Overview of HLA Identical and Haploidentical BMT in SCID: Duke Experience

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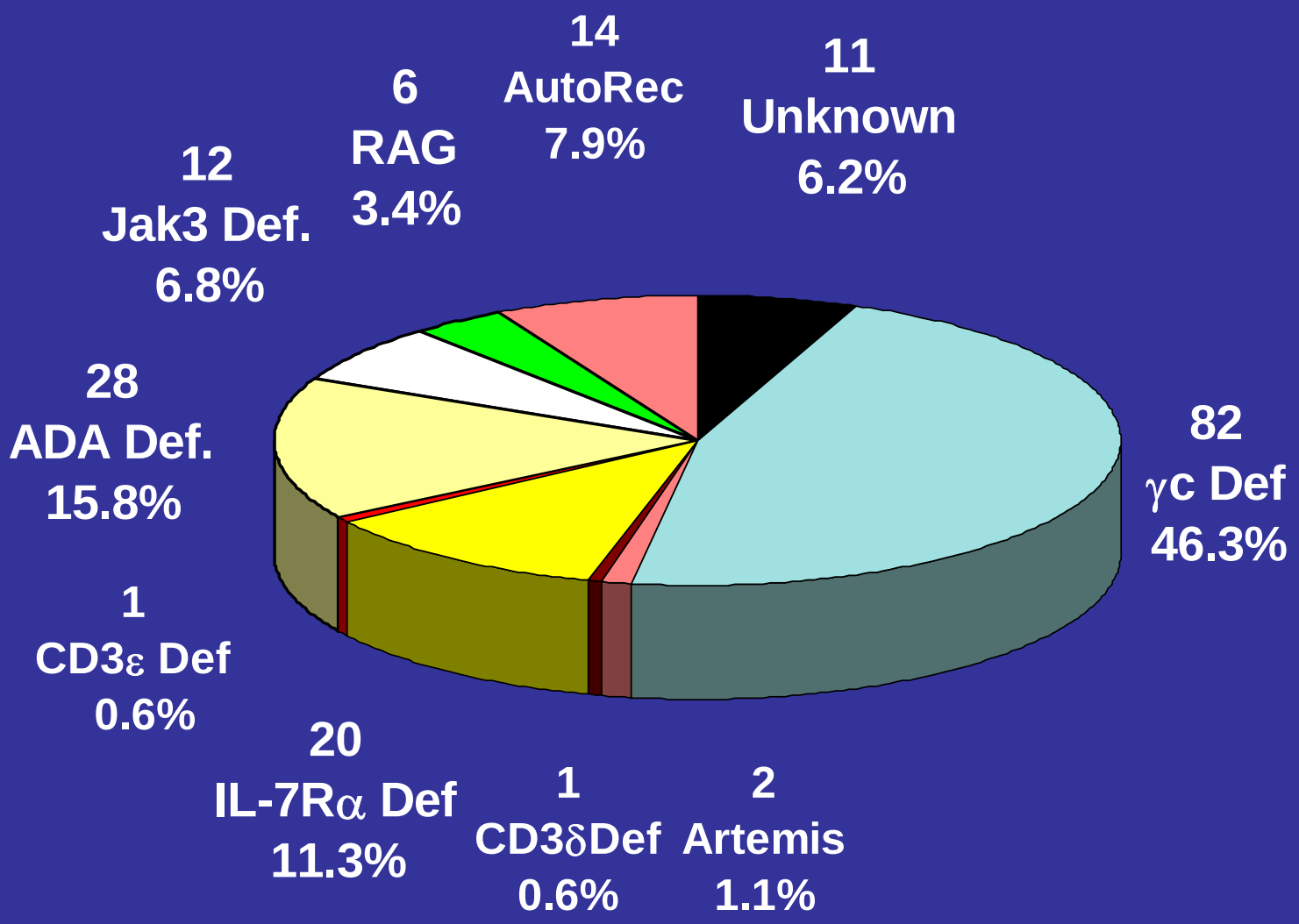
Human Severe Combined Immunodeficiency (SCID)

A fatal syndrome of diverse genetic origin, characterized by absence of T and B cell (and sometimes NK cell) functions.

Ten Abnormal Genes in SCID

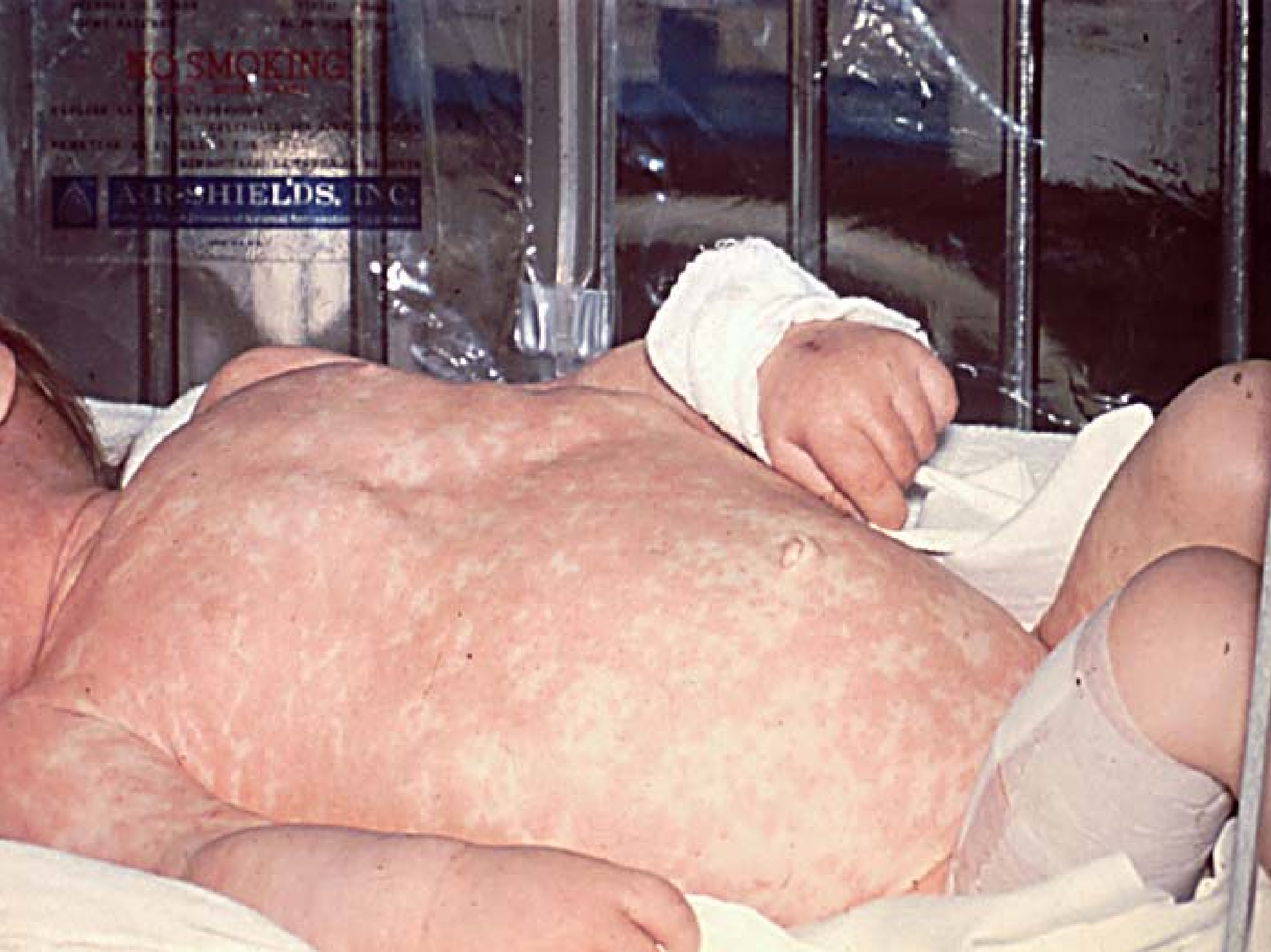
- Cytokine Receptor Genes
  - *IL2RG*
  - *JAK3*
  - *IL7Rα*
- Antigen Receptor Genes
  - *RAG1*
  - *RAG2*
  - *Artemis*
  - *CD3δ*
  - CD3ε
- Other Genes
  - *ADA*
  - *CD45*

