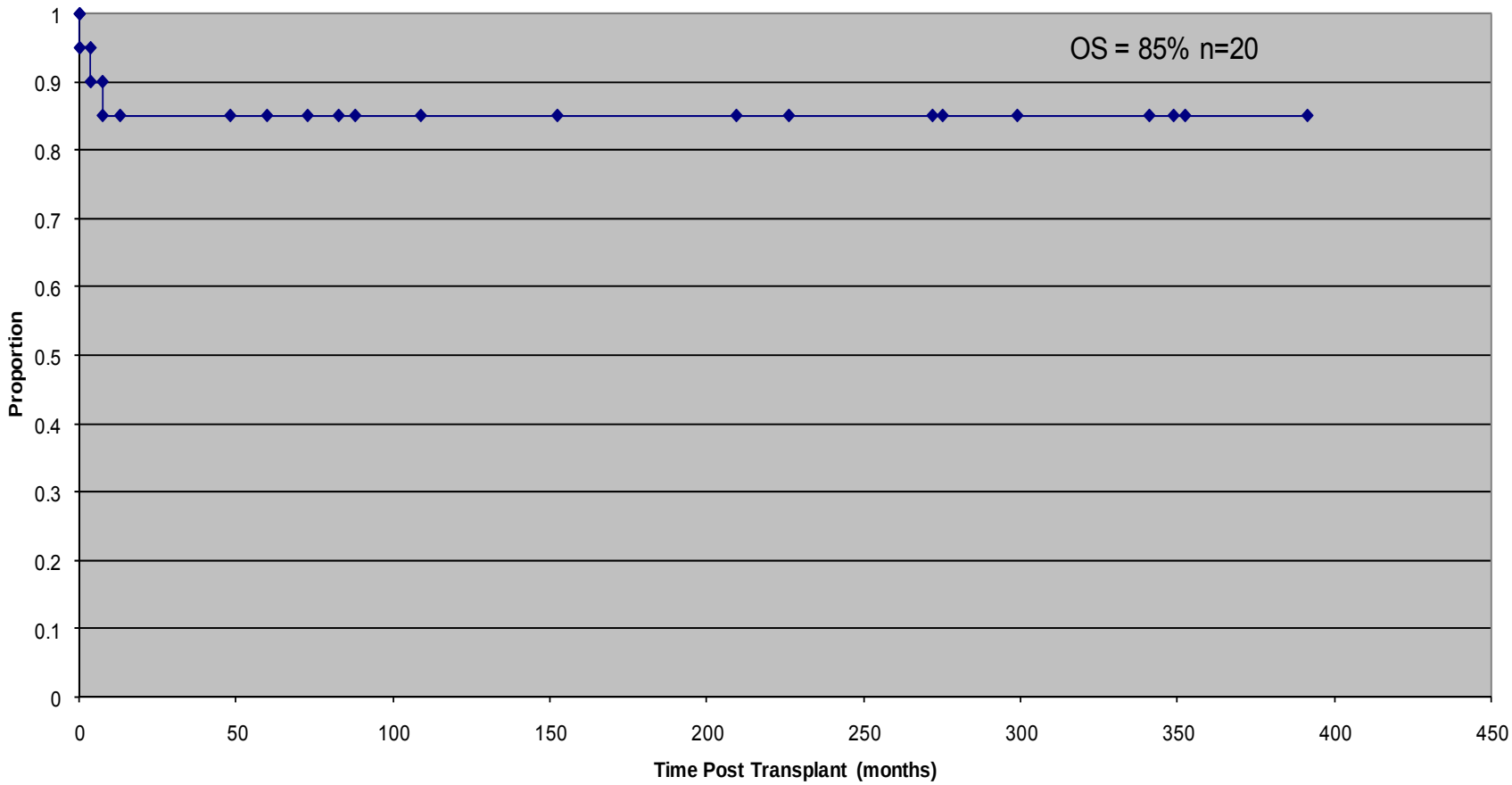
Overall Survival of SCID Patients with Matched Related Donors and Unmodified Transplants



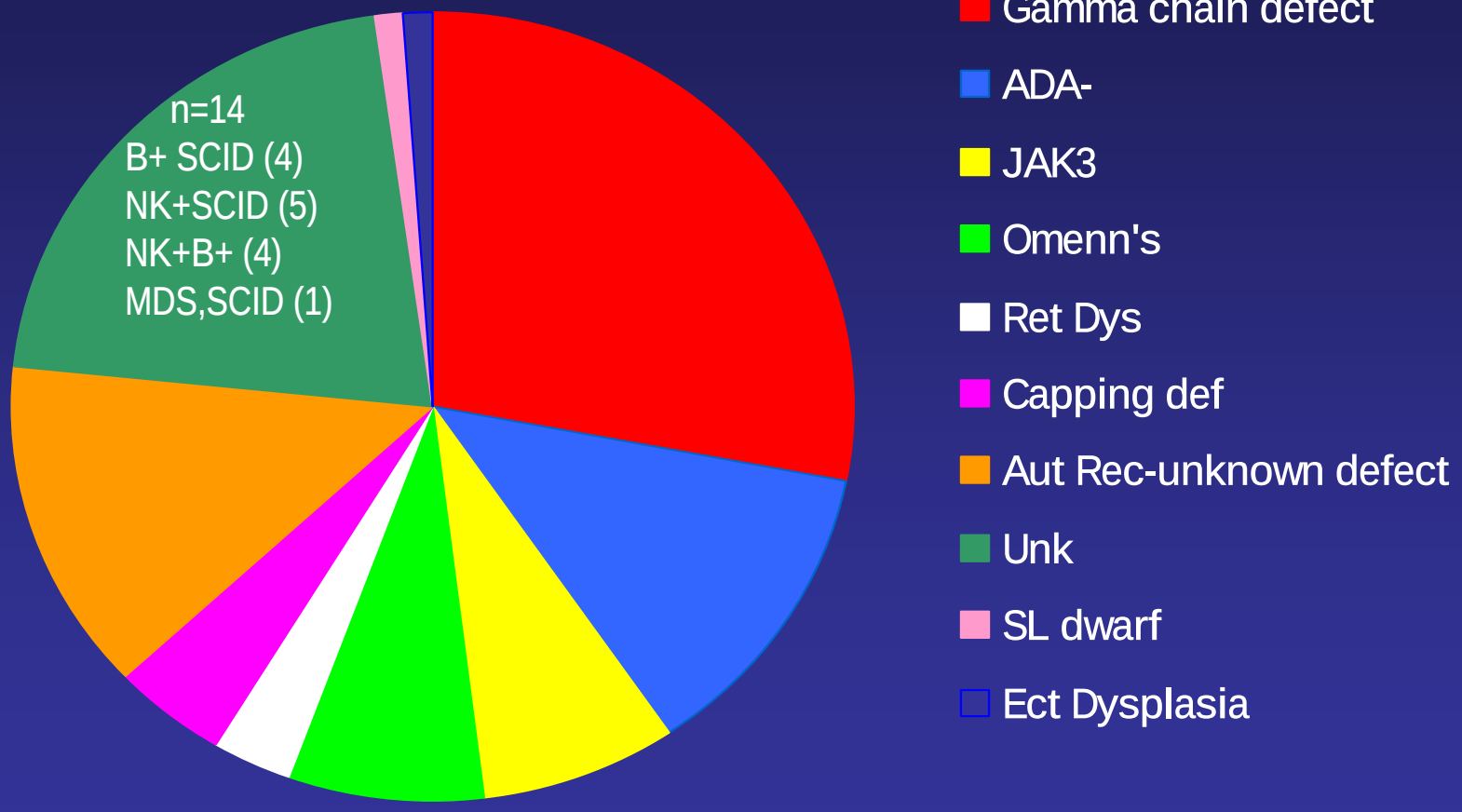
T-CELL DEPLETION METHODS

METHOD OF T-CELL DEPLETION	CELLS DEPLETED	LOG T-CELL DEPLETION	POST TRANSPLANT GVH PROPHYLAXIS
MoAb CD2, CD3, CD5, or CD6	T	1-2.5	YES
MoAb CD4 or CD8	T	1-2	YES
T10B9 (TCS) + Cplt	T	1.0-1.5	YES
Anti-CD5 Ricin A-chain Immunotoxin	T	1.5-2.0	YES
Immunomagnetic seperation (CD3-CD8)	T	2	YES
Rat MoAb Campath-1 (CD52) + Human Cplt	T,B	1.7-2.5	YES
Multiple E-rosetting depletion	T, NK, B	1.5-2.0	YES
Counterflow Elutriation	T, +/-	Fixed: 1.5-3.0	YES
Soybean Aglutinin + E-rosetting	T, NK, B	2.5-3.0	NO
Isoplex CD34+ E^{-}	T	3.0-4.0	NO
Milteny	T	3.0-4.0	NO

MSKCC
PATIENTS WITH SCID
TRANSPLANTED WITH PARENTAL SBA¯E¯BMT
N=71

SCID VARIANTS	
X-LINKED γc DEFICIENT	19
ADA DEFICIENT	8
JAK 3 MUTATION	6
RAG MUTATION	6
CAPPING DEFECT	3
SCID WITH SHORT_LIMBED DWARFISM	1
RETICULAR DYSGENESIS	2
SCID WITH ECTODERMAL DYSPLASIA	2
OTHER AUTOSOMAL	9
UNKNOWN INHERITANCE	15

SCID defect of 71 consecutive recipients of an HLA TCD MM unrelated BMT MSKCC 1980-2007



SBA$^-$E$^-$ BMT FOR SCID

HLA Disparities Between Donor and Host

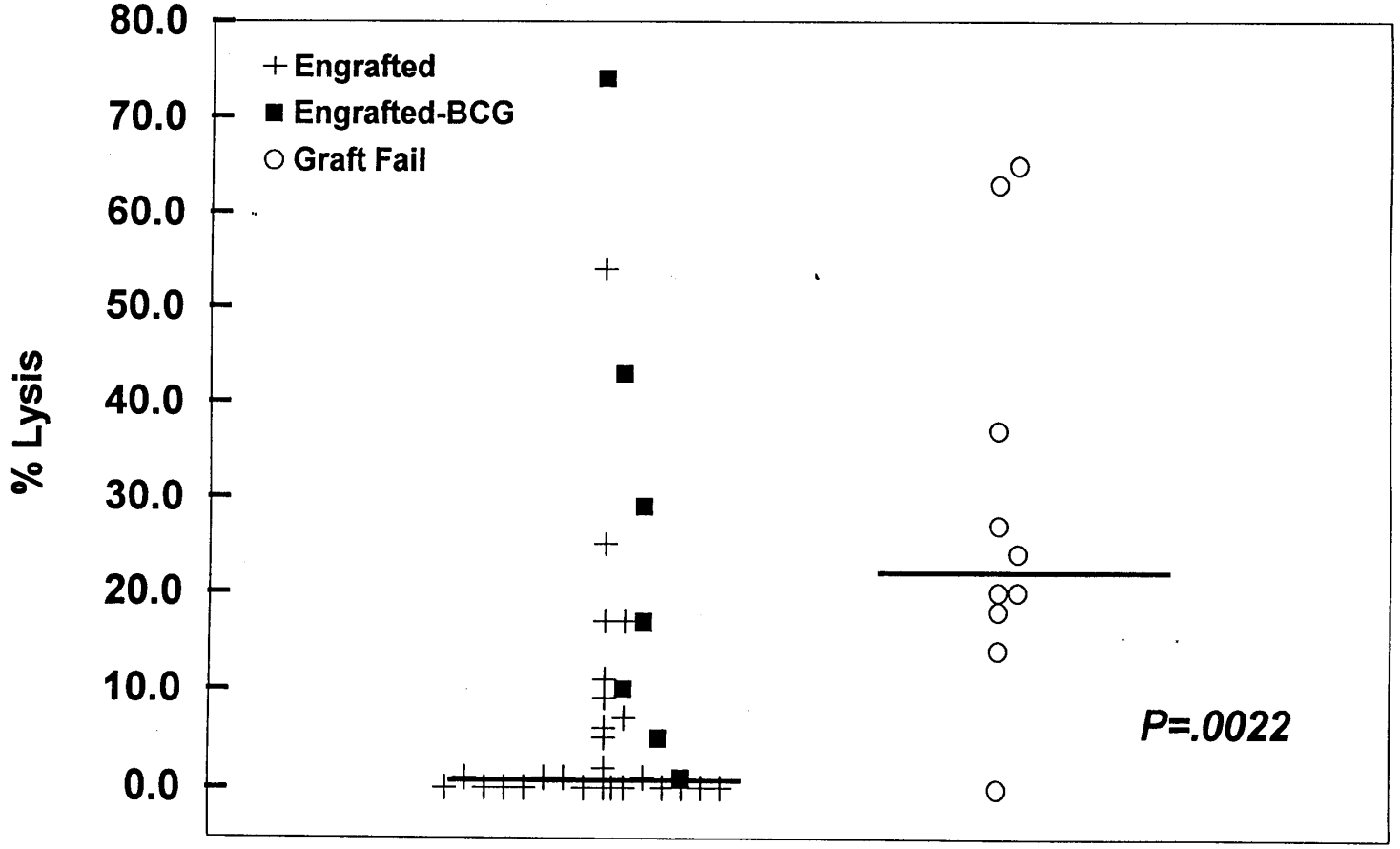
HLA ALLELES	HLA ALLELES UNIQUE TO HOST (GvHD)
3 alleles	49
\ 2 alleles	19
1 allele	3
no alleles	0

MSKCC EXPERIENCE
HLA HAPLOTYPE NON-IDENTICAL
SBA¯E¯MARROW TRANSPLNTS FOR SCID

TOTAL PATIENTS	71
EARLY DEATH: ENGRAFTMENT NOT EVALUABLE	8
DURABLE ENGRAFTMENT	62
ENGRAFTMENT NOT ACHIEVED	1
T-CELL RECONSTITUTION	
FULL	59
PARTIAL	4
B-CELL RECONSTITUTION	26
GRAFT VS HOST DISEASE II – IV	5
SURVIVING WITH FULL/PARTIAL RECONSTITUTION	48
DEATHS	23

Engraftment by NK Function Pre

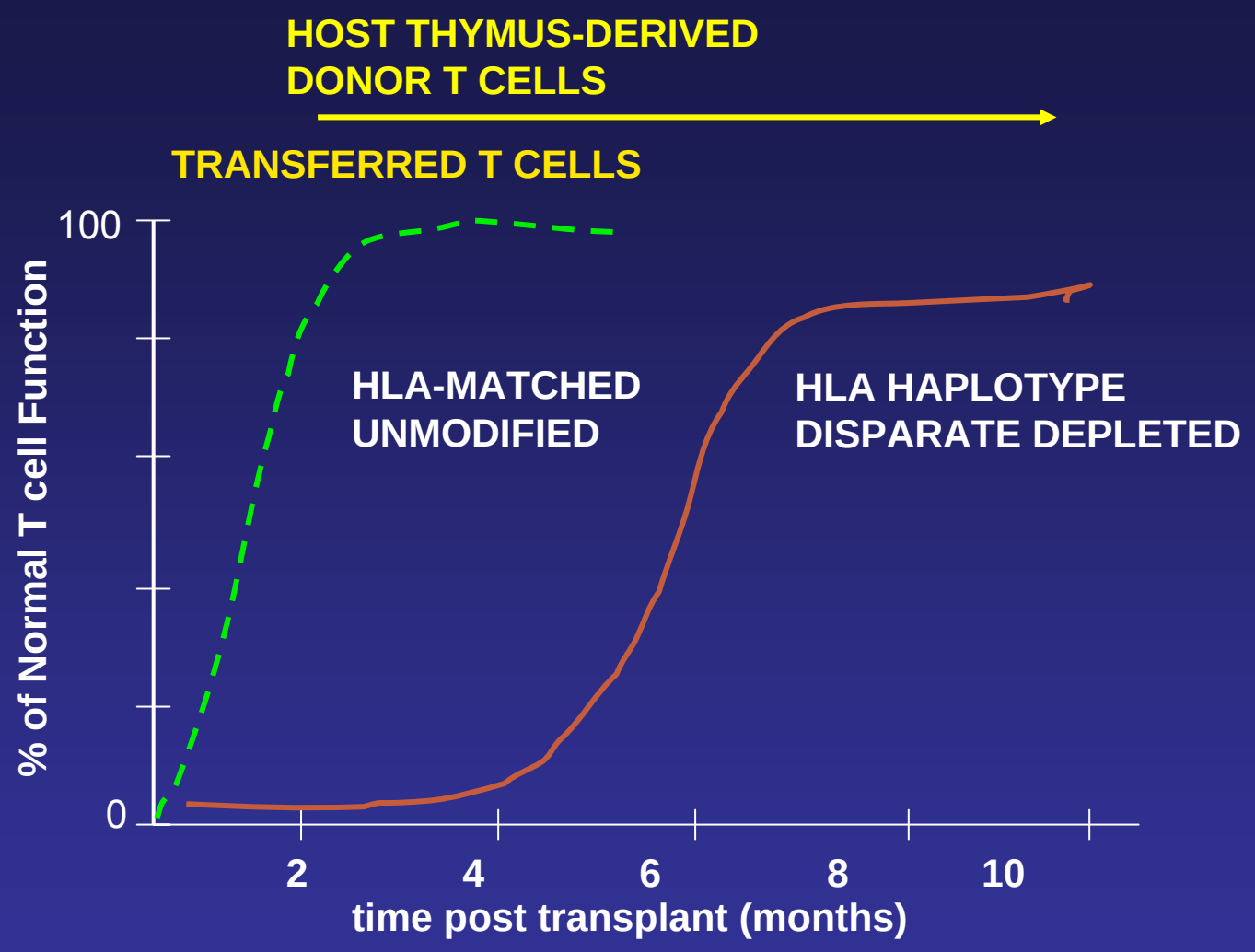
No Cytoreduction, Mismatched T-Depleted BMT for SCID



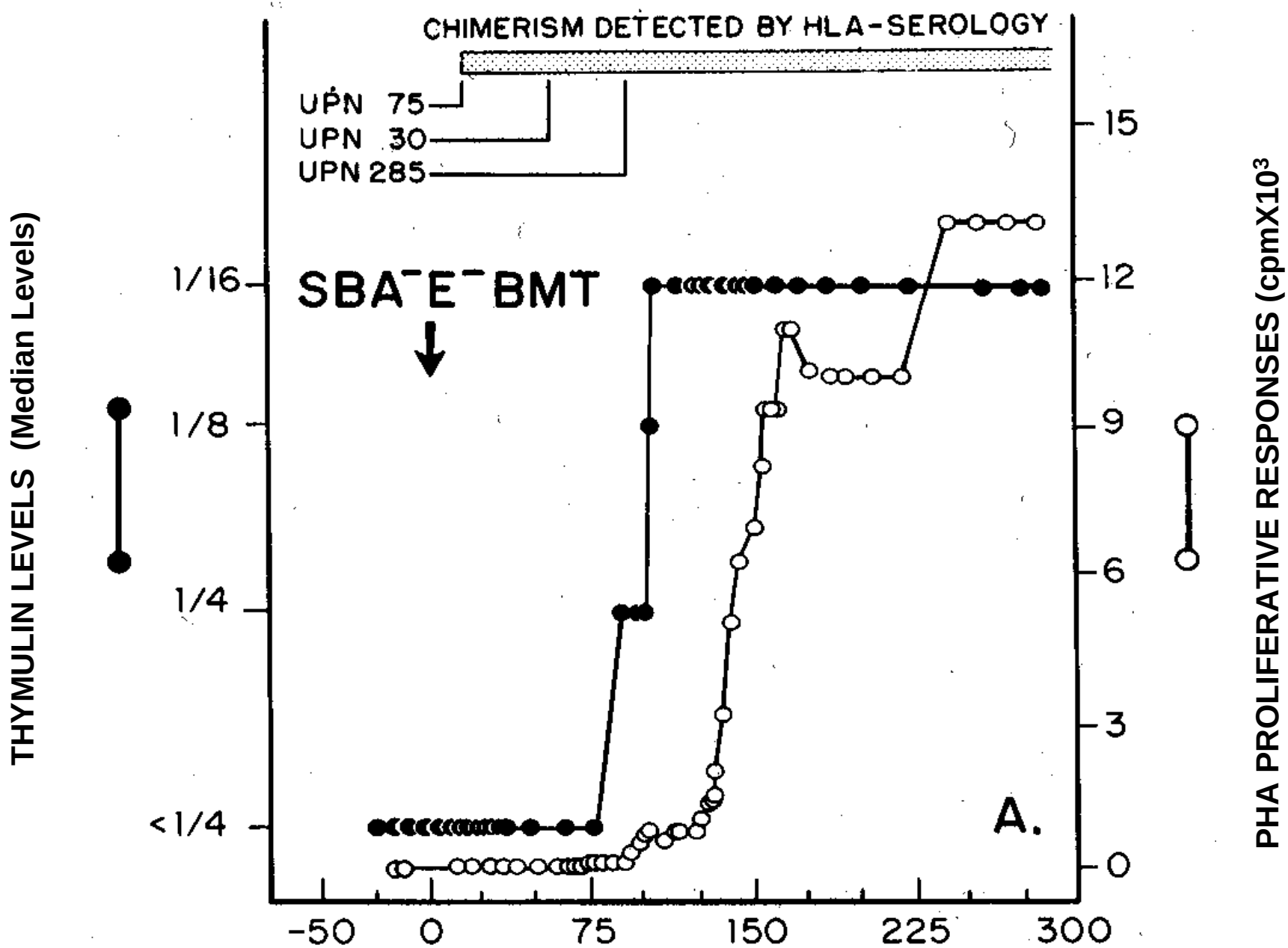
Preoperative Regimen			T Cell Engraftment		T Cell Function				B Cell Engraftment			B Cell Function			
	N	Eval	+	-	Full	Partial	None	NE	+	-	NE	Full	Partial	None	NE
BU/CY	33	31	31	0	24	7	0	3	25	3	3	22	2	3	4
THIO/CY	9	9	8	1	8	0	0	0	8	1	0	8	0	1	0
BU Alone	5	5	3	2	2	1	2	0	3	2	0	2	0	2	1
CY/ARA-C	3	2	2	0	2	0	0	0	1	1	0	1	0	1	0
ATG Alone	1	1	0	1	0	0	1	0	0	1	0	0	0	1	0
ATG/THIO	1	1	0	1	0	0	1	0	0	1	0	0	0	1	0
ATG/CY	1	1	0	1	0	0	0	0	0	1	0	0	0	1	0
CY Alone	2	2	1	1	1	0	0	0	1	1	0	1	0	1	0
Totals	*55*	*52*	*45*	*7*	*37*	*8*	*4*	*3*	*38*	*11*	*3*	*34*	*2*	*11*	*5*

T CELL ENGRAFTMENT AND FUNCTION FOLLOWING AN SBA¯E¯BMT WITH OR WITHOUT CYTOREDUCTION

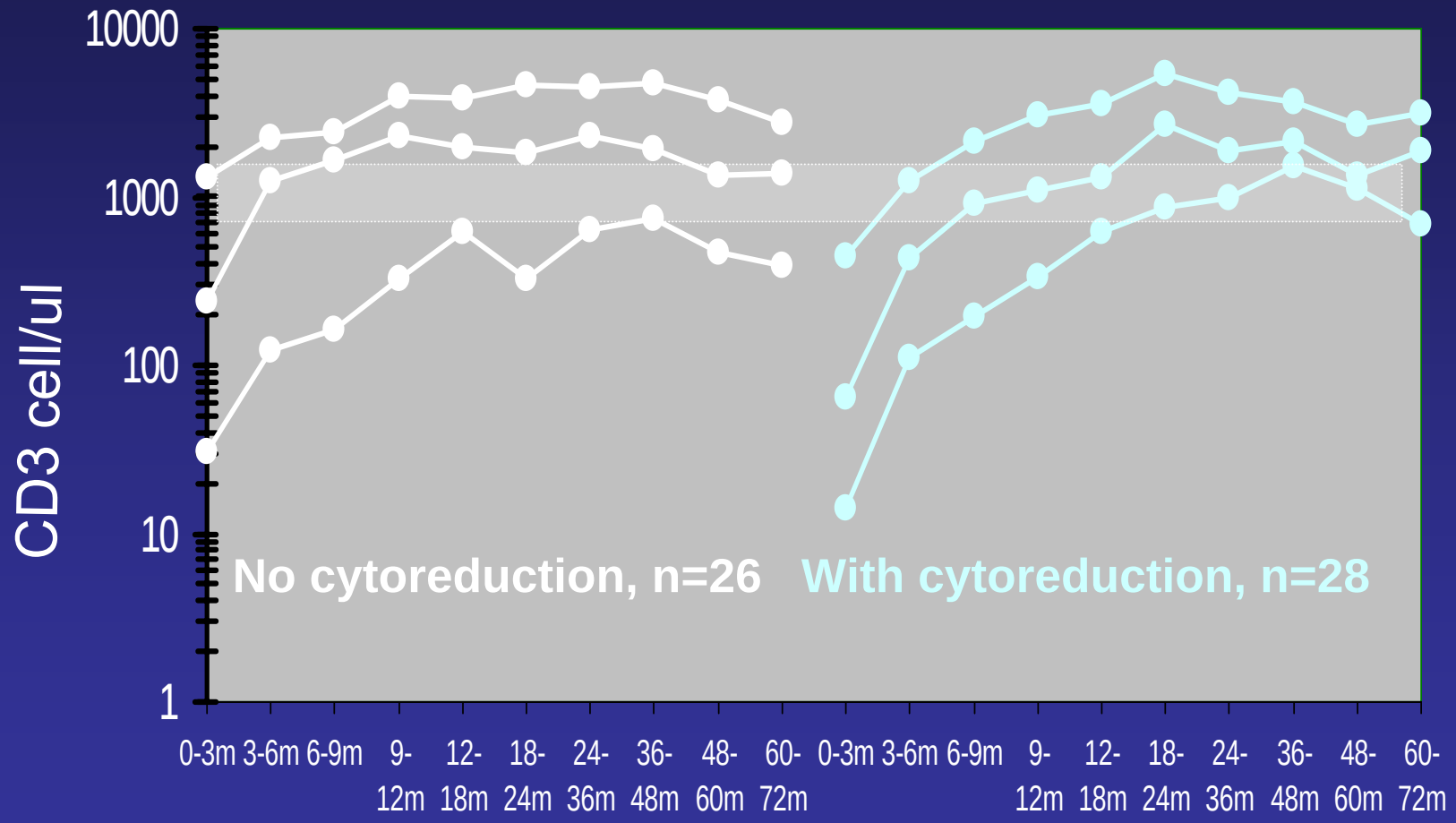
		Engraftment		Function			Not Eval.
		Yes	No	Full	Partial	No	
Myeloablative Cytoreduction	33	29	0	26	3	0	4
Non-Myeloablative Cytoreduction	6	4	1	4	0	0	1
No Cytoreduction	34	27	4	24	3	4	3