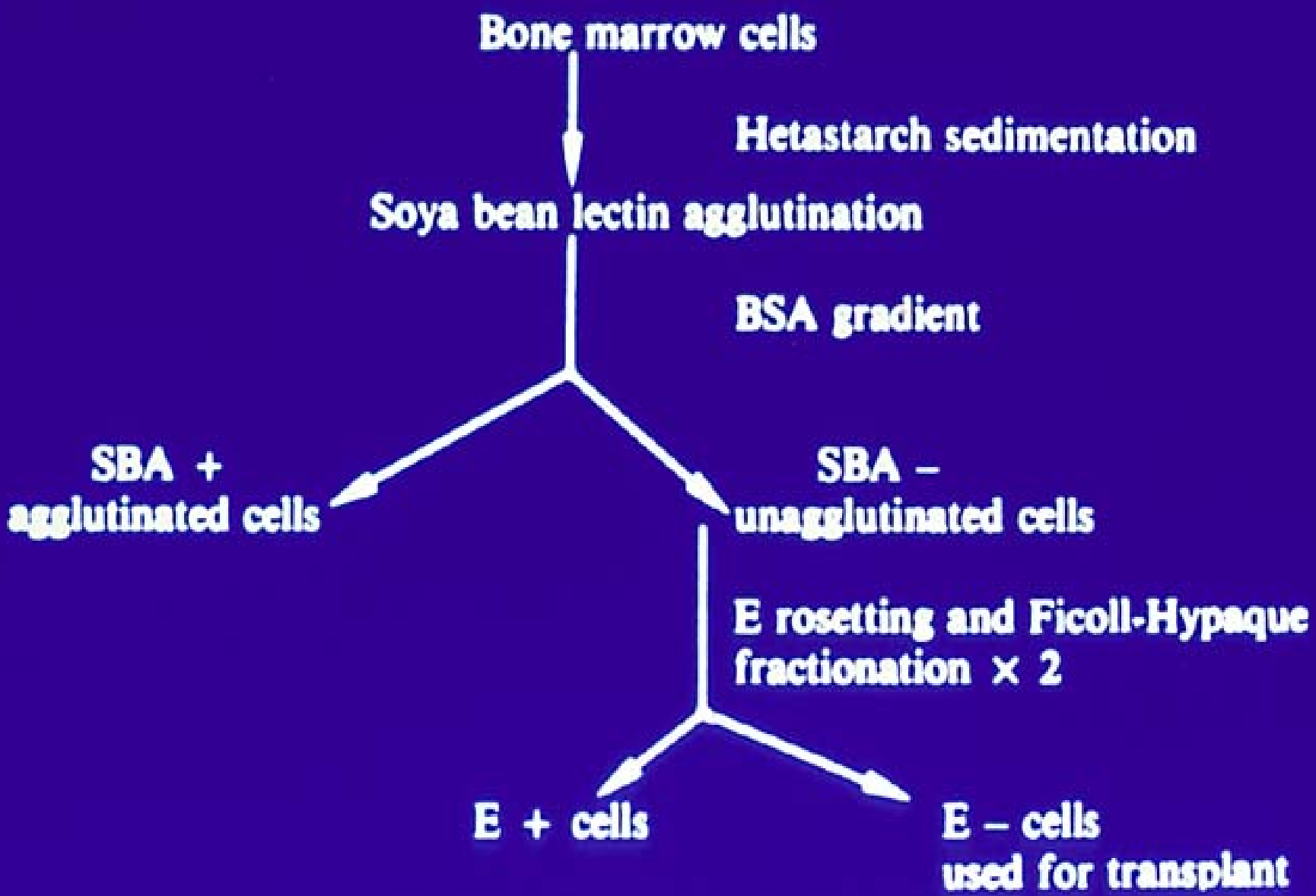
177 SCIDs: Genetic Types

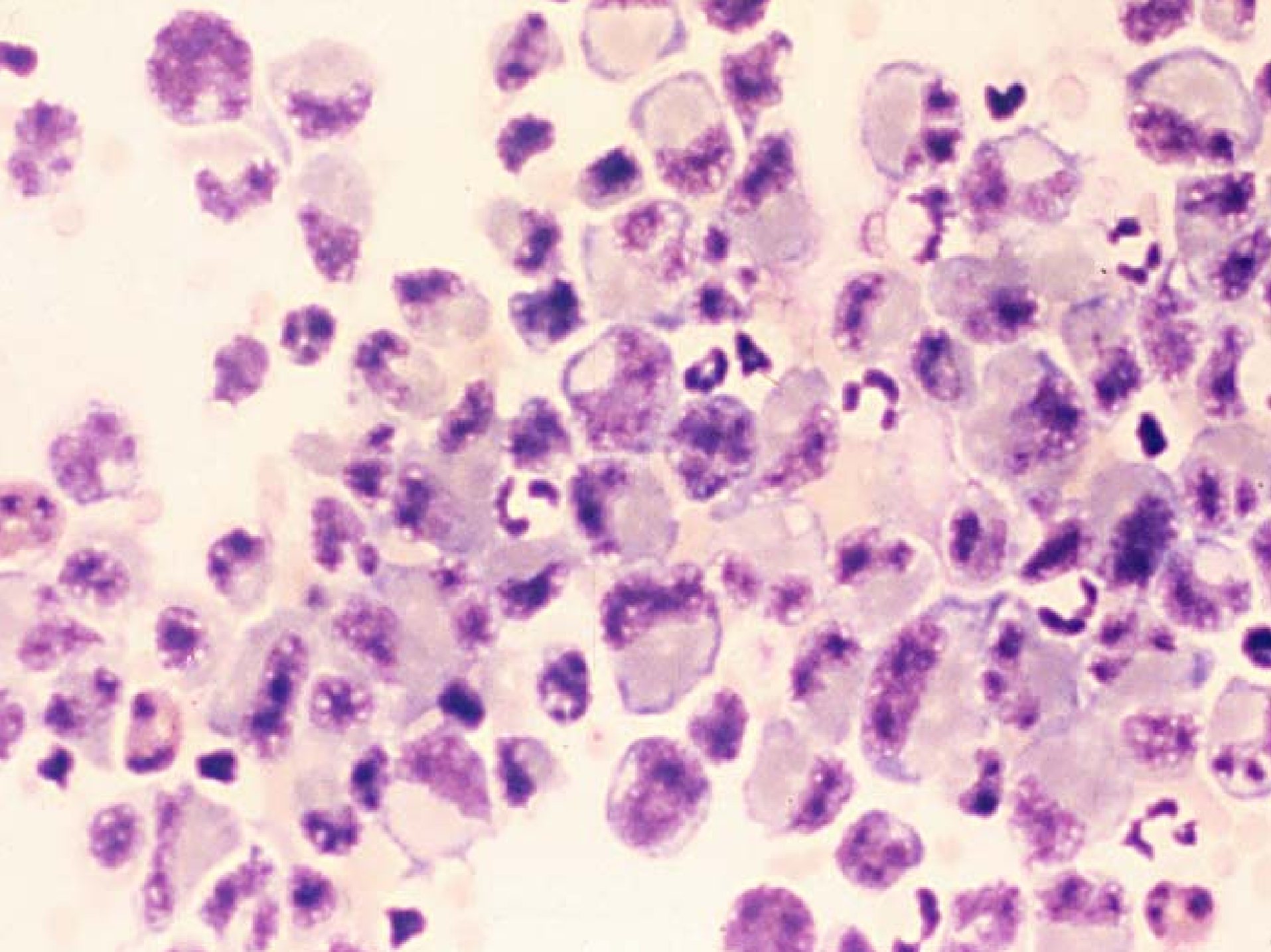


SCID : Characteristics Common to All Types

- Known since 1968 that all types can be treated successfully by bone marrow transplantation, without a need for pre-transplant chemotherapy.
- Until 2 decades ago this required strict HLA identity between donor and recipient to avoid lethal graft-versus-host disease (GVHD) .
- Now possible to avoid this by T cell depletion, which also allows omission of GVHD prophylactic drugs.

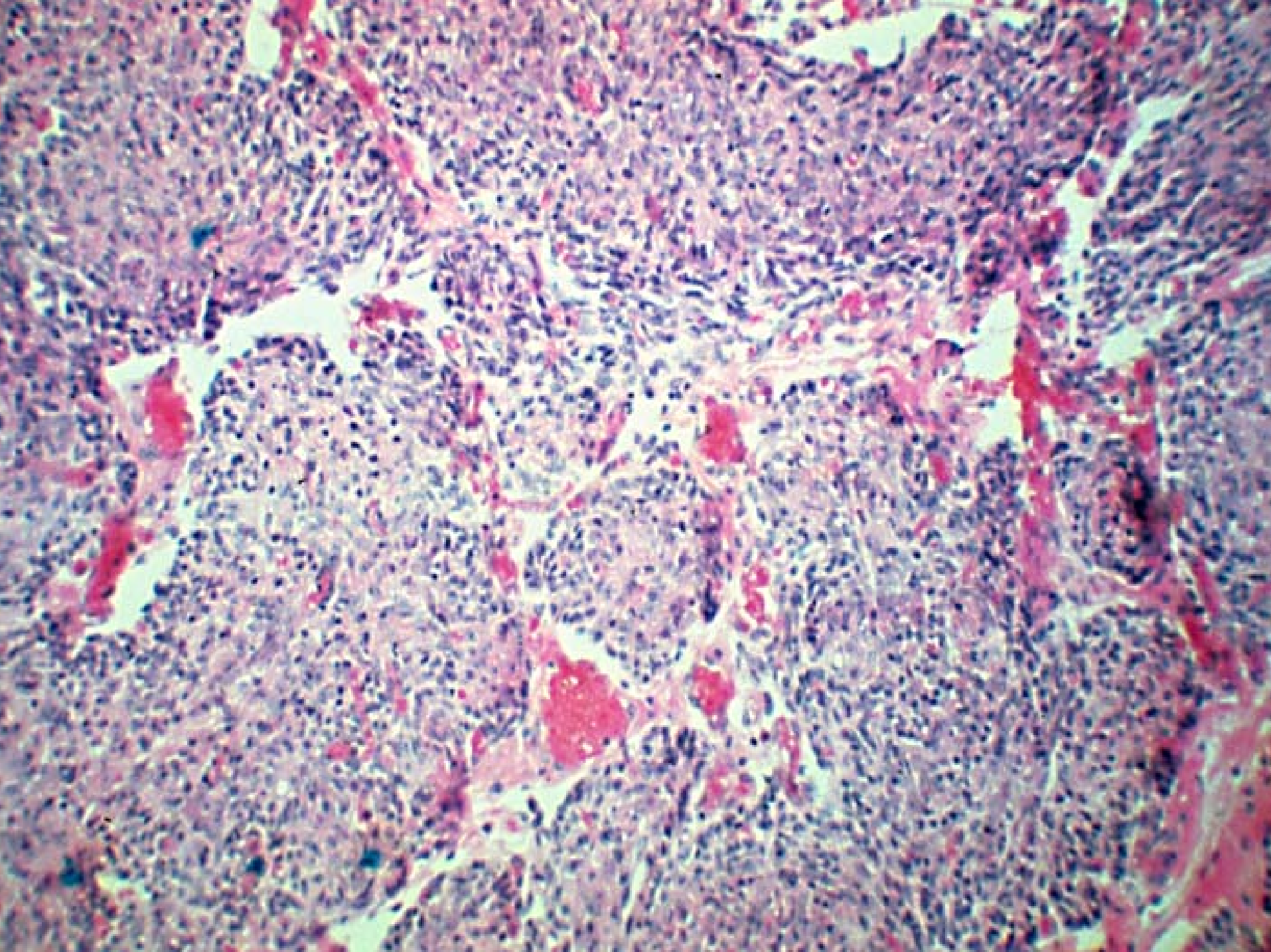

NO SMOKING
AIR-SHIELDS, INC.


Bone marrow cells
Hetastarch sedimentation
Soya bean lectin agglutination
BSA gradient
SBA +
agglutinated cells
SBA –
unagglutinated cells
E rosetting and Ficoll-Hypaque
fractionation × 2
E + cells
E – cells
used for transplant