RECONSTITUTION FOLLOWING ALLOGENEIC MARROW GRAFTS IN SCID

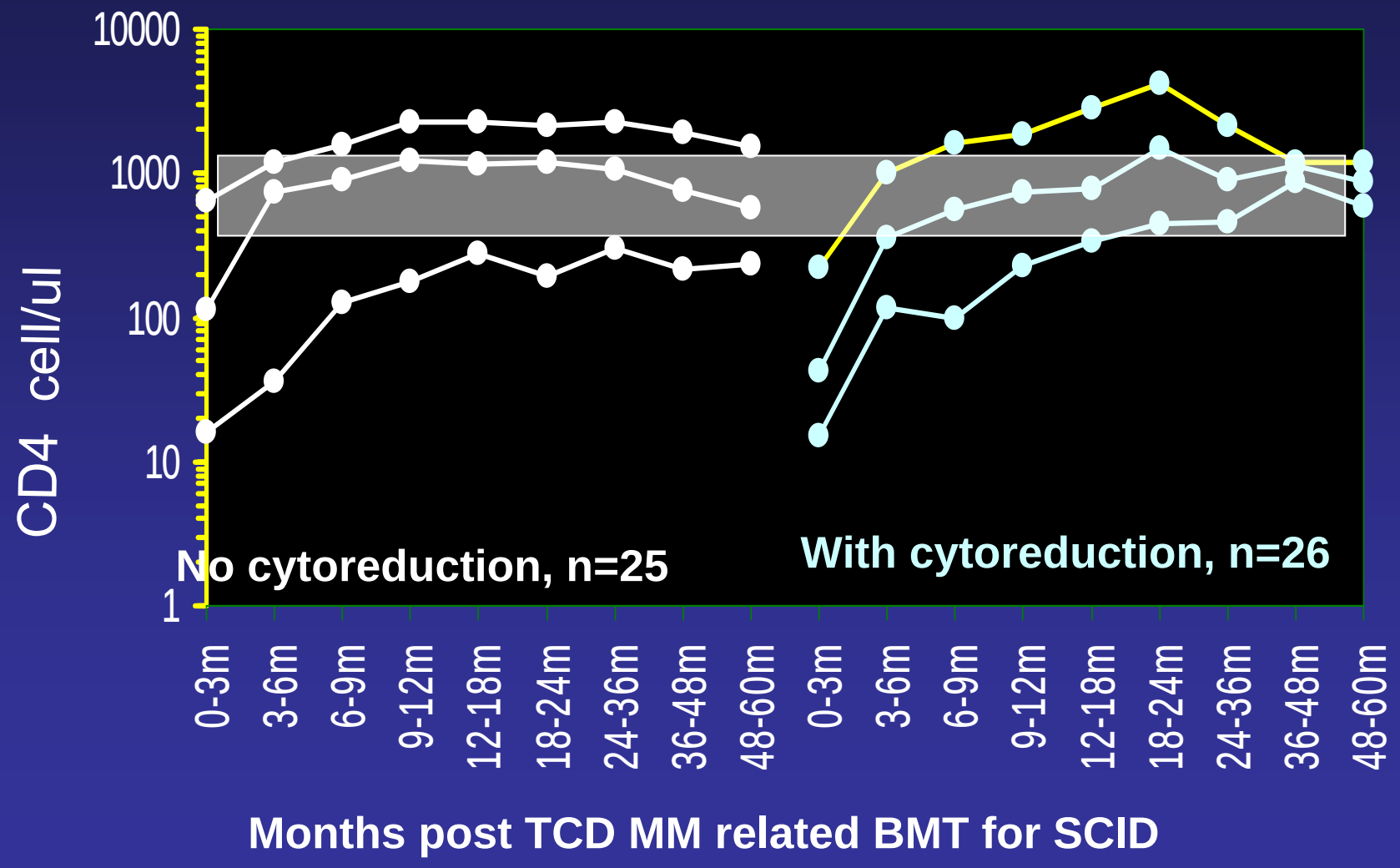

CHIMERISM DETECTED BY HLA-SEROLOGY
UPN 75
UPN 30
UPN 285
SBA⁻E⁻BMT
THYMULIN LEVELS (Median Levels)
1/16
1/8
1/4
<1/4
PHA PROLIFERATIVE RESPONSES (cpmX10³)
15
12
9
6
3
0
-50
0
75
150
225
300
A.

10th-50th-90th CD3 cell counts/ul



Months post TCD MM related BMT for SCID, 2007

10th-50th-90th CD4 cell counts/ul



MSKCC
Transplants For SCID

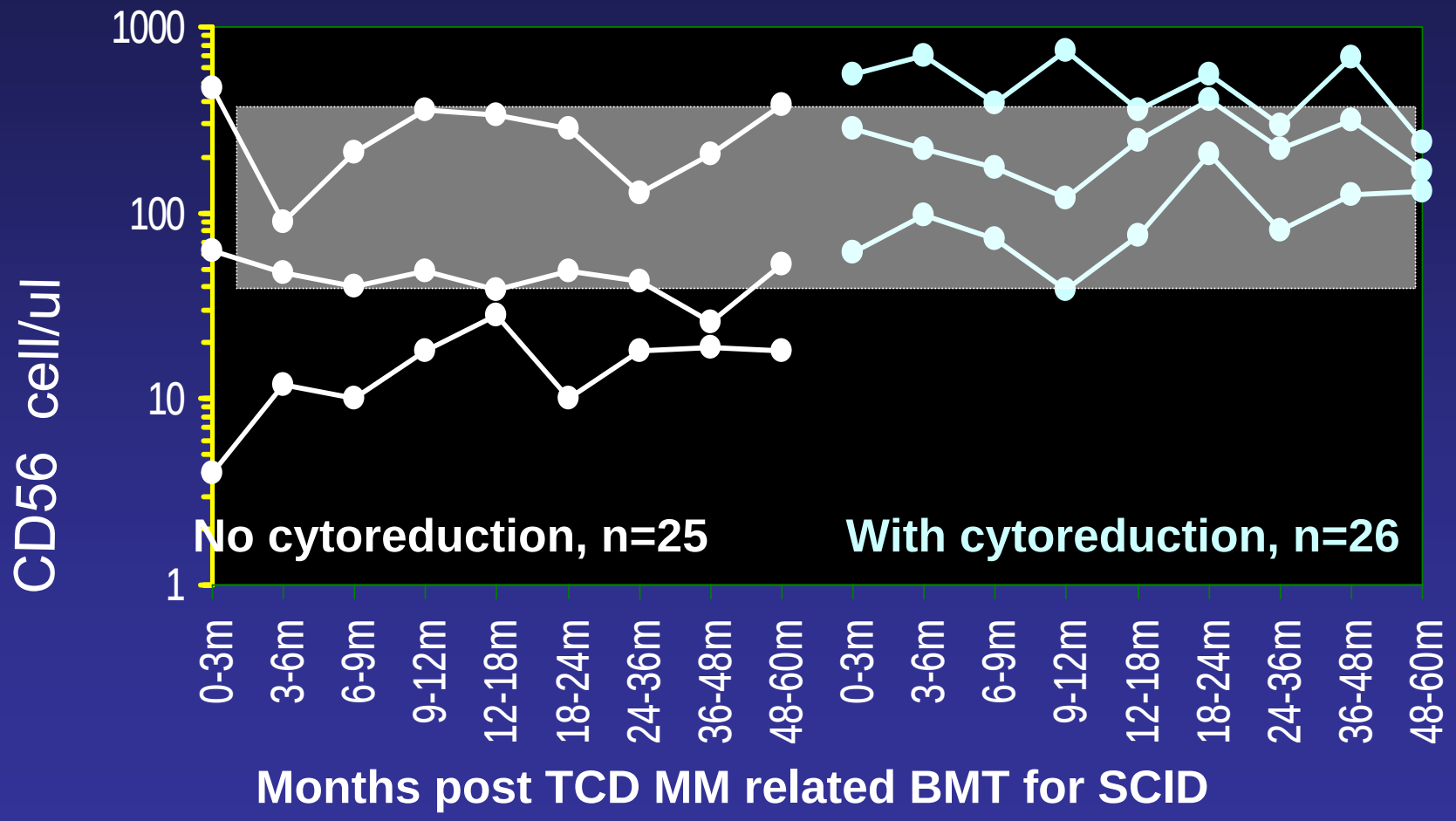
Incidence of GVHD Post $SBA^{-}E^{-}$ BMT From Parental Donors

Host HLA Unique Disparities	N	Eng^{+} Eval.	Acute GVHD I	Acute GVHD II-IV	Chronic GVHD
1	3	3	0	0	0
2	19	19	0	0	0
3	49	46	1	5	1
TOTAL	71	68	1	5	1

Effect of Engrafted Donor T cells on Anti-Patient Cytolytic Response

			% Specific ^{51}Cr release Targets				
Effector	Stimulator	E:T ratio	Father a/b	Mother (donor) c/d	Sister a/c	Pat. B-LCL b/c	DR3^{+} B-LCL B
Mother (T_D)	FatherX	100:1 50:1	62 68	4 5	53 39	69 69	69 69
Patient 30 (T_{DE})	FatherX	100:1 50:1	22 23	4 6	20 20	3 2	3 1
T_D(50%) +T_{DE}(50%)	FatherX	100:1 50:1	60 56	5 3	51 41	59 55	64 60

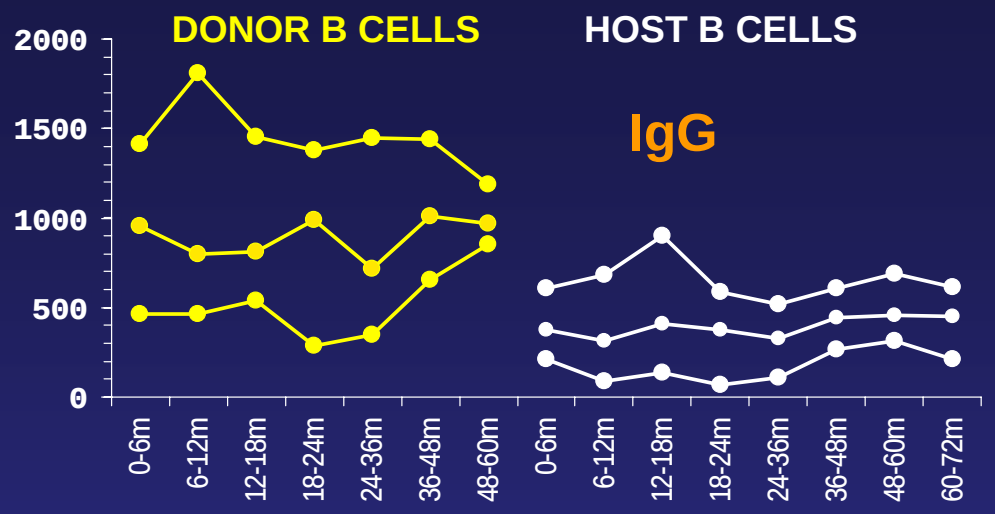
10th-50th-90th CD56 cell counts/ul

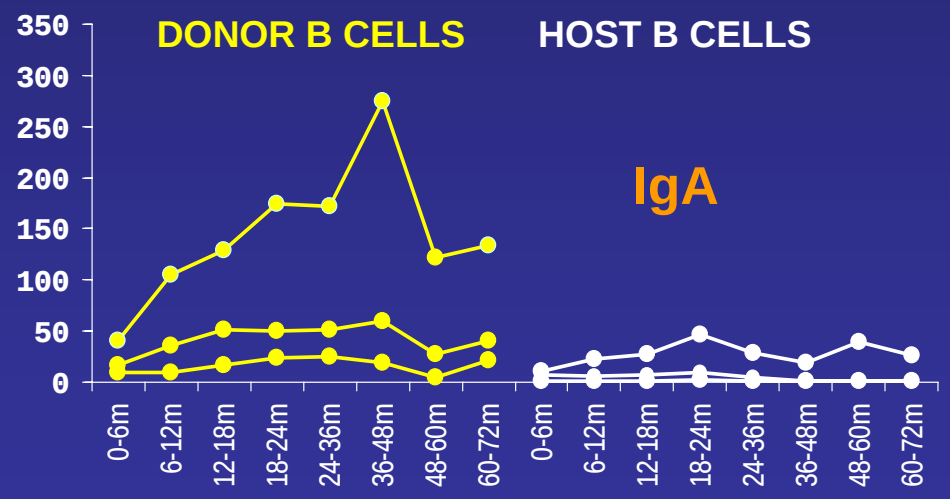


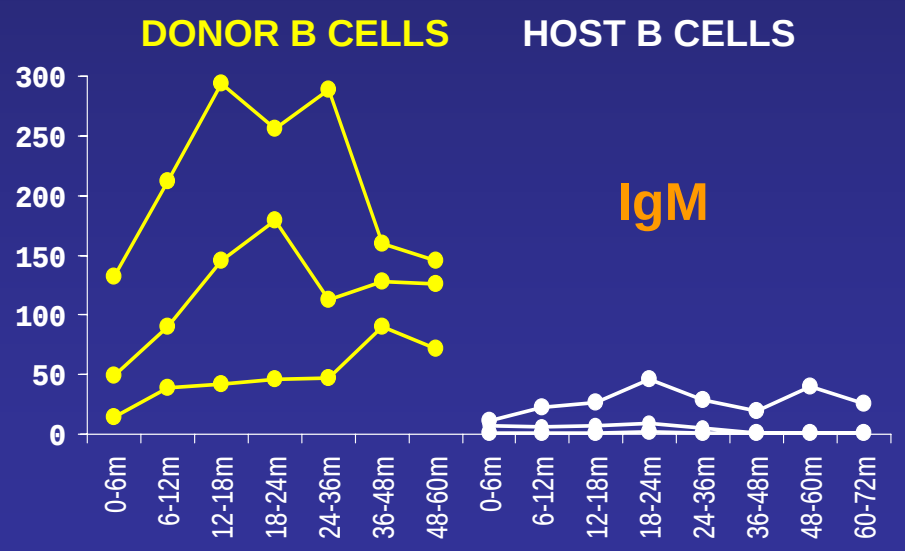
B CELL ENGRAFTMENT AND FUNCTION FOLLOWING T-CELL ENGRAFTMENT OF MM SBA¯E¯BMT WITH OR WITHOUT CYTOREDUCTION

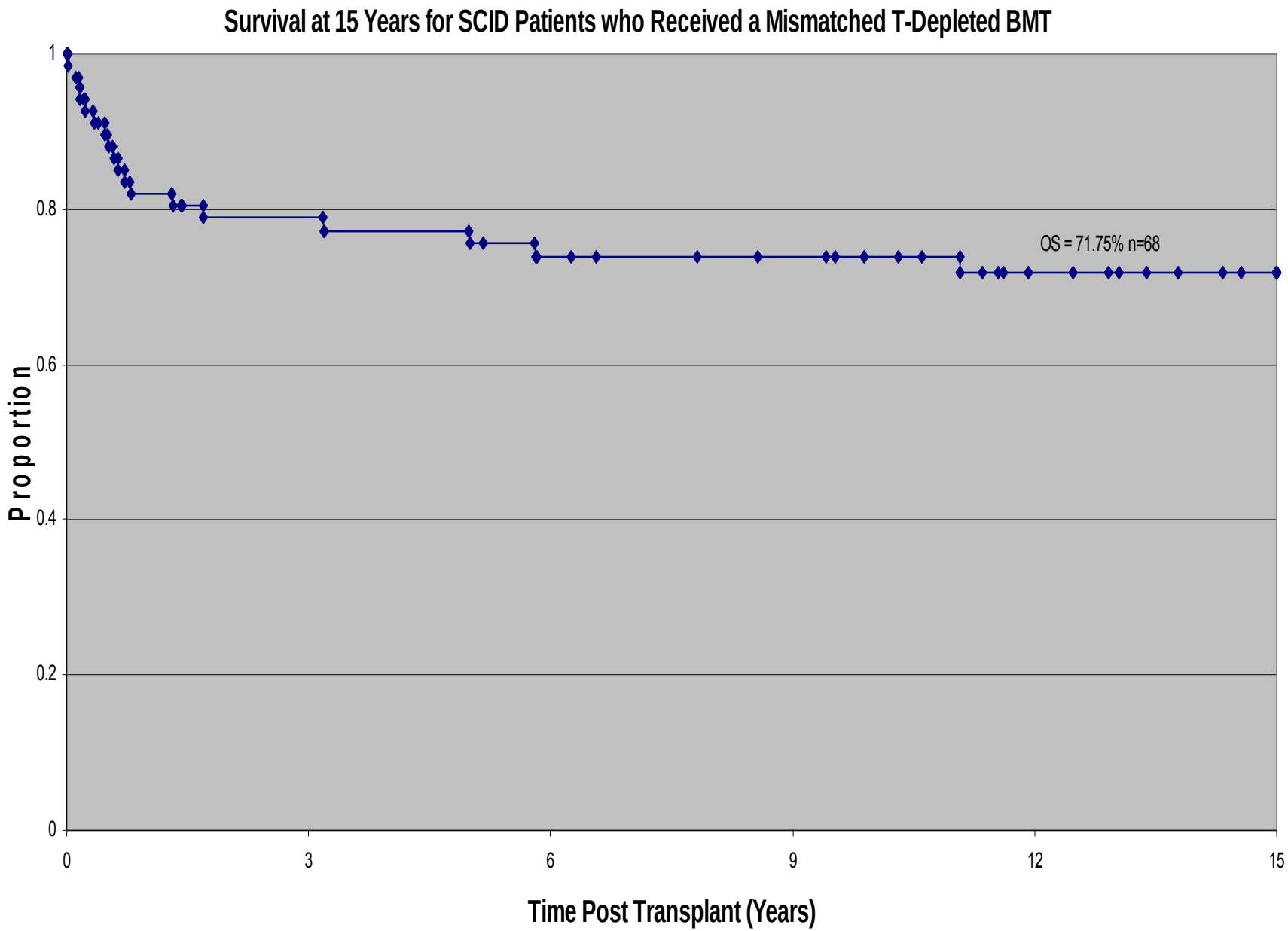
	B-CELL ENGRAFTMENT			B CELL FUNCTION		
	TOTAL	YES	NO	YES	NO	NE
MYELOABLATIVE CYTOREDUCTION	27	22	4	22	4	1
NON-MYELOABLATIVE CYTOREDUCTION	2	1	1	1	1	0
NO CYTOREDUCTION	23	3	24	2	24	3