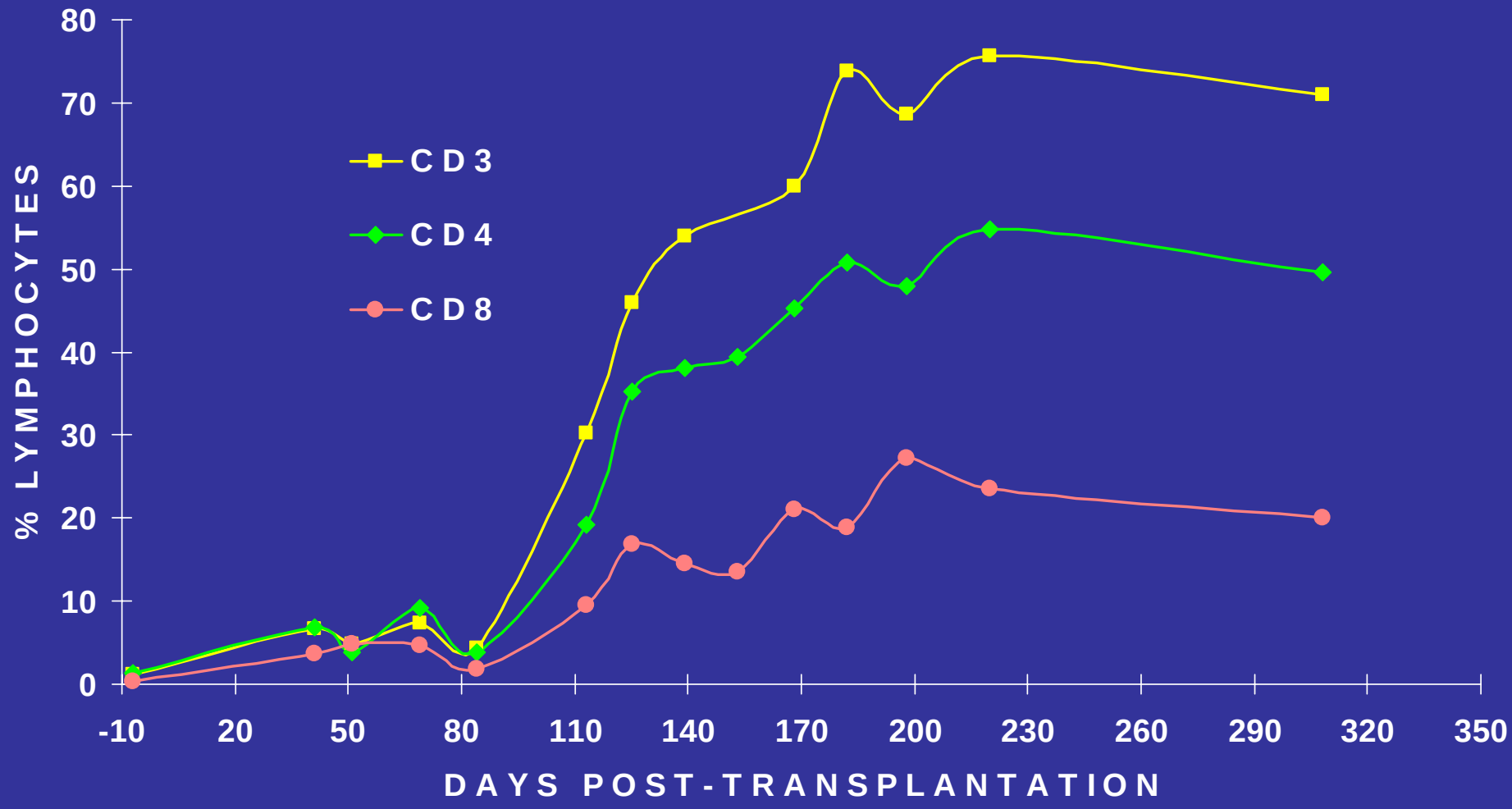


SCID : Characteristics Common to All Types

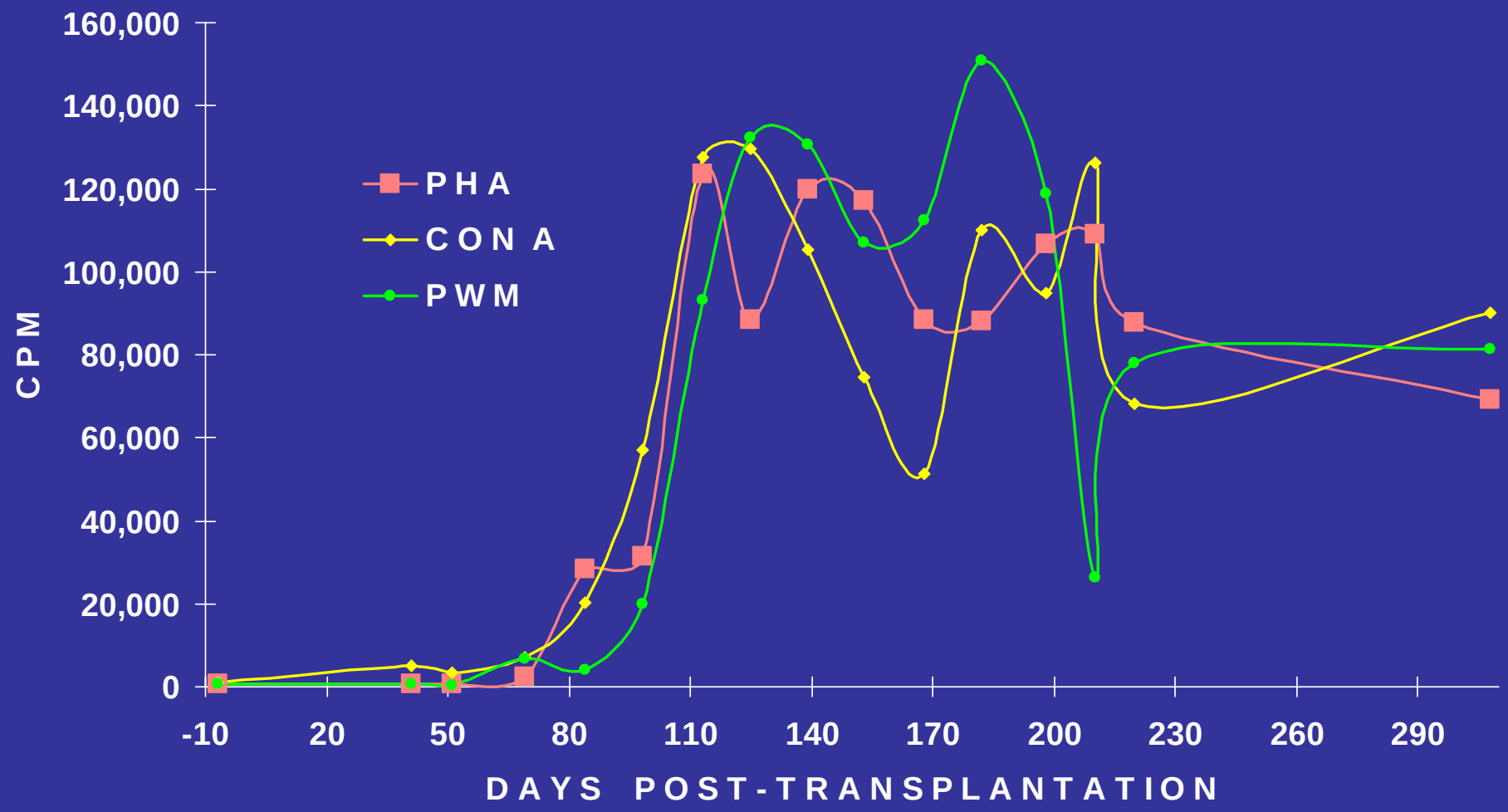
- Thymus is present but small (< 1 gram).
- Lacks corticomedullary distinction.
- Absence of thymocytes.
- Absence of Hassell's corpuscles.



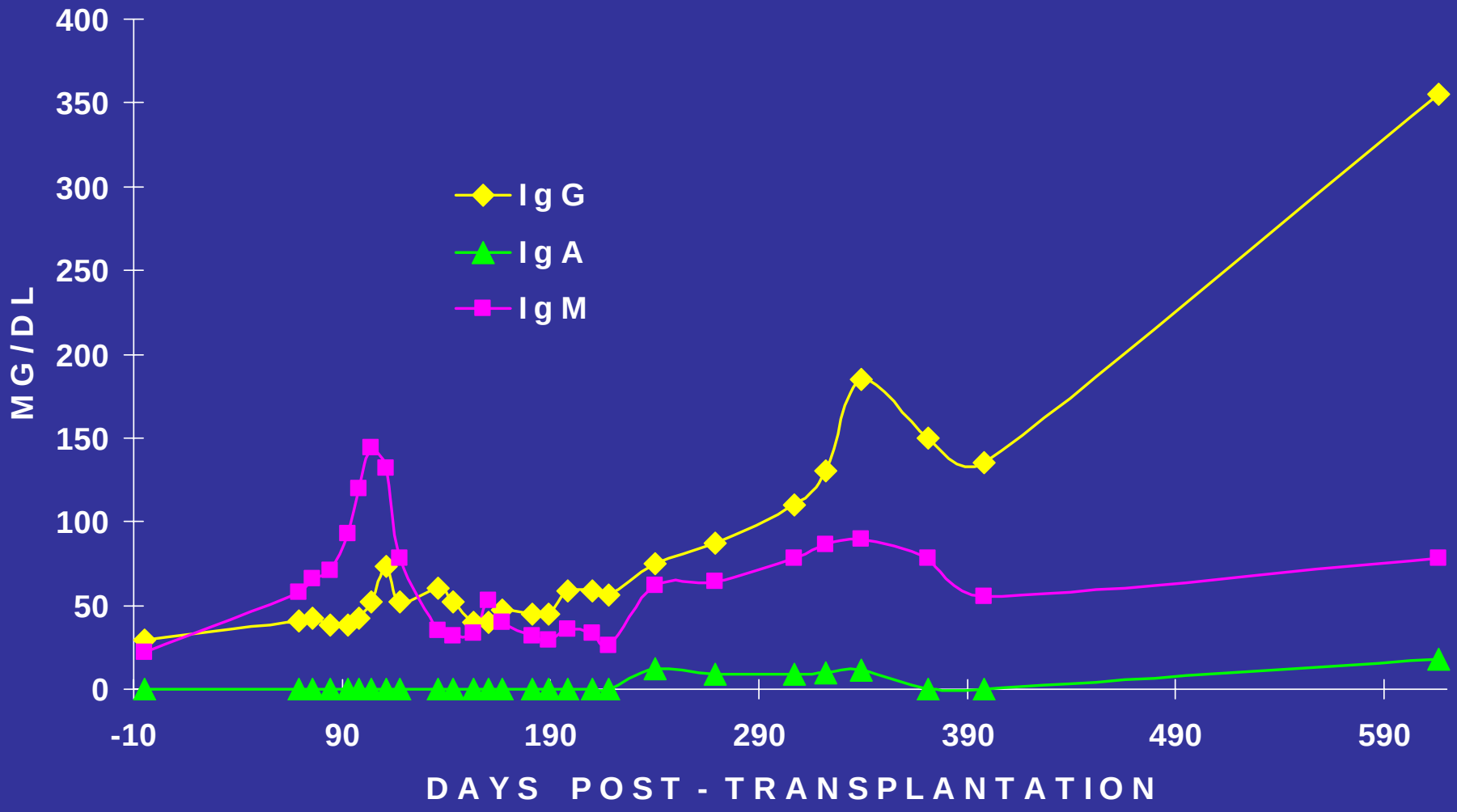
T Cell Development in a Jak3 Def SCID Patient after T Cell-Depleted Haploidentical Marrow Transplantation



Mitogen Responses in a Jak3 Def SCID after T Cell-Depleted Haploidentical Marrow Transplantation

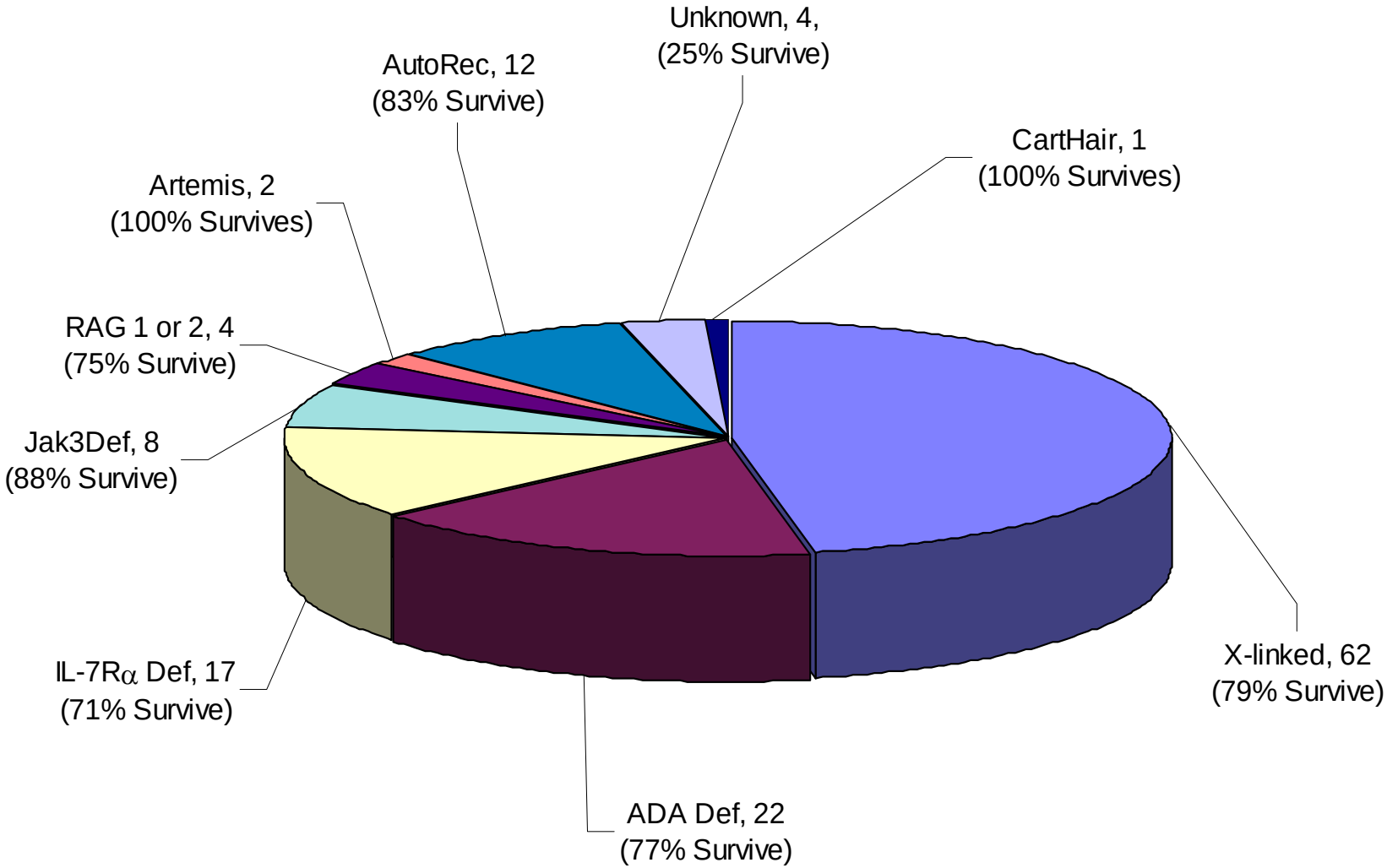


Immunoglobulins in a Jak3 Def SCID Patient after T Cell-Depleted Haploidentical Marrow Transplantation



Bone Marrow Transplantation for Severe Combined Immunodeficiency at Duke University Medical Center 5/19/82-3/15/05

- Number surviving: 109 of 141 or 77%.
- Survivors range from 1 month to 22.9 years post-transplantation.
- HLA-identical: 16 of 16 or 100%.
- HLA haploidentical: 93 of 125 or 74%.



Survival Rates by Genetic Type in 141 SCIDs Transplanted (125 Haplo, 16 Ident) at Duke University Medical Center, 1982-2005

Causes of Death in 32 SCIDs After Marrow Transplantation

CMV	8
Adenovirus	7
EBV /Lymphoma	4
Enterovirus, Rotovirus	3
Parainfluenza 3, Varicella	2 ea
Herpes simplex/RSV	1 ea
Candida sepsis	2
Pulmonary disease	2
Mitochondrial defect	1
Nephrotic syndrome/chemo	1
VOD	1

Lymphoproliferative Disorders in SCID*

- Incidence estimated at 1-5%. (4/141 or 2.8% EBV lymphoproliferative disease at Duke over 23 years).
- Mean age at diagnosis: 1.6 years; M:F =3.3:1
- Approximately 74% non-Hodgkin's lymphoma
- 9.5% Hodgkin's disease
- Carcinomas much less frequent
- Not always EBV +

* Elenitoba-Johnson KSJ & Jaffe ES: Seminars in Diagnostic Pathology 14: 35-47, 1997.