10TH – 50TH – 90TH PERCENTILE OF SERUM IMMUNOGLOBULIN CLASS FOR SCID DONOR B vs. HOST B CELL

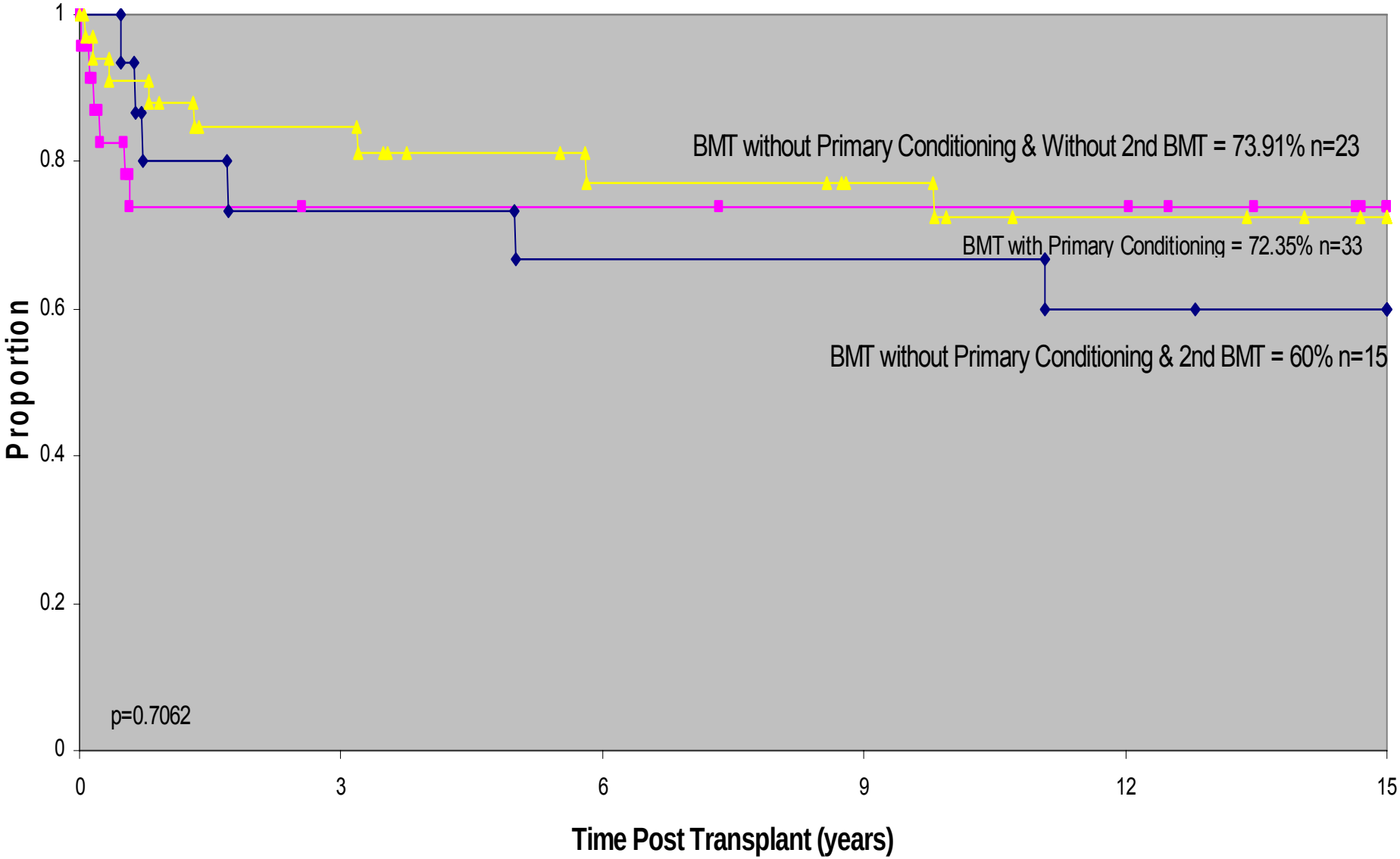




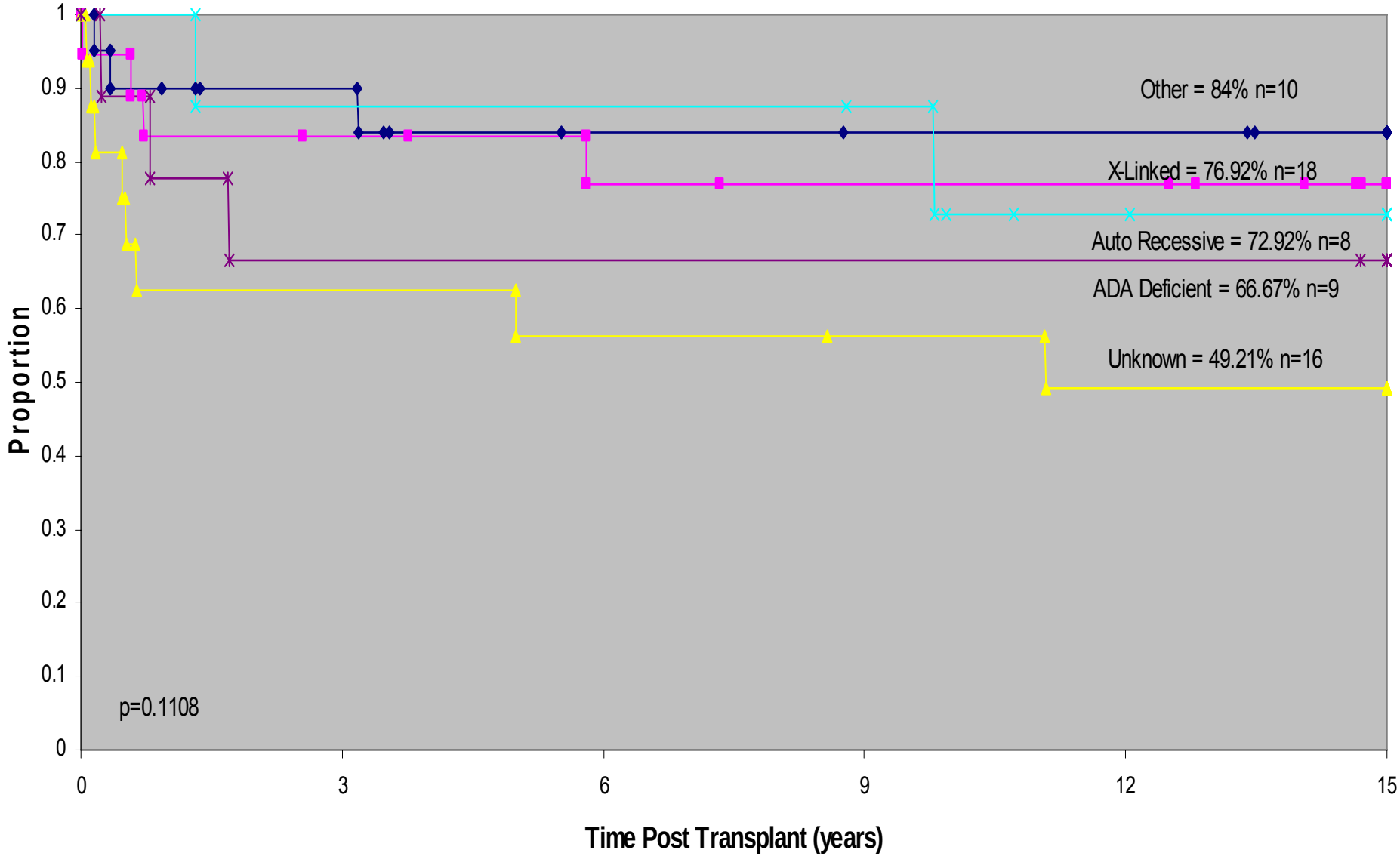



Survival at 15 Years for SCID Patients who Received a Mismatched T-Depleted BMT
Proportion
1
0.8
0.6
0.4
0.2
0
OS = 71.75% n=68
0
3
6
9
12
15
Time Post Transplant (Years)

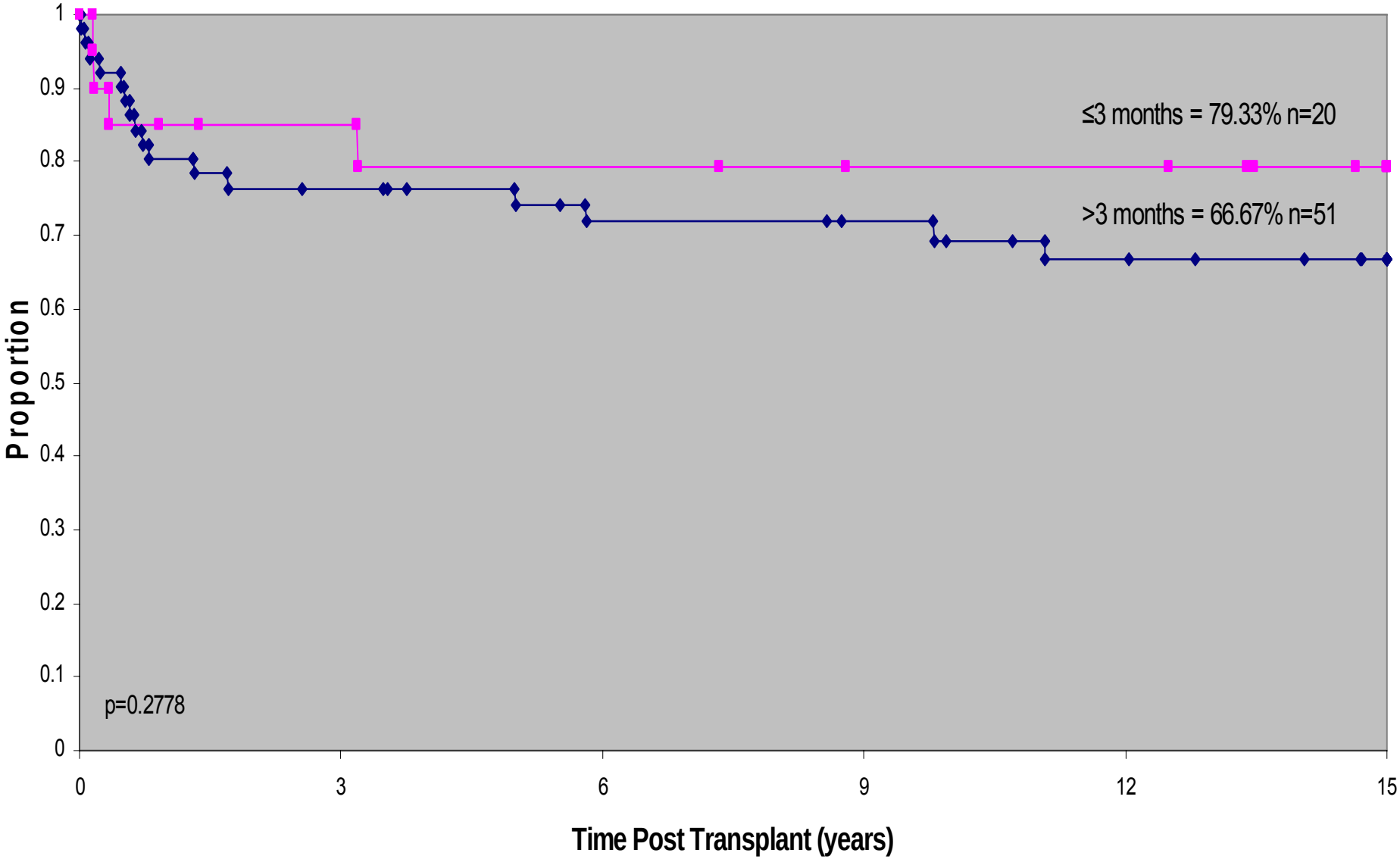
Survival at 15 Years by Primary Conditioning and 2nd BMT
Mismatched T-Depleted BMT for SCID



Survival at 15 years by SCID Variant
Mismatched T-Depleted BMT



Survival at 15 Years of SCID Patients Transplanted at 3 Months of Age
Mismatched T-Depeted BMT



LATE COMPLICATIONS IN T-CELL RECONSTITUTED HOSTS

	Cytoreduced	Non-cytoreduced
TOTAL PATIENTS	25	28
Affected Patients	2 (8%)	11 (37%)
® COPD + Hepatitis + Nephritis	0	1
® Chronic Obstructive Lung Disease	0	7
® Chronic Non-Viral Hepatitis	0	1
® Interstitial Nephritis	0	2
® Polymyopathy	2	0
Persistent Infections	0	6
Warts		5
Molluscum		1

Function Late (10 years +) post TCD MM parental HCT with SCID

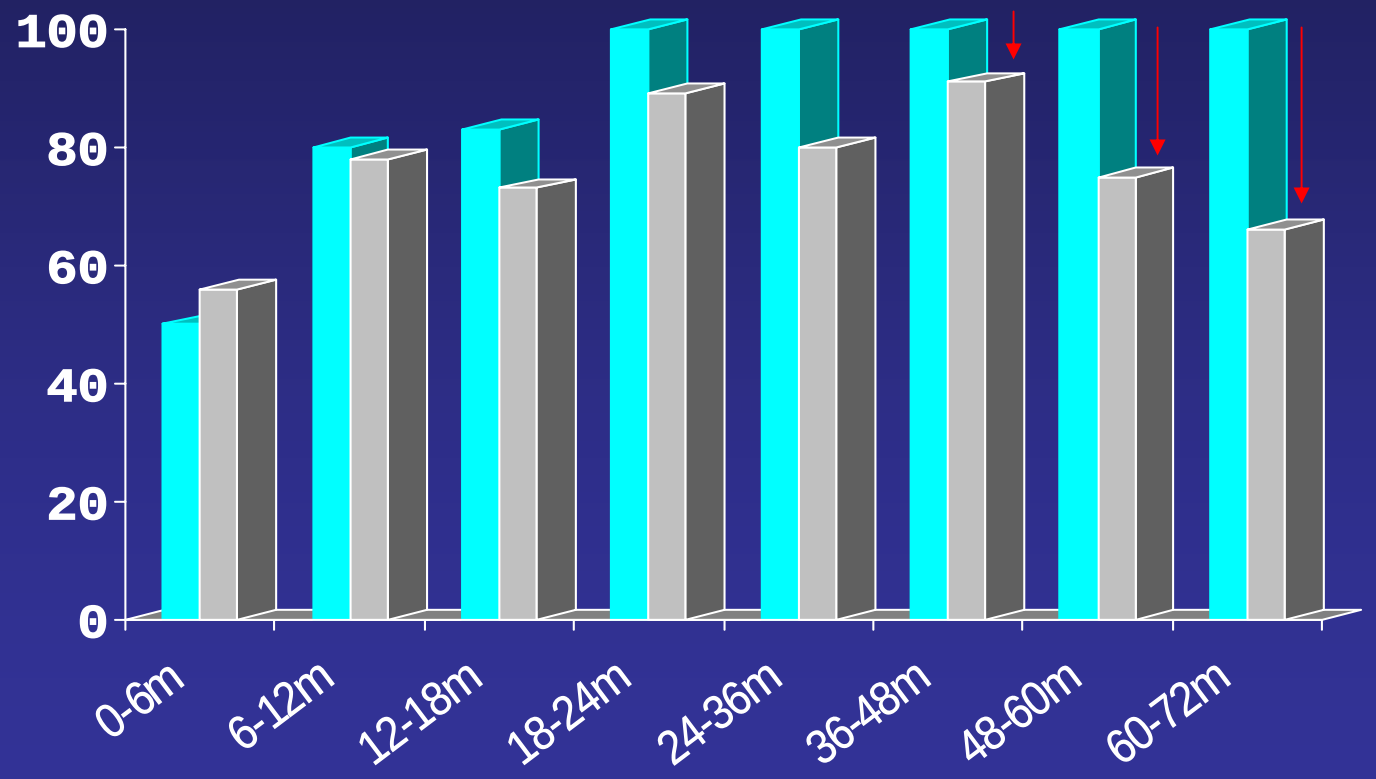
	Function		Achieved normal T cell function	Late Decline in T Cell function
	B cell	NK		
(-) Cytoreduction, n=33 Not evaluable, n=8 n=25	2/25	3/25	25/25	10/25
(+) Cytoreduction, n=30 Not evaluable, n=6 n=24	24/24	24/24	18/22* *TETE, n=2	0/24

Function of surviving patients with X-linked SCID, n=14*

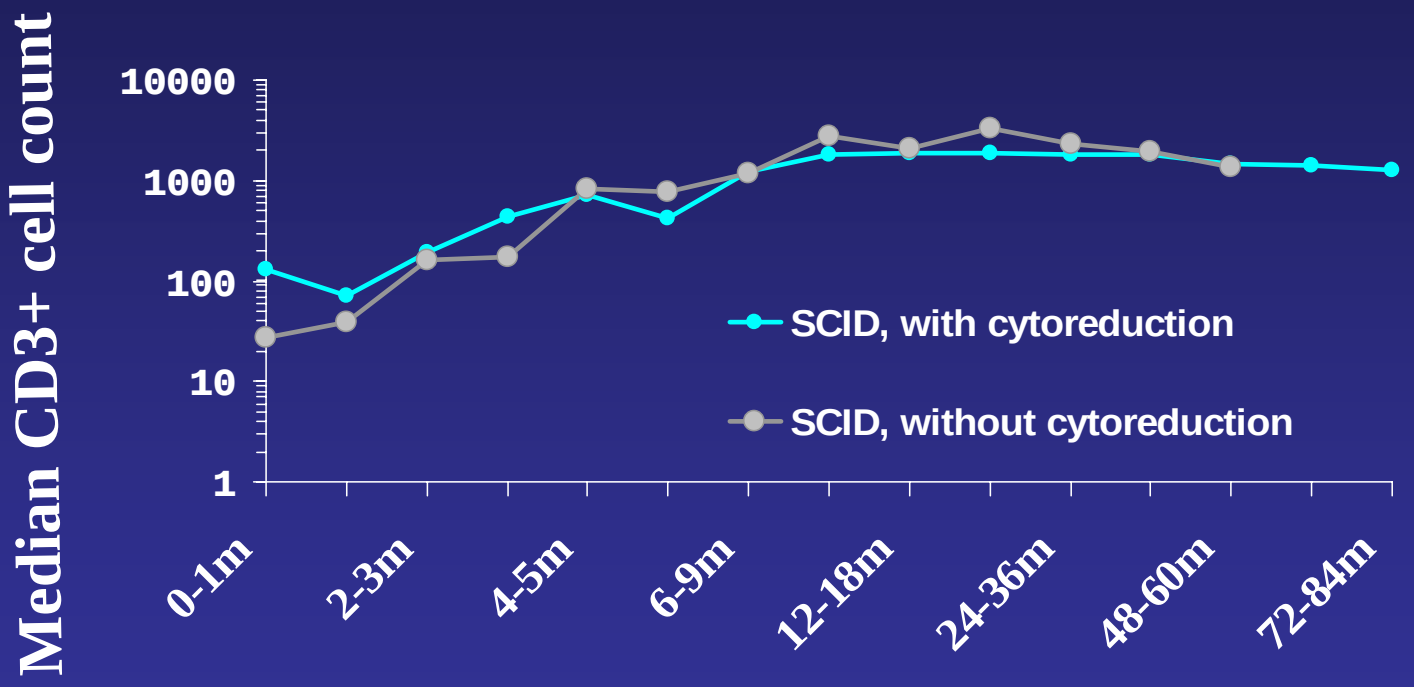
	Function		ACHIEVED NORMAL T cell function	Late Decline in T Cell function
	B cell	NK		
(-) Cytoreduction, n=13 Without infection	0	3/14	13/13	6/13
(+) Cytoreduction, n=2	2 /2	2/2	2/2	0/2

* 1 patient TETE (4 m+), 1 late death @ 70m

Comparison of the percentage of children with normal PHA post SBA- E- BMT for SCID: With and Without pre-transplant cytoreduction



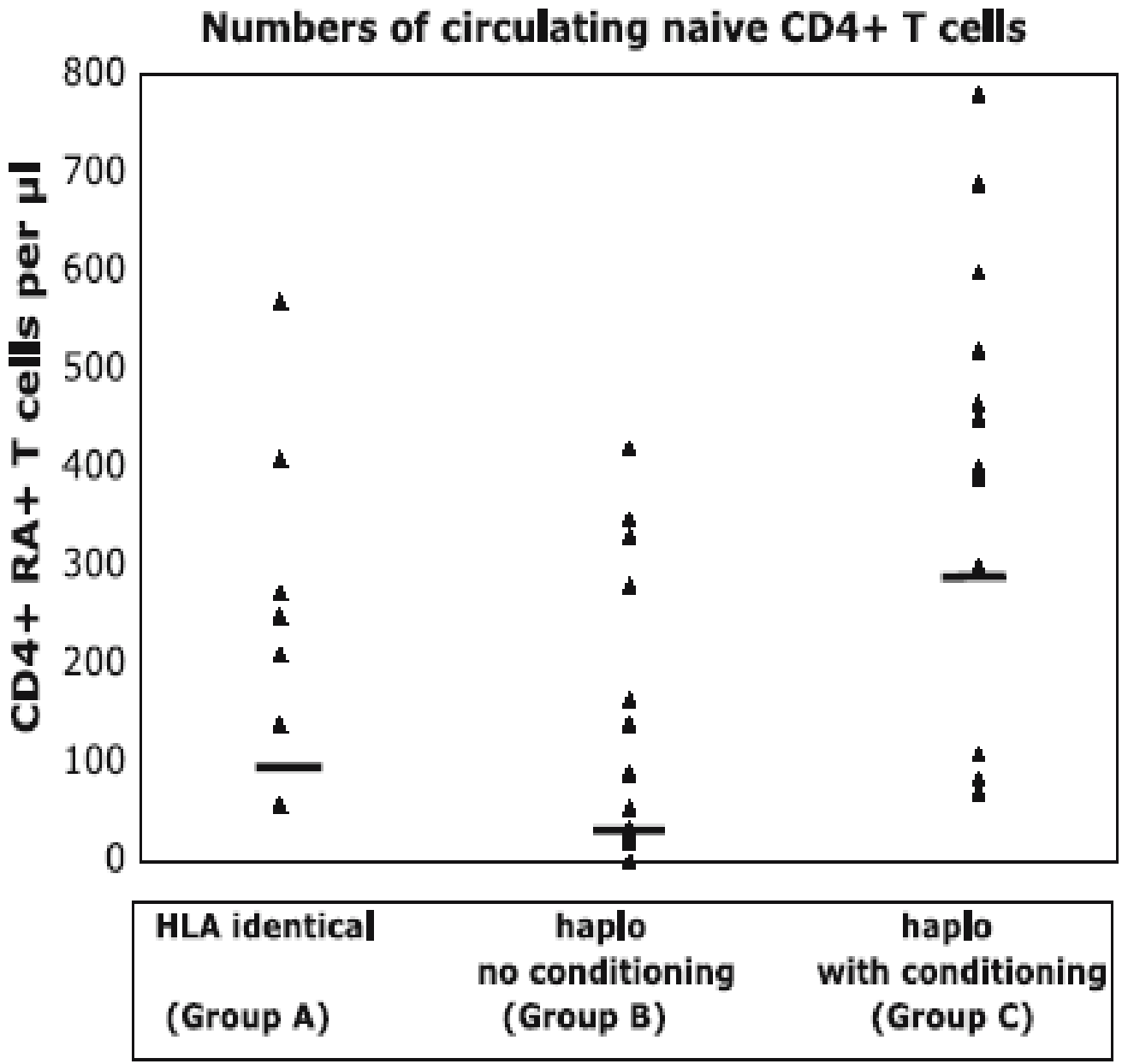
Recovery of T cells post SBA- E- parental BMT for SCID



Months post Mis-related parental TCD BMT for SCID

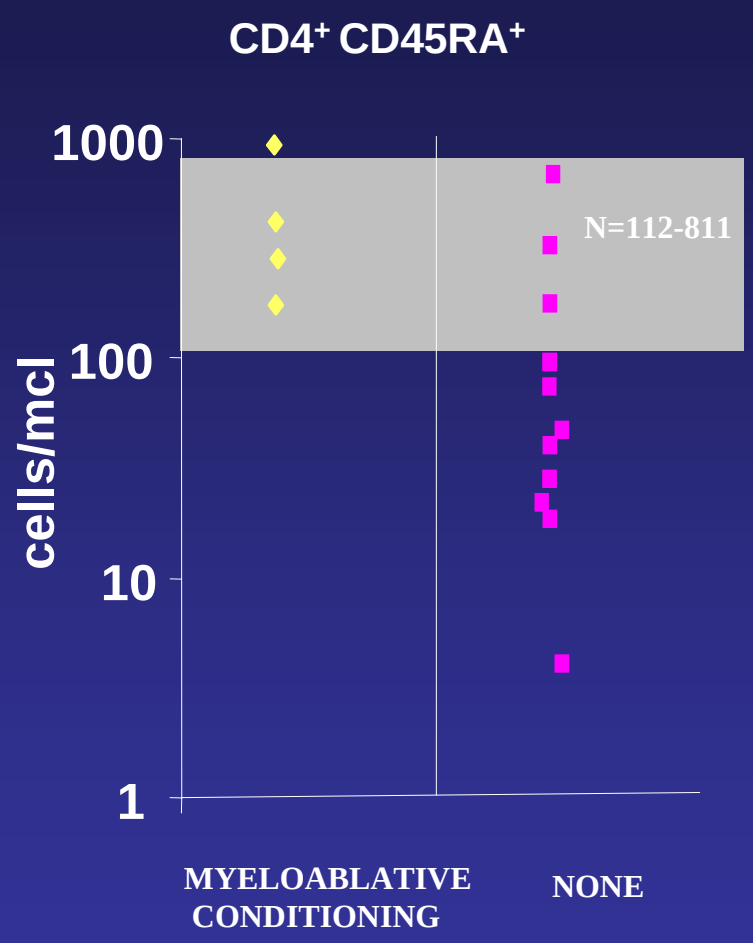
Recovery of CD4+ T cells post SBA- E- parental BMT for SCID

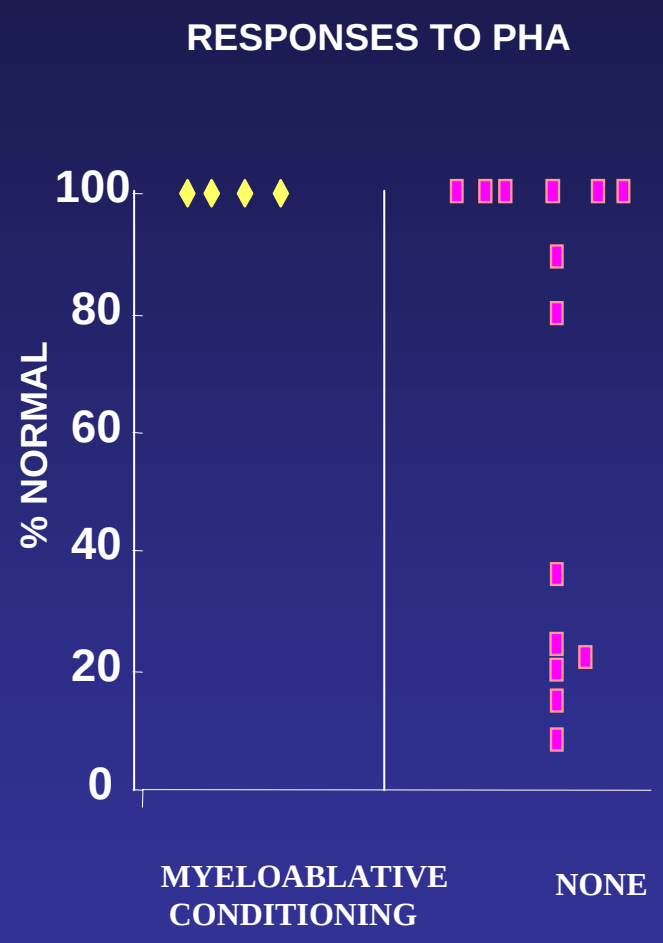
Months post Mis-related parental TCD BMT for SCID