Immunodeficiency Transplant Survey: 1968-1997

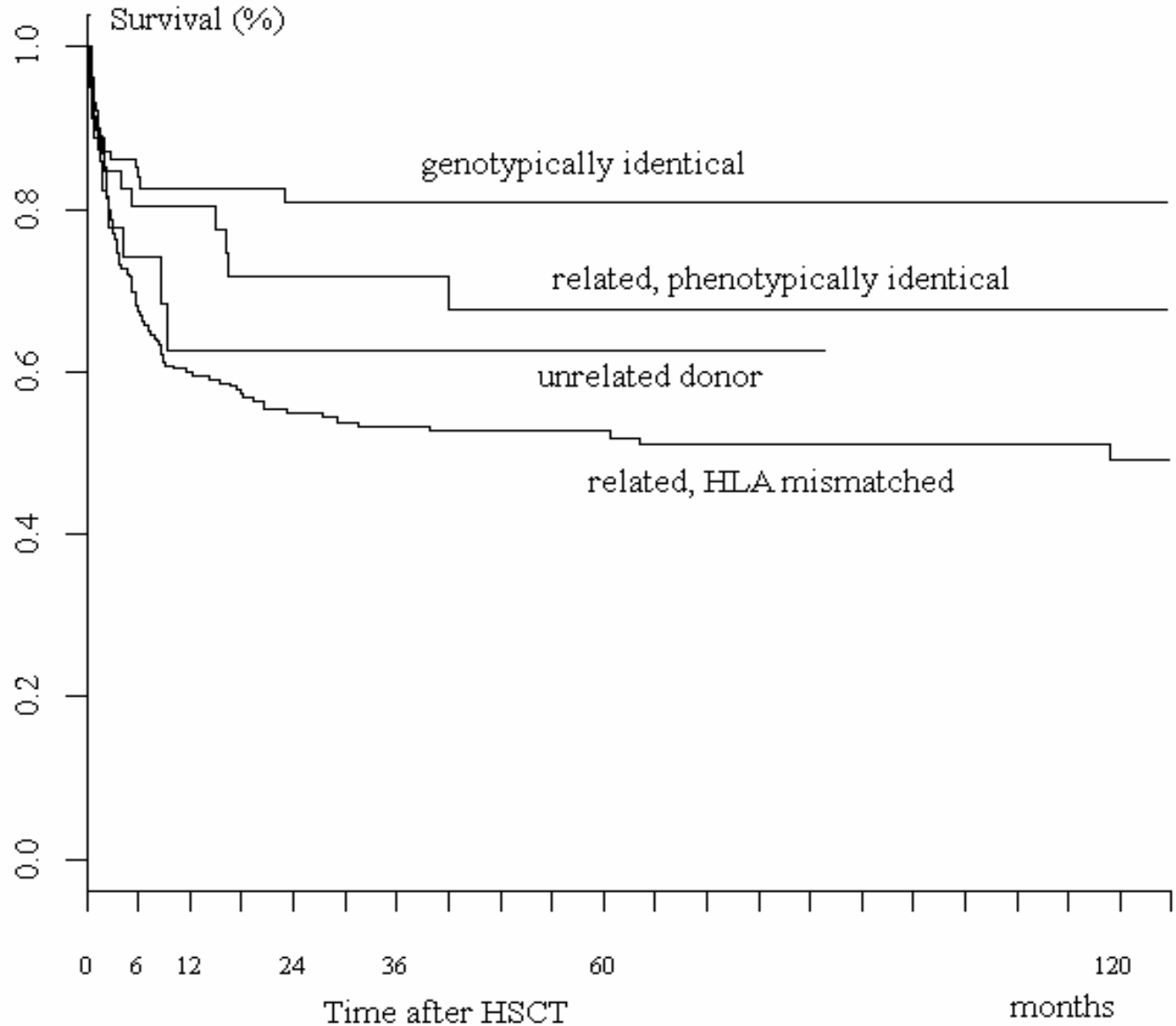
TYPE OF IMMUNE DEFECT:	TOTAL # PTS TRANSPL.	TOTAL # PTS SURV.	# WITH HLA-ID. DONOR	# PTS SURV.	# WITH HAPLO DONOR	# PTS SURV.	# WITH UNREL. DONOR	# PTS SURV.	# WITH CORD DONOR	# PTS SURV.
SCID	576	371	125	105	417	252	17	12	3	2
WISK.-ALD.	150	95	65	57	58	20	29	20	1	0
NEZELOF	53	25	13	10	35	12	2	0	3	3
O'MENN'S	39	18	9	8	24	7	6	3	0	0
LAD	27	21	7	6	18	13	2	2	1	0
MHC ANT.DEF.	24	13	8	4	20	7	2	2	0	0
CHED.-HIG.	20	16	11	10	4	0	5	5	0	0
DIGEORGE	11	2	3	2	3	0	0	0	0	0
CGD	11	6	8	4	0	0	3	2	0	0
PNP DEF.	8	4	5	2	2	2	1	0	0	0
CART-H HYP.	6	3	2	2	3	1	1	0	0	0
HYPER-IGM	6	3	2	1	3	1	1	1	0	0
ID. ALBINISM	6	3	6	3	0	0	0	0	0	0
XLP	5	2	5	2	0	0	0	0	0	0
OTHER	19	10	10	5	6	5	2	0	0	0
ALL DEFECTS	961	592	278	220	594	321	71	47	8	5
		62%		79%		54%		65%		63%

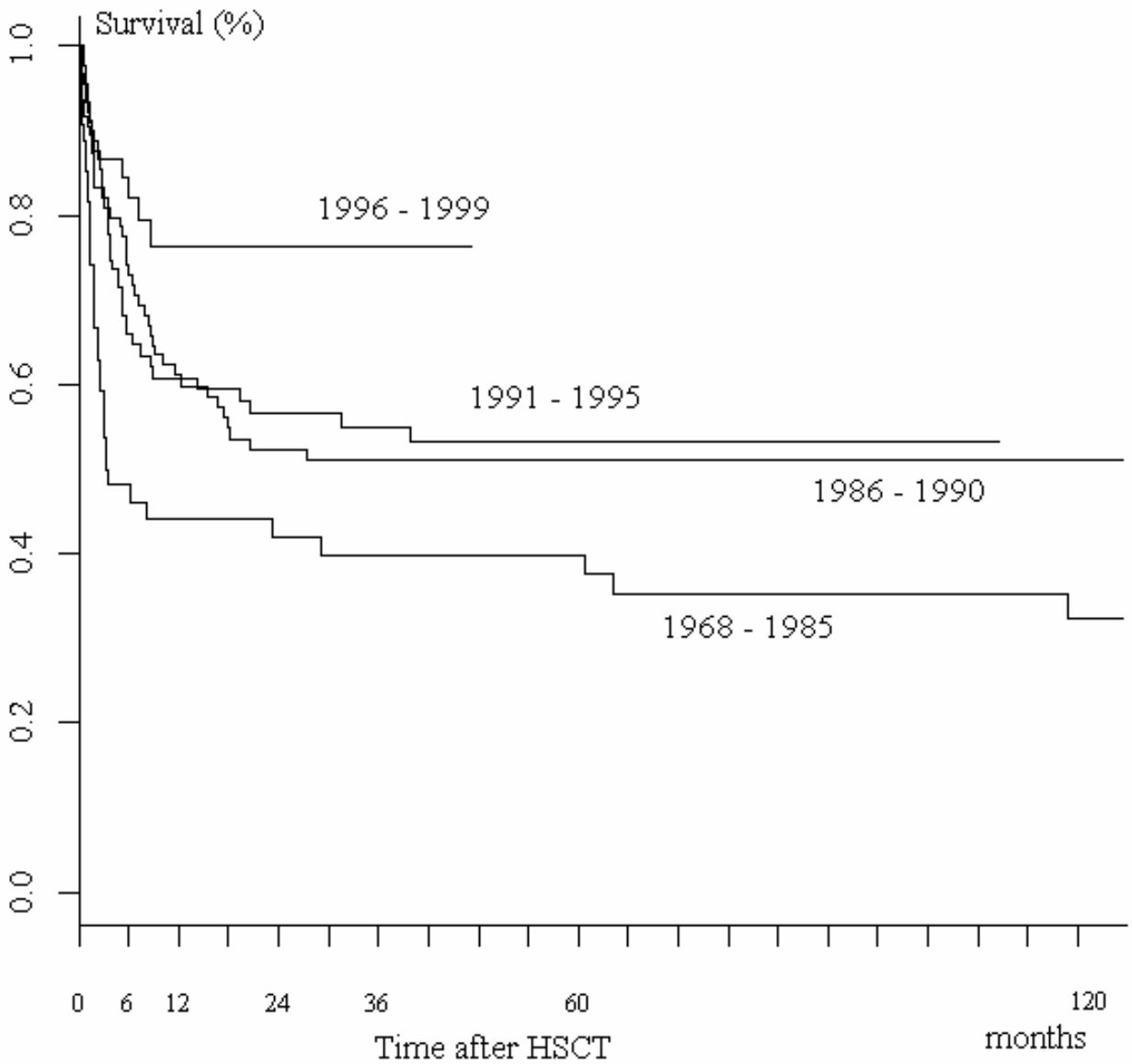
Survival Rates in SCID Transplants Performed At Centers Where Pre-Transplant Chemotherapy is Used in a Majority of Patients

Authors	Location	Total # SCIDs	Overall Survival
Haddad et al. 1998	European Soc. ID	193	48% N
Bertrand et al., 1999	European Soc. ID	178	52% N
Smogorzewska et al.,2000	LA Childrens	48	100% I vs 46% N
O'Marcaigh et al.2001	UCSF	16	100% I vs 55% N
Antoine et al., 2003	European Soc. ID	475	77% I vs 54% N

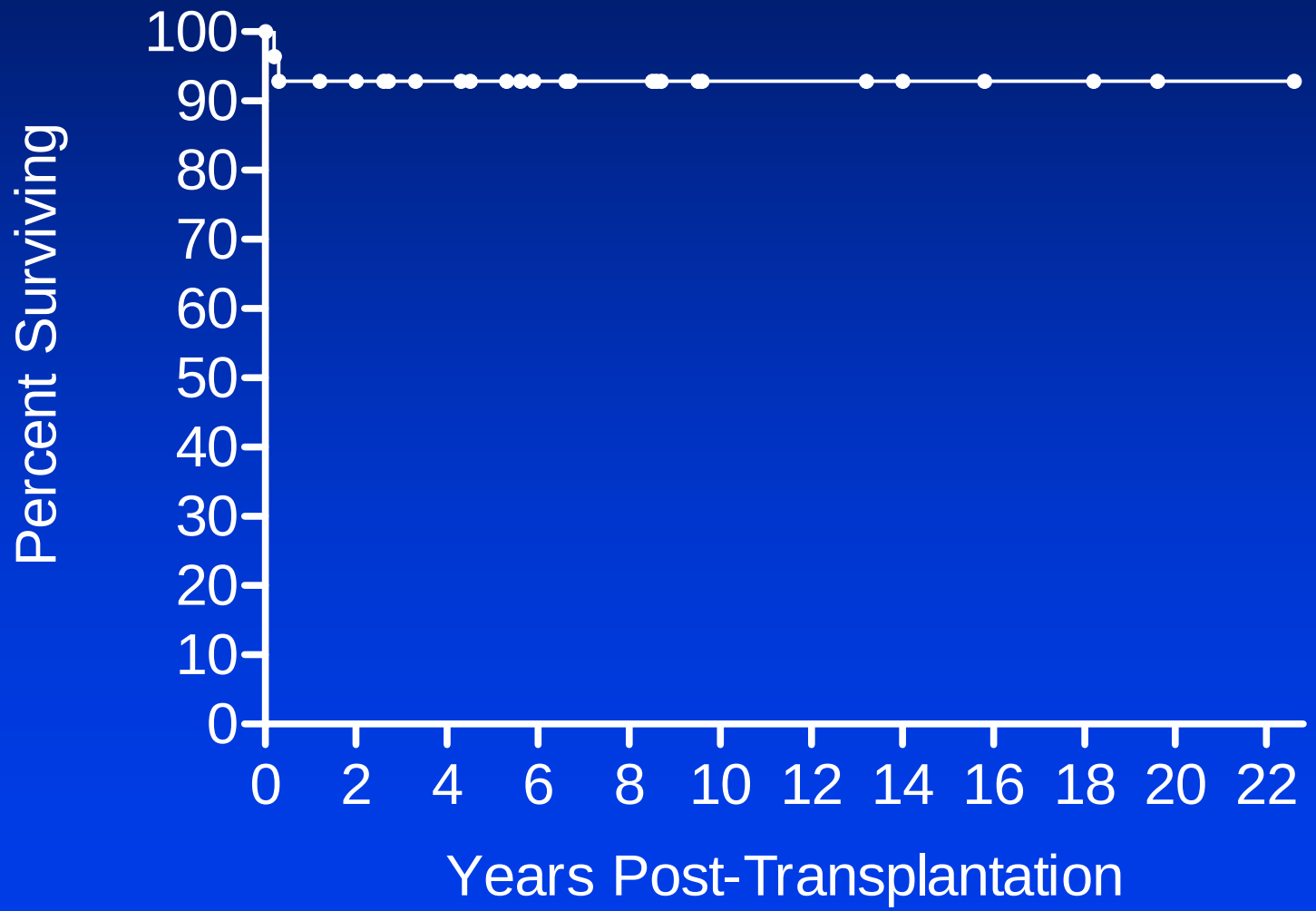
Survival Rates in SCIDs Transplanted Before 3.5 Months of Life

Authors	Location	Total # SCIDs	Overall Survival
Kane et al., 2001	Newcastle	13	100%
Myers et al., 2002	Duke	28	93%
Buckley et al., 2005	Duke	39	95%

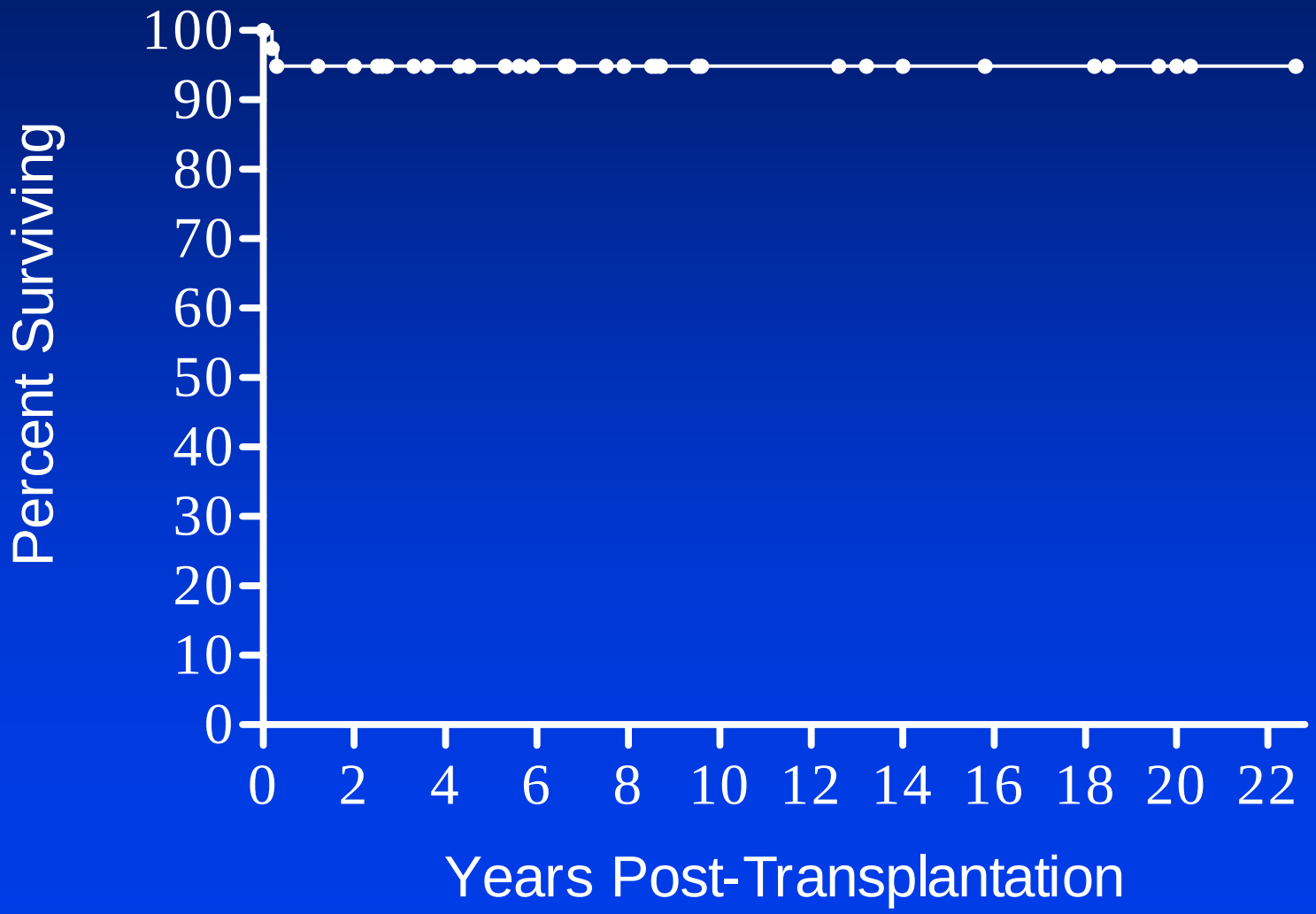

Survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
genotypically identical
related, phenotypically identical
unrelated donor
related, HLA mismatched
0
6
12
24
36
60
120
Time after HSCT
months


Survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
1996 - 1999
1991 - 1995
1986 - 1990
1968 - 1985
0
6
12
24
36
60
120
Time after HSCT
months

Kaplan Meier Plot of 28 SCIDs Transplanted in the Neonatal Period



Kaplan Meier Plot of 39 SCIDs Transplanted in the First 3.5 Months of Life

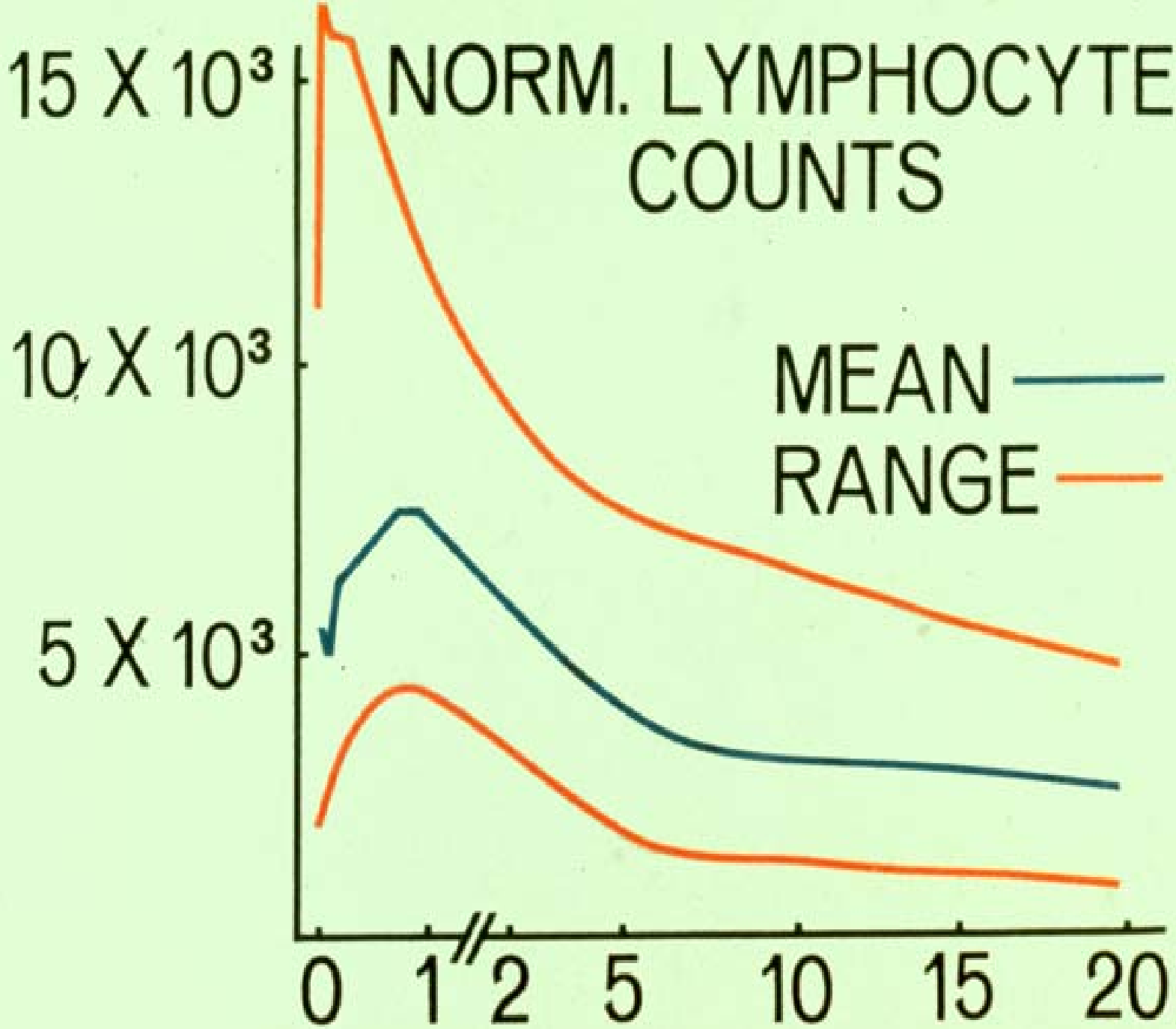


Immune Function After Bone Marrow Transplantation

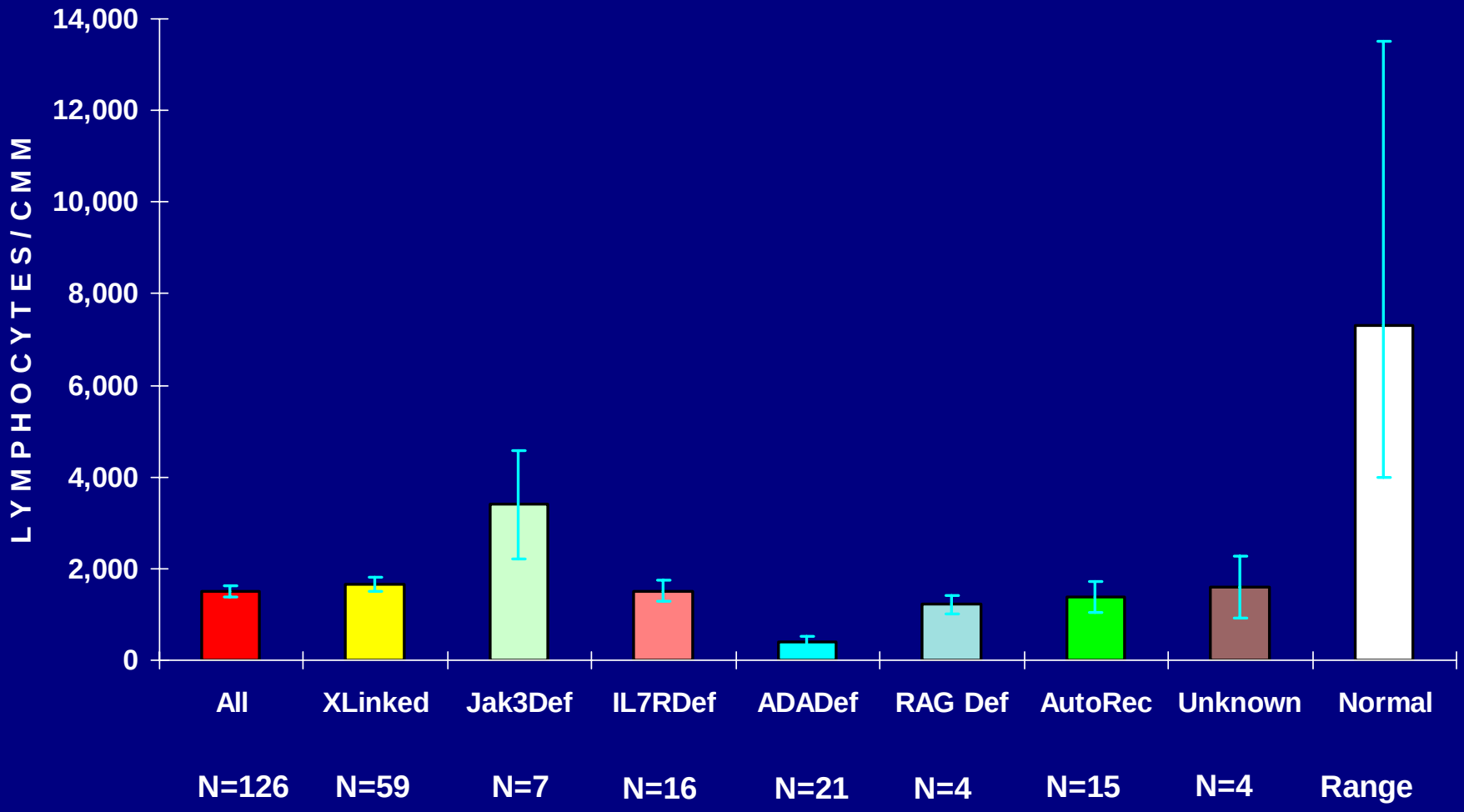
- 100/109 surviving patients transplanted at Duke are T cell chimeras
- 9 patients not chimeric
  - 7/22 ADA deficient SCIDs; 2 have undergone successful gene therapy in Italy, and 5 are on PEG-ADA.
  - 1 X-linked, 1 RAG1-deficient.
- 30/109 have donor B cells; 58/109 on IVIG.