Friedrich W, Honig M, Muller SM Immunologic Res, 2007;38 (1-3),

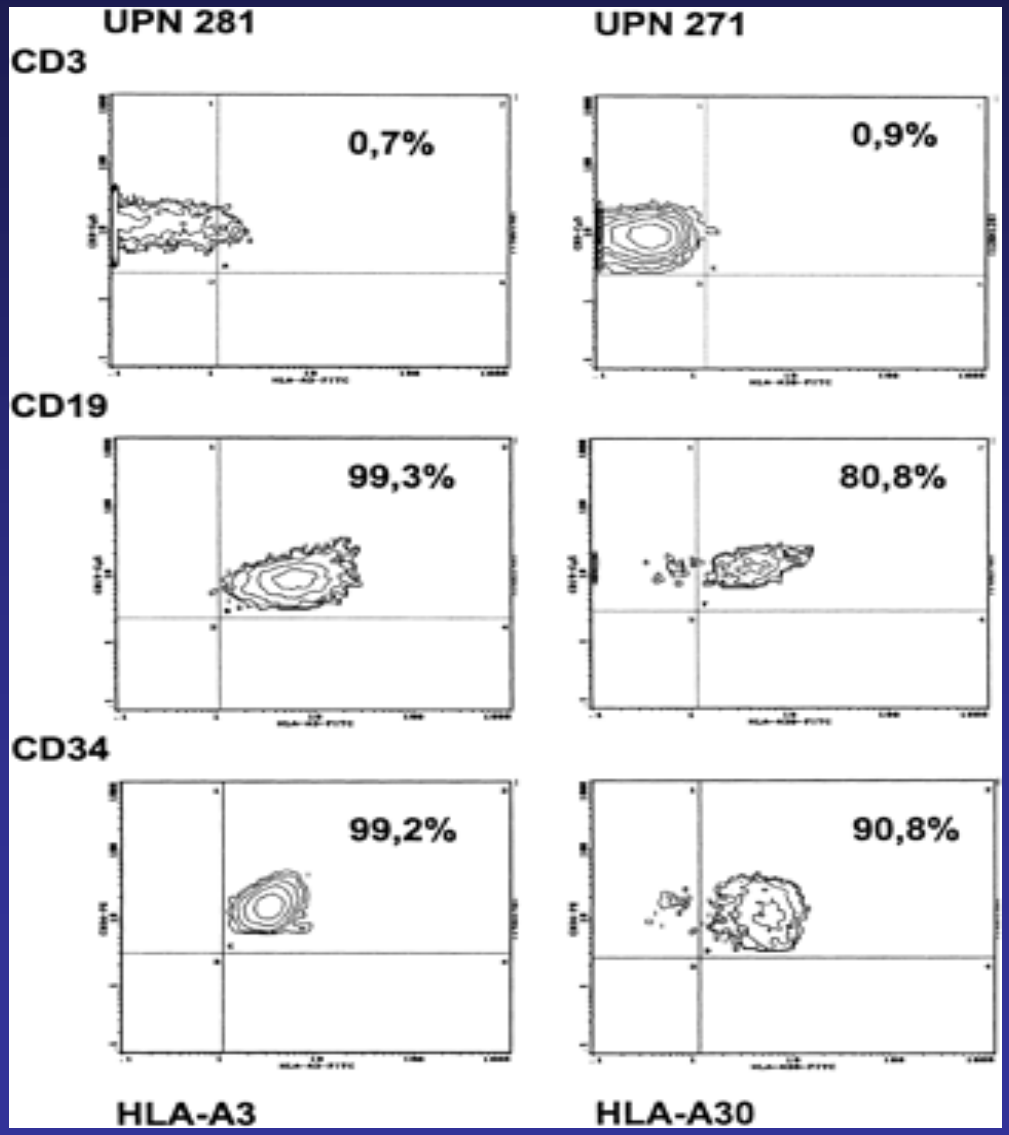
ANALYSIS OF T-CELL RECONSTITUTION 10+ YRS POST TRANSPLANT





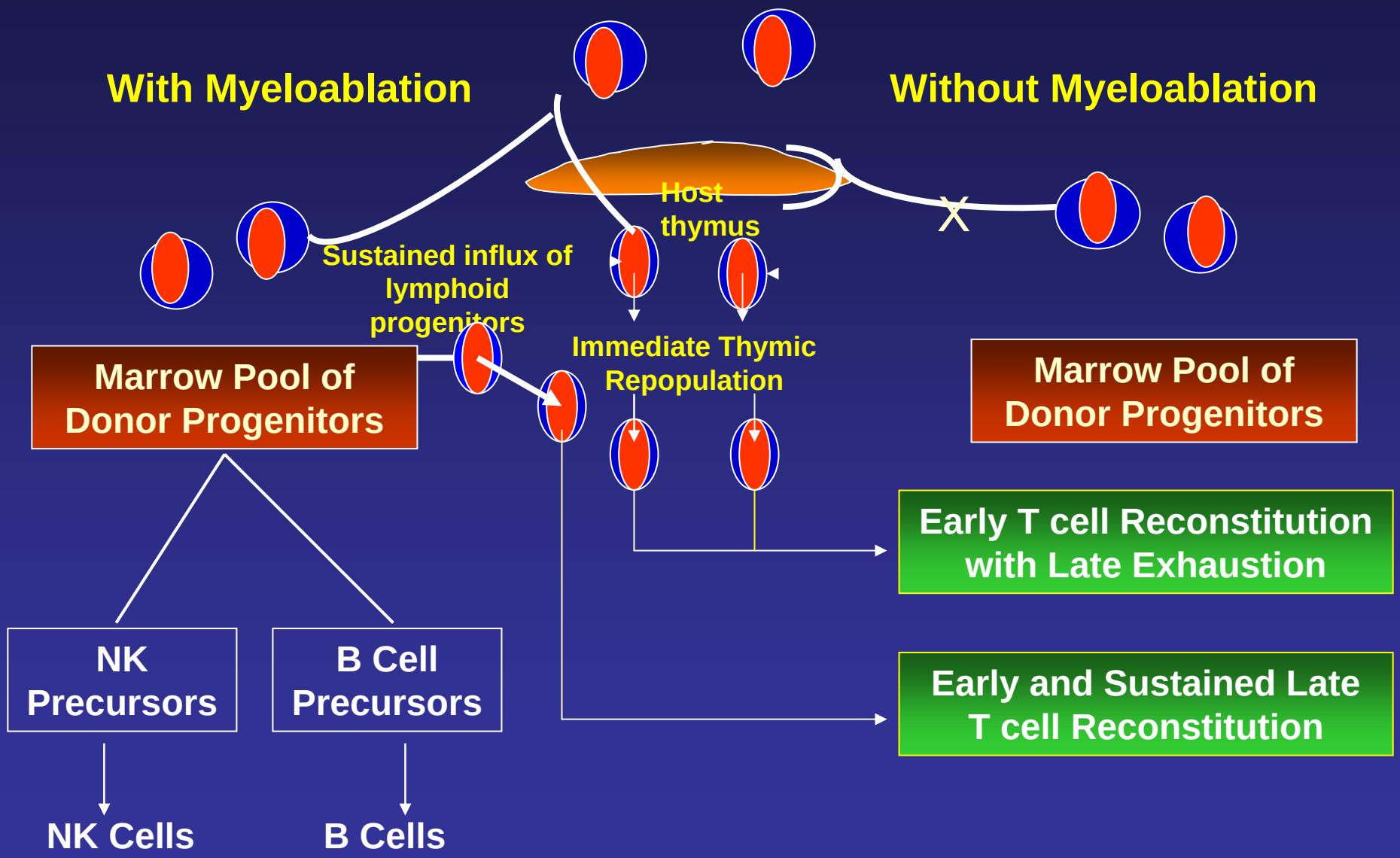
CONDITIONING

NO **YES**



FRIEDRICH et al.
Immun. Res., 2007

Hematopoietic Cell Transplant



HLA Haplotype Disparate SBA^{-}E^{-} T cell Depleted Marrow Grafts

	No Cytoreduction	Myeloablative Cytoreduction
T cell chimerism	+	+
T cell function	+	+
B cell chimerism	Rare	Consistent mixed or full chimerism
Antibody production	Rare	Consistent
NK cell function	Persistent deficiency	Consistent normal function
Late reductions in thymic output and new T cell production	>80%	10%
Late development of “autoimmune” nephritis and hepatitis	5-10%	0%
HPV infections	Common	Rare
Viral hepatitis	Significant risk	Rare

CONCLUSIONS:

1. HLA haplotype disparate T cell depleted hematopoietic progenitor grafts can provide durable reconstitution of immunity in patients with SCID.
2. Engraftment and T cell reconstitution is impaired in SCID patients with NK function or ADA deficiency unless preparatory myeloablation is employed.
3. Without myeloablation, engraftment of donor B cells and NK cells is rare, leading to sustained deficiency of humoral immunity and NK cell functions.
4. Without myeloablation, engraftment may provide full reconstitution of T cell immunity. However, thymic output and T cell activity declines in a proportion of these patients over 15-20 years, which may predispose patients to chronic infection and “autoimmune” disorders.
5. SCID patients prepared with myeloablation have consistently achieved full reconstitution, mediated by donor T, B and NK cells which has been sustained through 15-24 years of follow-up.
6. Novel, less toxic approaches for preparatory myeloablation and the use of secondary grafts administered before adolescence to reconstitute B and NK cell populations in T cell chimeras are being evaluated.

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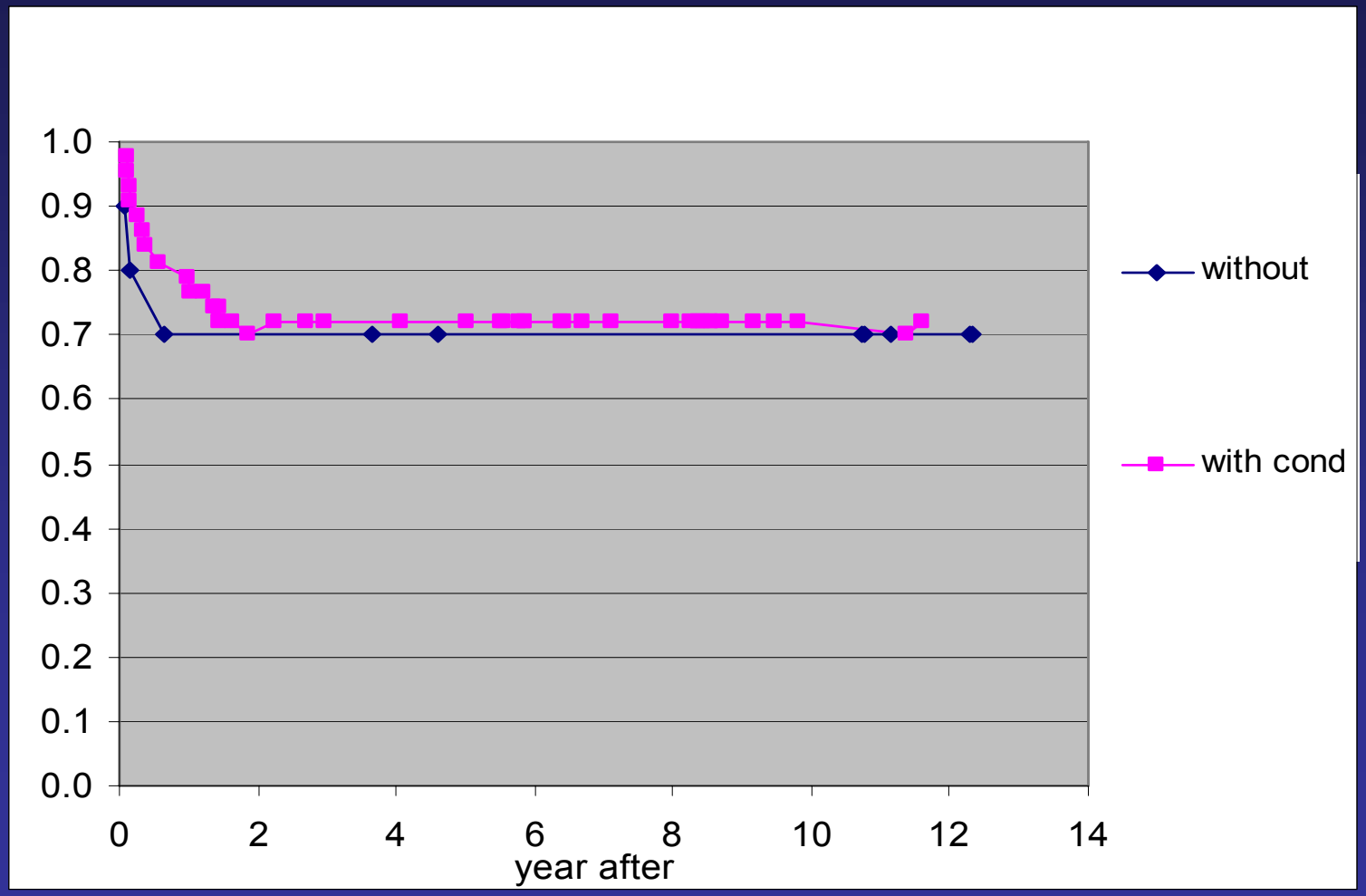
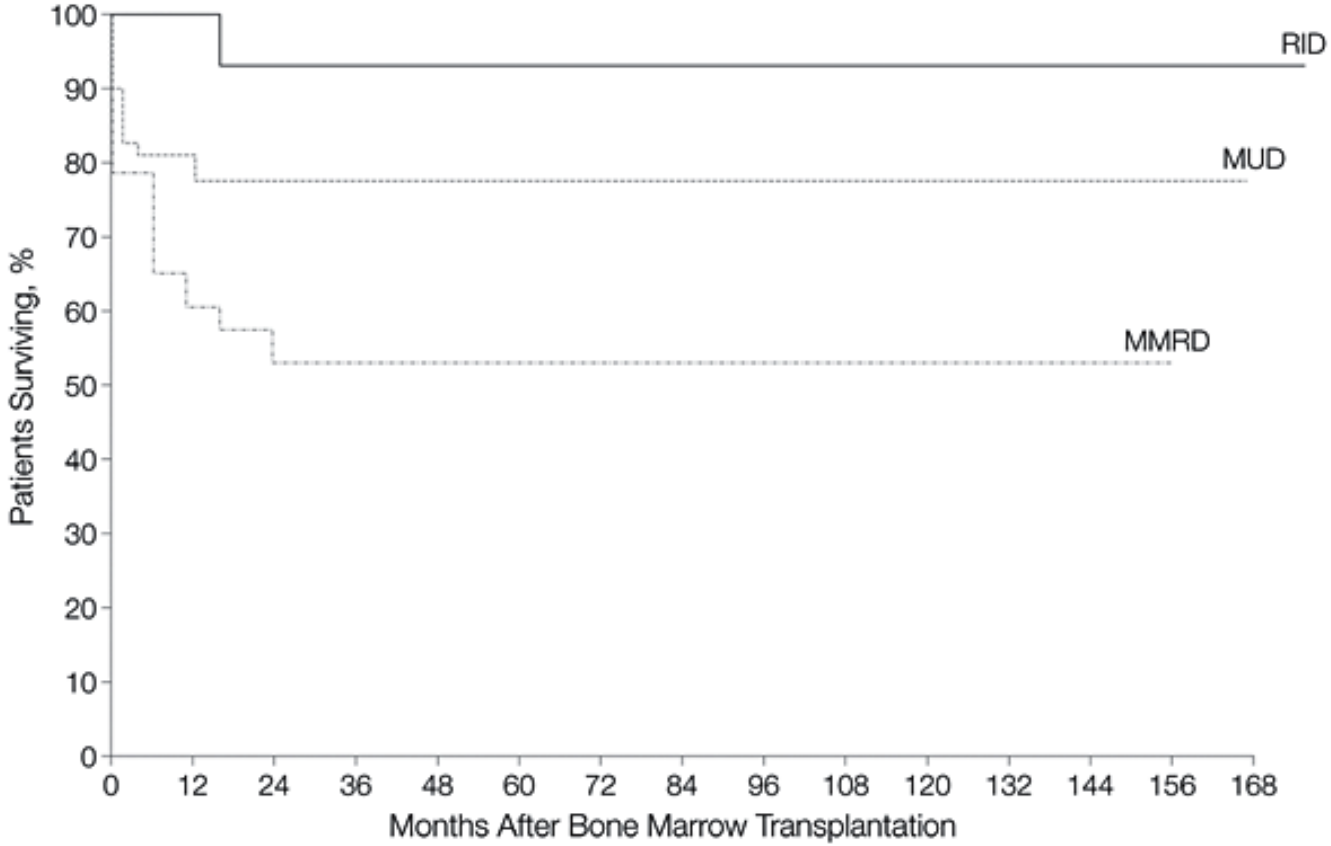
Figure 2. Outcome of TCD PBSCT for SCID:
with and without pre-transplant cytoreduction
(University of Ulm: 1995-2004)



Survival of Patients With SCID Who Received a Bone Marrow Transplant From a RID, MUD, or MMRD



No. at Risk					
RID	13	13	12	8	5
MUD	41	33	26	17	10
MMRD	40	23	19	12	4

Grunebaum, E. et al. JAMA 2006;295:508-518.

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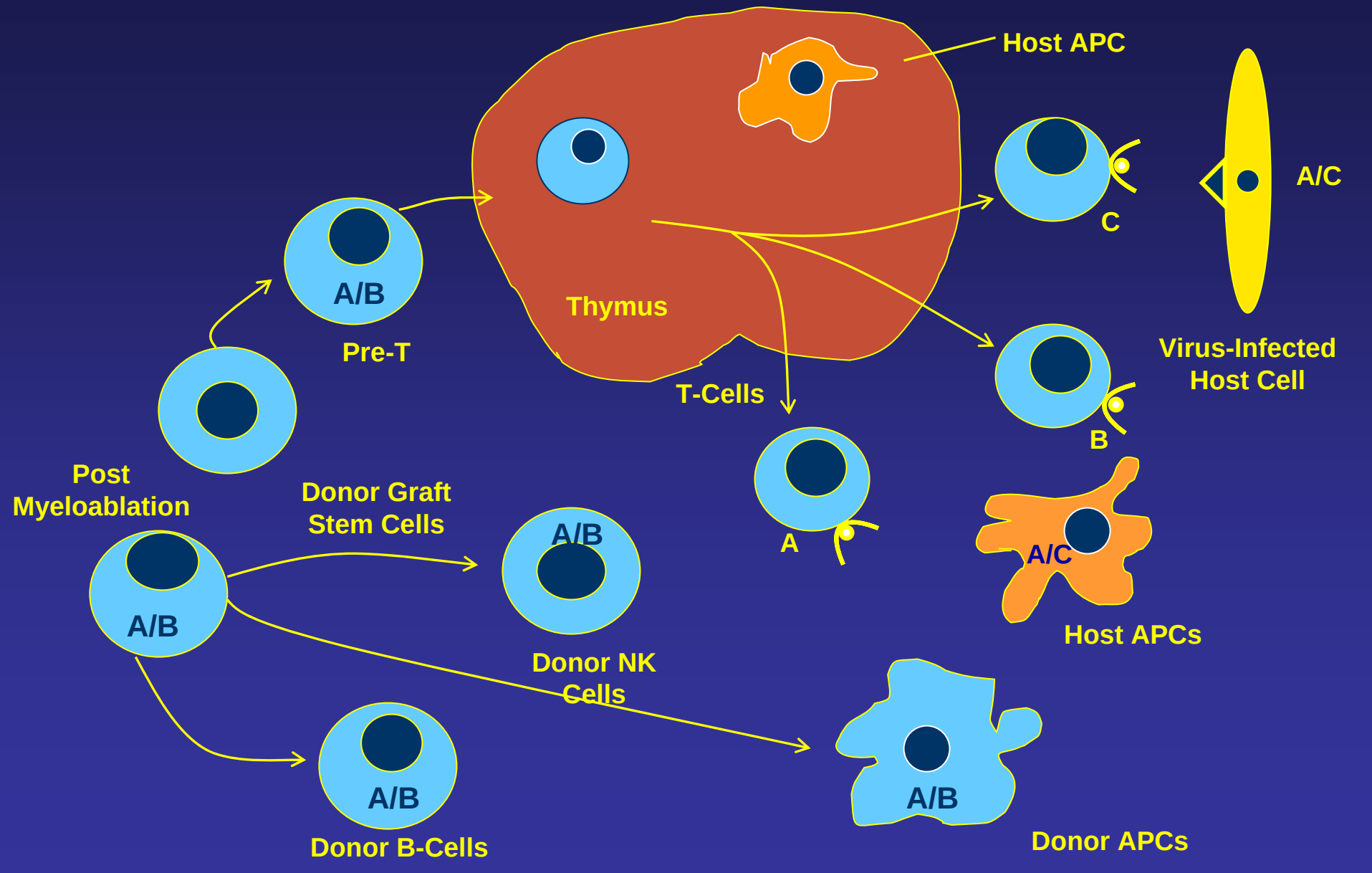
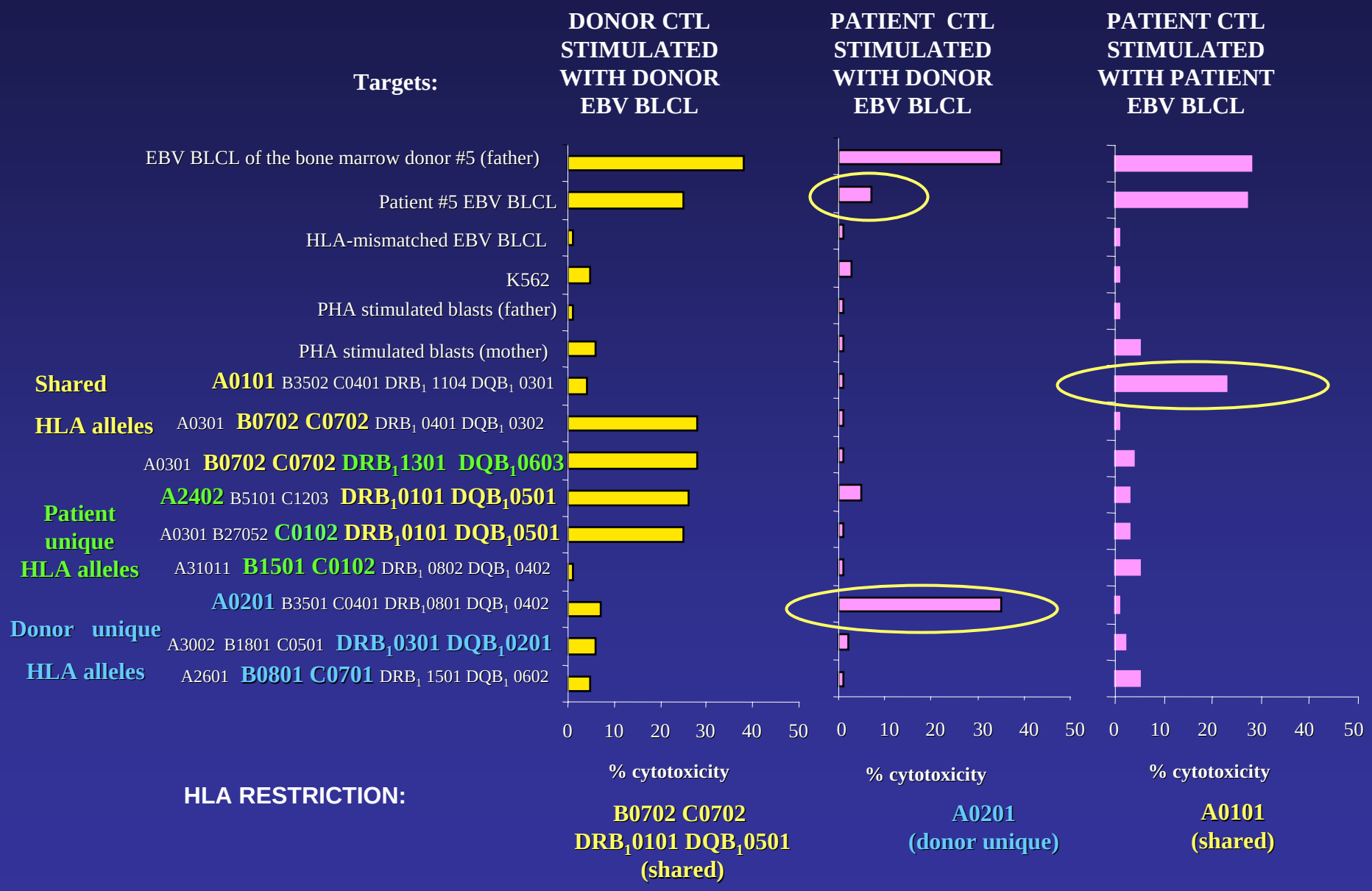
JAMA

DEVELOPMENT OF ANTIGEN-SPECIFIC T-CELLS POST HLA HAPLOTYPE DISPARATE TRANSPLANTS



HLA RESTRICTION OF DONOR ORIGIN EBV-CTL FROM PATIENT # 6 (T cells donor, B cells –host) 12 YEARS AFTER TCD BMT FROM HLA HAPLOTYPE DISPARATE MOTHER DETERMINED BY % OF LYSIS

HLA RESTRICTION OF DONOR ORIGIN EBV-CTL FROM PATIENT # 5 (T cells donor, B cells –host/donor) 17 YEARS AFTER TCD BMT FROM HLA HAPLOTYPE DISPARATE FATHER DETERMINED BY % OF LYSIS



HLA RESTRICTION OF EBV SPECIFIC T CELL LINES FROM SCID PATIENTS AFTER TCD HLA MISMATCHED BMT

PATIENT CHIMERISM	HLA RESTRICTING ALLELES OF THE BONE MARROW DONOR T CELLS		HLA RESTRICTING ALLELES OF THE POST BMT PATIENT DERIVED T CELLS		
	DONOR UNIQUE	SHARED	DONOR UNIQUE	SHARED	PATIENT UNIQUE
1. T CELLS DONOR B CELLS DONOR		A2402 B4001 $DRB_1$0701		A2402 C0304 $DQB_1$0303	
2. T CELLS DONOR B CELLS DONOR	B4001	A2402 $DRB_1$0701		A2402 C0401 $DRB_1$0701	
3. T CELLS DONOR B CELLS DONOR		A0301		A0301	
4. T CELLS DONOR B CELLS HOST/DONOR		A0201 $DRB_1$1501 $DQB_1$0602		A3201 $DRB_1$1501 $DQB_1$0602	
5. T CELLS DONOR B CELLS HOST/DONOR		B0702 C0702 $DRB_1$0101 $DQB_1$0501	A0201	A0101	
6. T CELLS DONOR B CELLS HOST		A0201 DRB_1 1501 DQB_1 0602		A3201 $DRB_1$1501 DQB_1 0602	$DRB_1$1302 $DQB_1$0604
7. T CELLS DONOR B CELLS HOST	$DRB_1$1501 $DQB_1$0602	A6802 B3901 $DRB_1$0407		B3901 $DRB_1$0407	A0201 B1501 C0303
8. T CELLS DONOR B CELLS HOST		A0301 B3501 $DRB_1$1602 $DQB_1$0502		B3501 $DRB_1$1602 $DQB_1$0502	A0201 $DRB_1$0404 $DQB_1$0302
9. T CELLS DONOR B CELLS HOST		A0201		A0201 $DRB_1$0401	