SCID : Characteristics Common to All Types

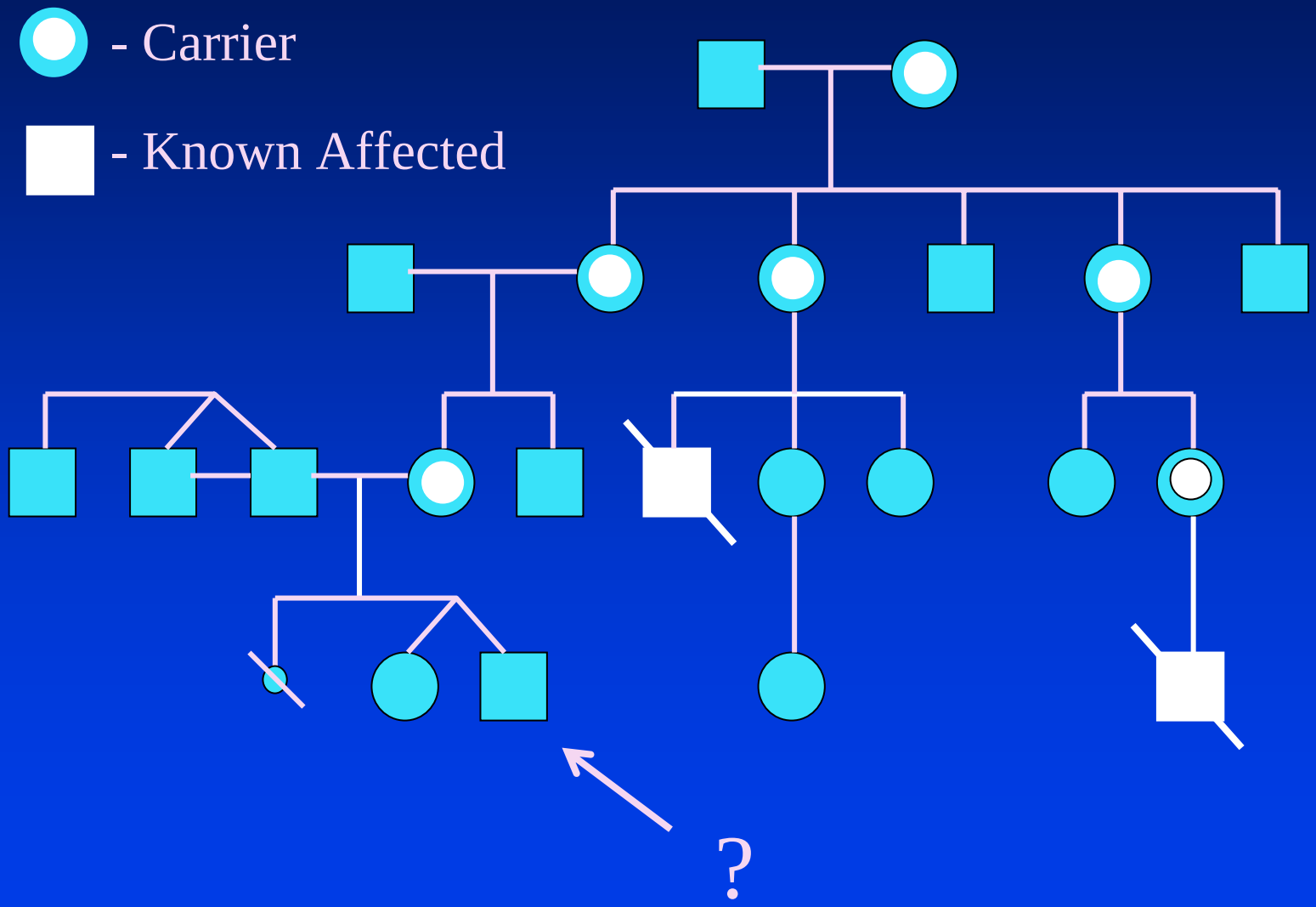
- Lymphopenia.
- May have persistence of transplacentally acquired maternal T lymphocytes.


NORM. LYMPHOCYTE COUNTS
15 X 10³
10 X 10³
5 X 10³
MEAN
RANGE
0
1
2
5
10
15
20

Mean Absolute Lymphocyte Counts in 126 SCIDs Pre-Transplantation



XSCID Pedigree



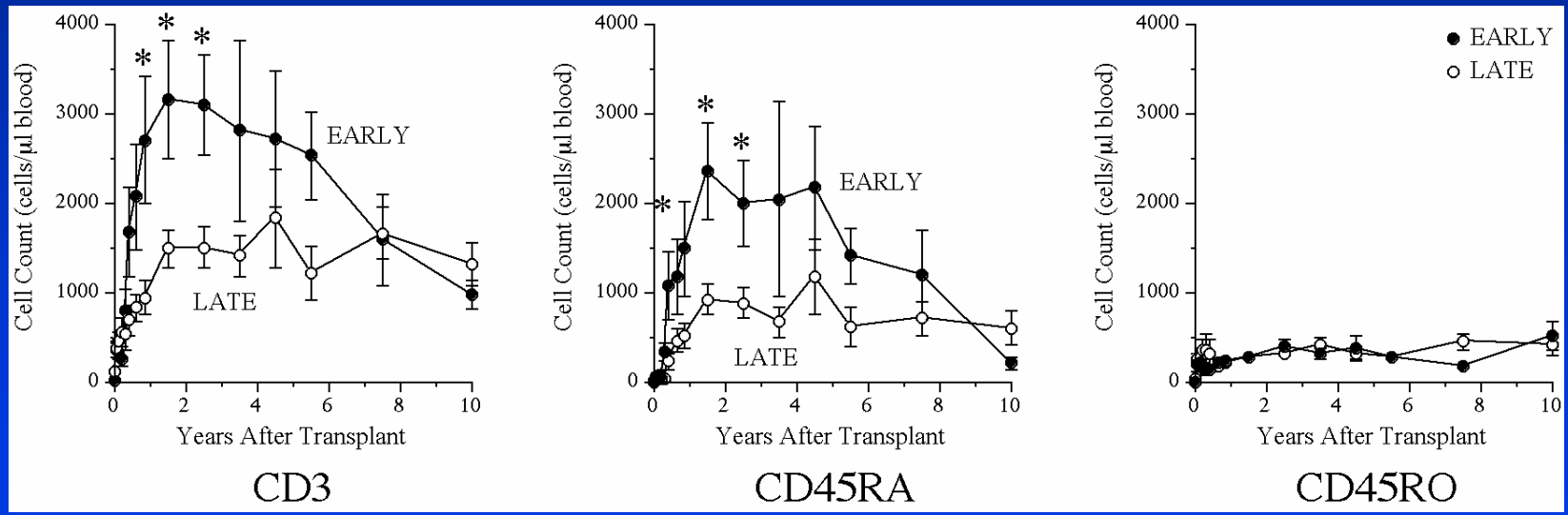
Cord Blood White Cells

Parameter	Boy	Girl	Normal
WBC	6,700	17,700	18,100 (9,000 -30,000)
Absolute lymphocyte count	2,211	5,133	5,500 (2,000-11,000)

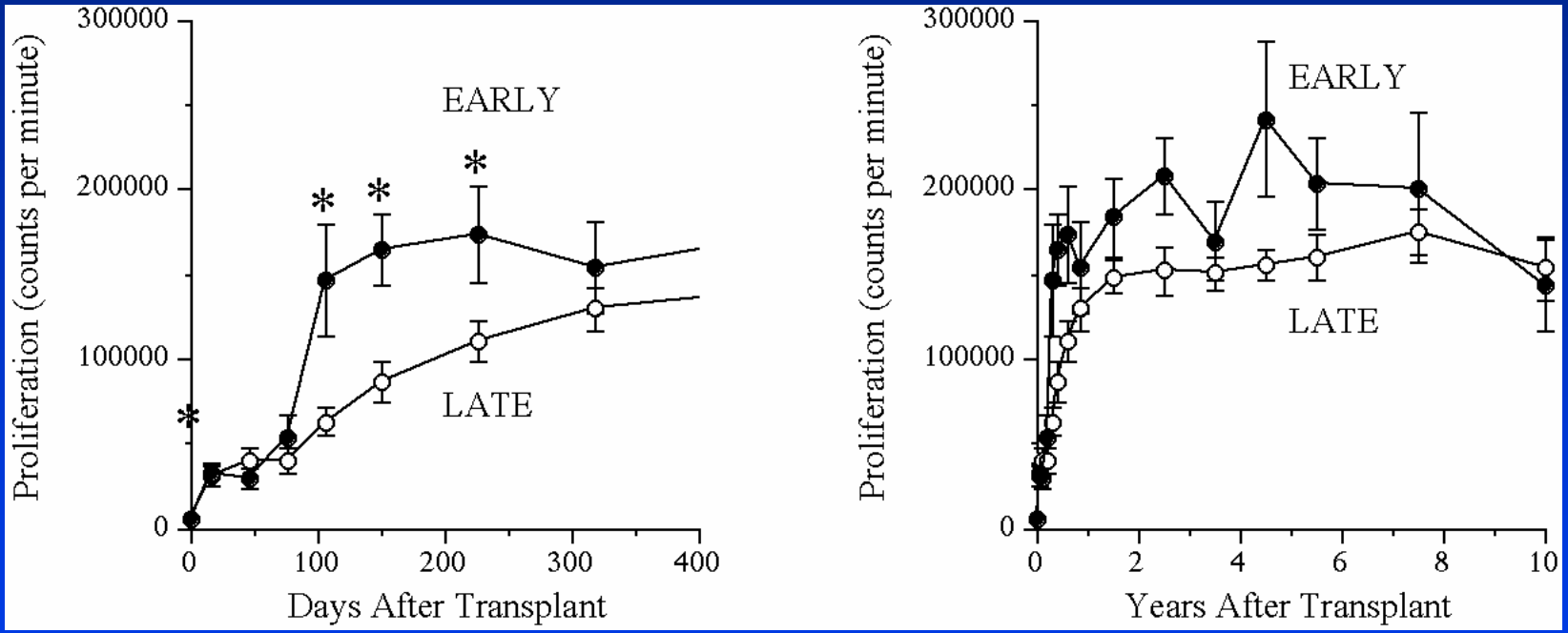
Flow Cytometry (cells/mm^3)

Subtype	Boy	Girl	Normal
CD3+ T Cells	23	1687	4072 (1481-8145)
CD4+ T Cells	3	1266	2475 (900-3424)
CD8+ T Cells	7	590	1581 (172-2309)
NK Cells	11	502	557 (203-1114)
B Cells	1198	886	527 (192-1055)

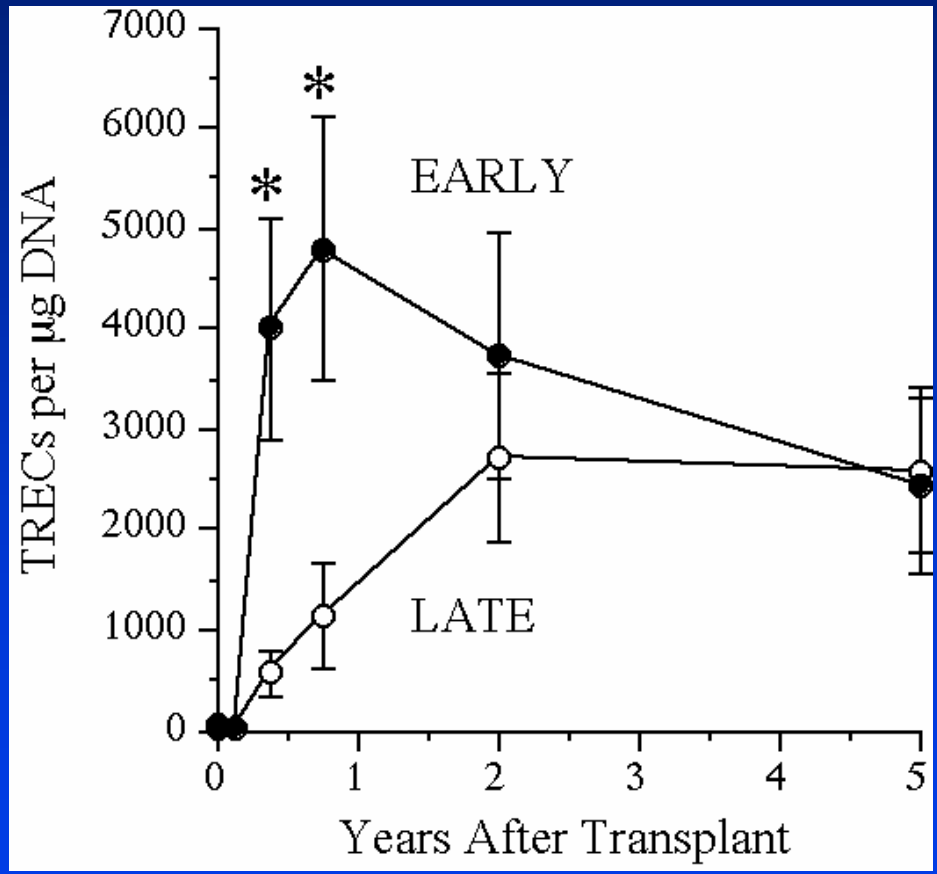
Total (CD3+), Naïve (CD45RA+) and Memory (CD45RO+) T Cells of SCIDs Transplanted in the Neonatal Period (Early) Compared with Those Transplanted beyond that Period (Late)

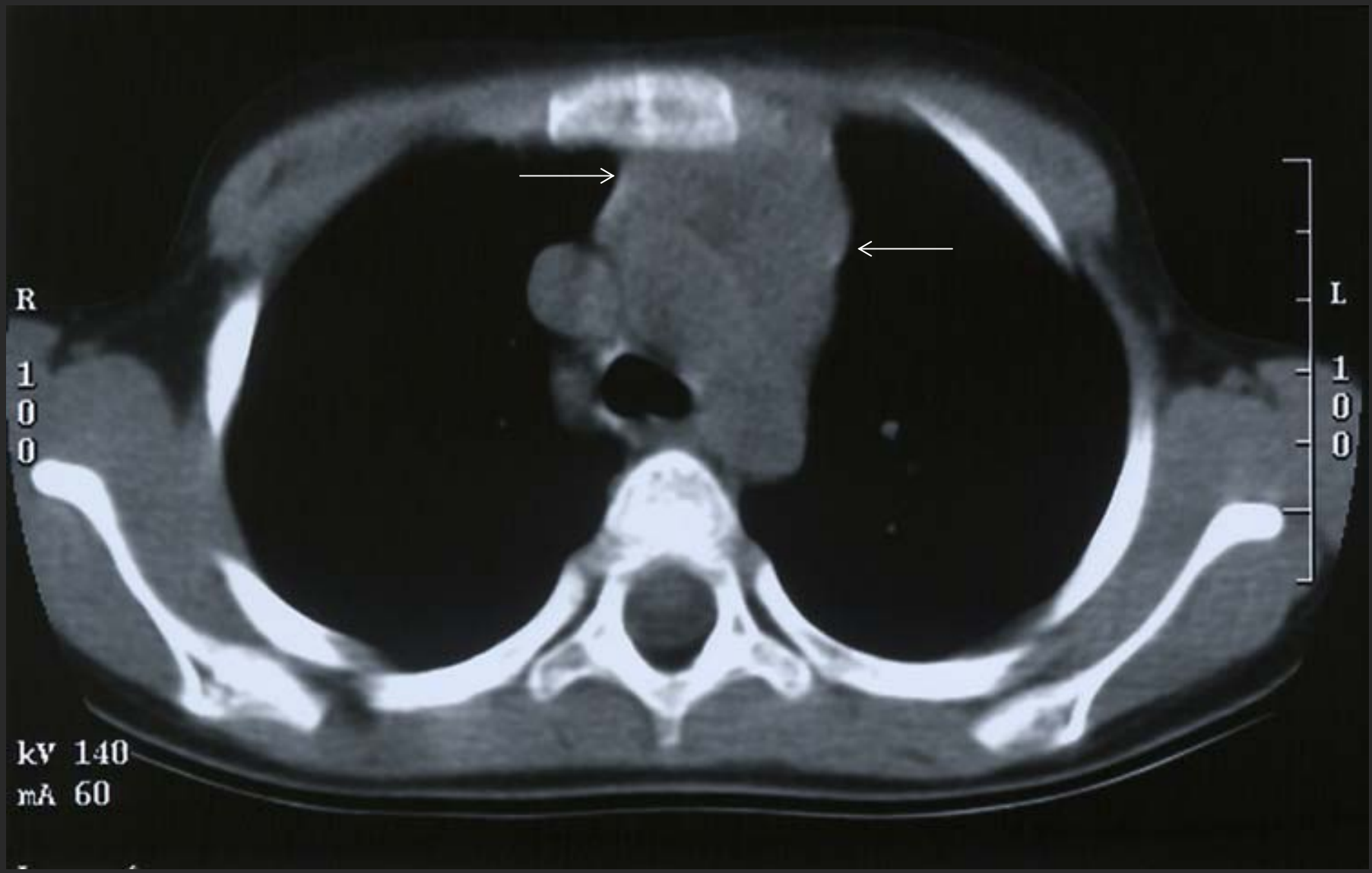


Responses to PHA by Lymphocytes of SCIDs Transplanted in the Neonatal Period (Early) Compared with Those Transplanted beyond that Period (Late)

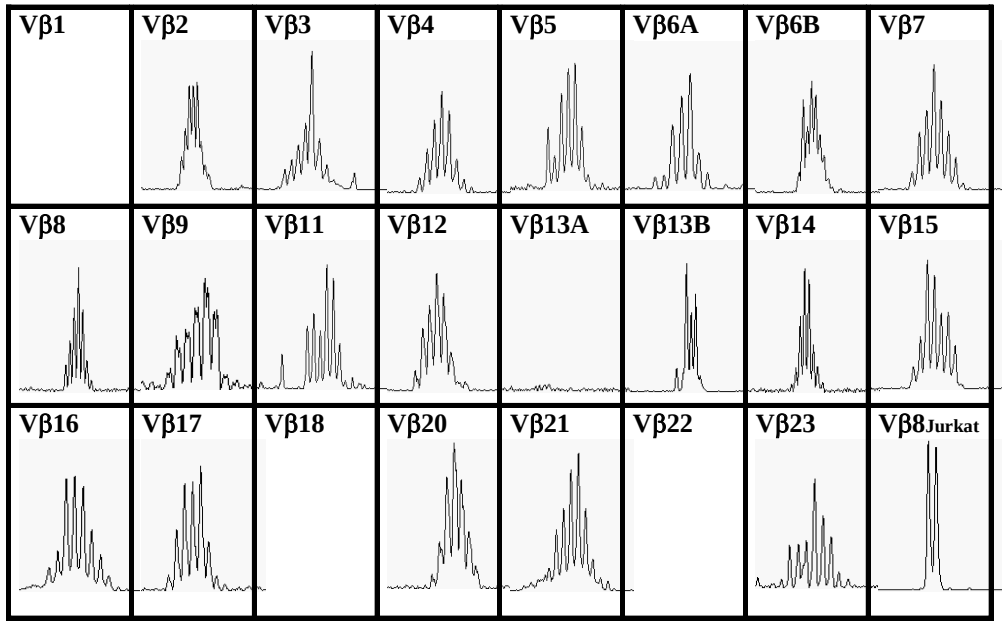


Thymic Output of SCIDs Transplanted in the Neonatal Period (Early) Compared with Those Transplanted beyond that Period (Late)

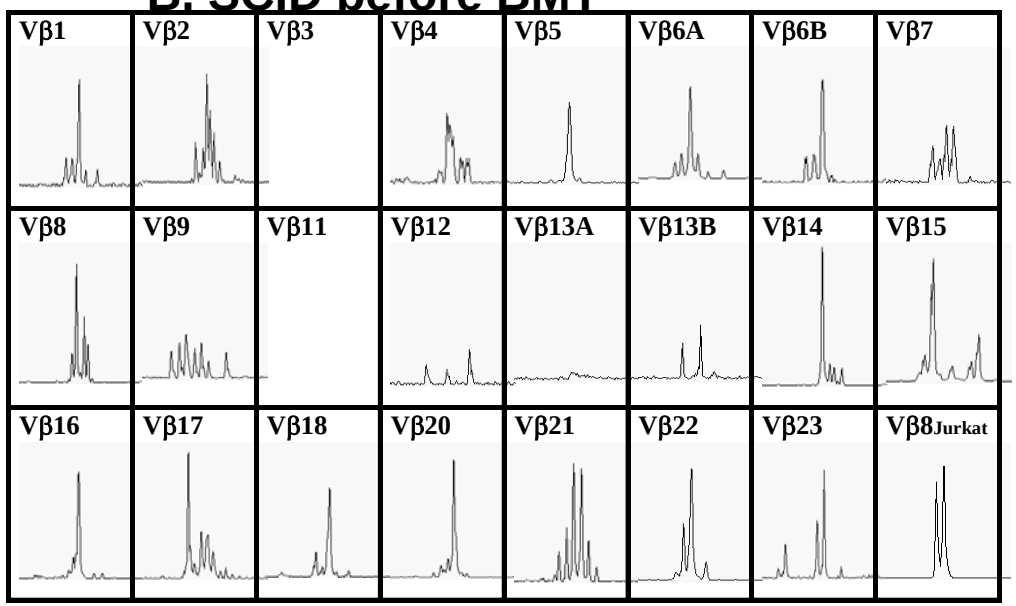



R
100
L
100
kV 140
mA 60

A. Normal control

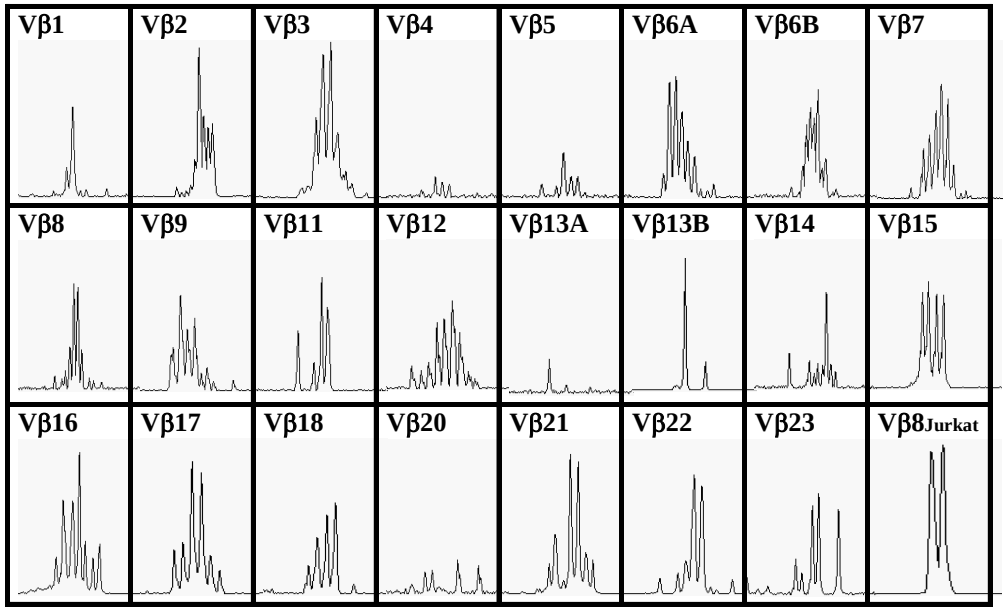


B. SCID before BMT

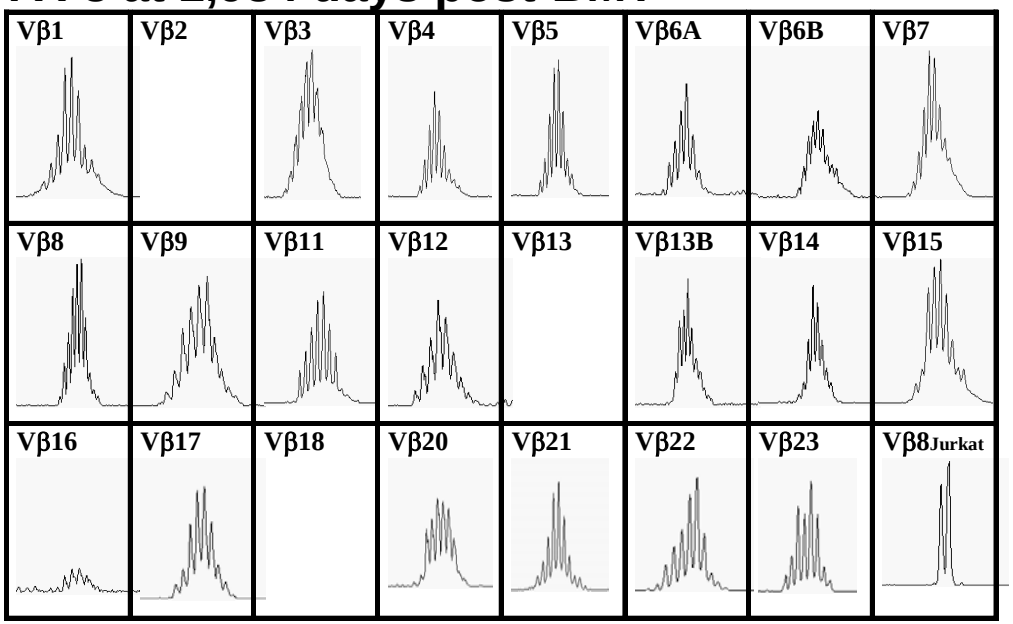


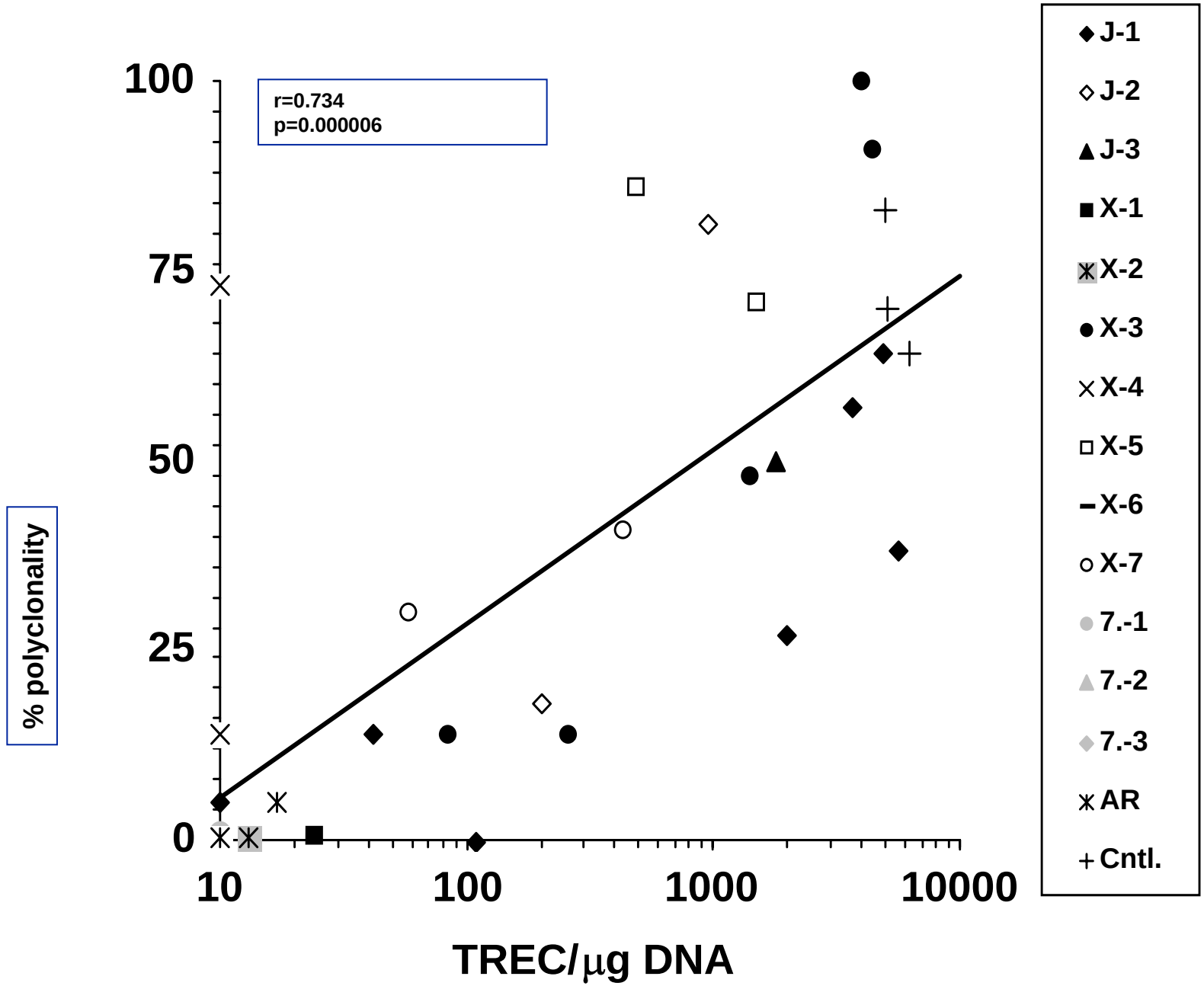
Sarzotti,M et al, JI,
270: 2711-2718, 2003

A. X-3 at 218 days post-BMT



B. X-3 at 1,984 days post-BMT




r=0.734
p=0.000006
100
75
50
25
0
% polyclonality
10
100
1000
10000
TREC/μg DNA
J-1
J-2
J-3
X-1
X-2
X-3
X-4
X-5
X-6
X-7
7.-1
7.-2
7.-3
AR
Cntl.

Factors Affecting Stem Cell Therapy in SCID

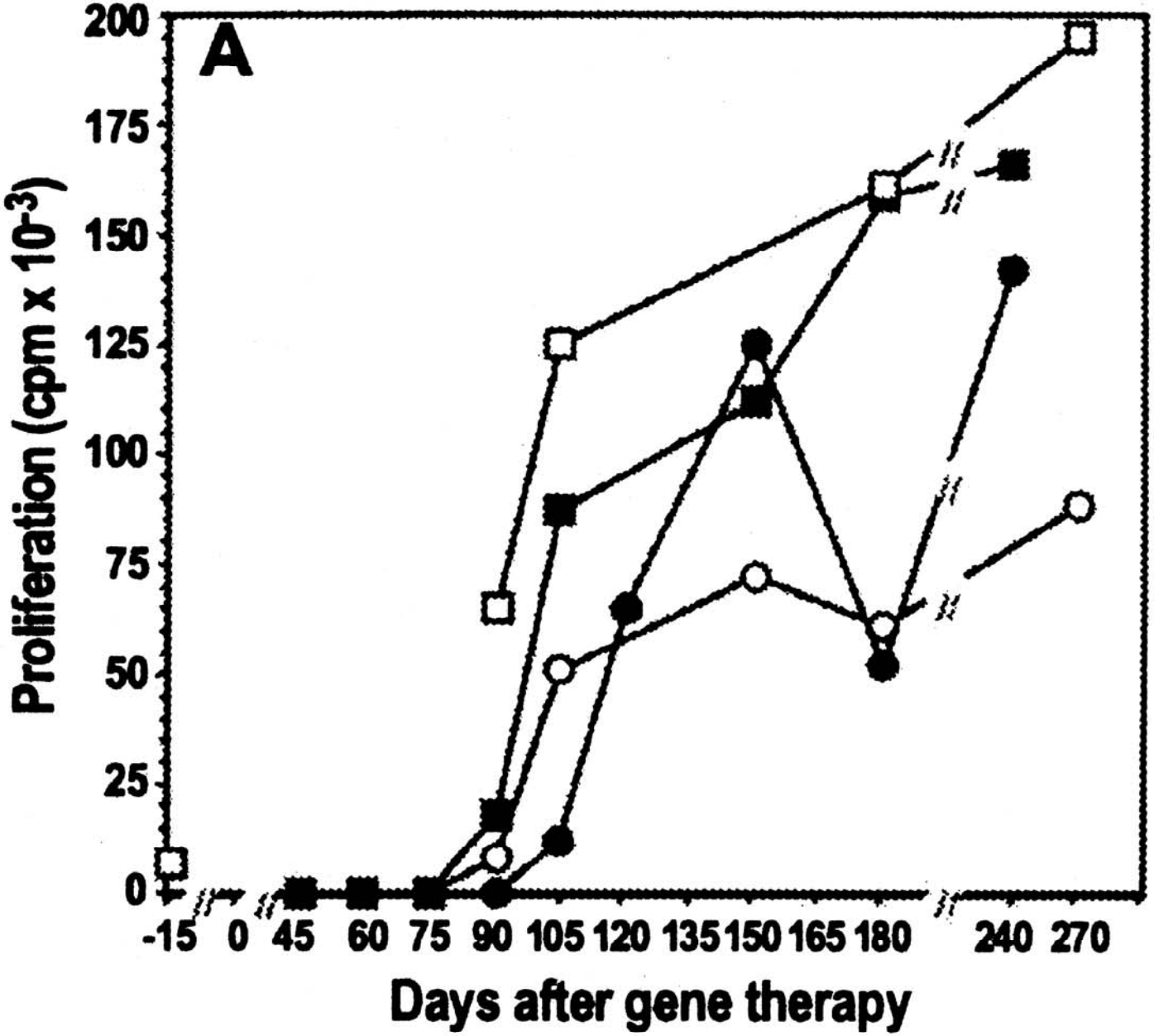
- Viral Infections
- Age at Transplantation: first 3.5 months of life best
- Genetic Types of SCID: Resistance to engraftment in ADA-deficient and RAG SCIDs
- B Cell Function best in IL-7Rα, CD3δ, CD3ε and ADA-deficient SCIDs
- Pre-transplant NK cells in IL-7Rα, CD3δ and CD3ε-deficient SCIDs do not interfere with engraftment
- Donor-derived NK cells disappear in X-linked and Jak3-deficient SCIDs post-transplantation

Summary of B Cell Function

SCID Type	# w Nl Igs	# w Donor B	# on IVIG
X-linked, N=49	15 (31%)	20 (41%)	37 (76%)
Jak3-Def, N=7	3 (43%)	3 (43%)	4 (57%)
IL-7Rα-Def, N=11	11 (100%)	2 (18%)	3 (27%)
ADA-Def, N=17	13 (93%)	5 (36%)	7 (41%)
RAG 1 or 2, N=3	1 (33%)	1 (33%)	2 (67%)
AutoRec, N=14	6 (43%)	3 (21%)	7 (50%)
Unknown N=1	1 (100%)	1 (100%)	0

Conclusions

- SCID is a pediatric emergency, and the potential exists to diagnose this condition routinely at birth.
- If a stem cell transplant from a relative can be done in the first 3.5 months of life, before infections develop, there is a high (>95 percent) probability of success.
- T cell-depleted haploidentical marrow transplantation provides life-saving therapy for all forms of SCID, but it is not a perfect treatment.
- The initial success with gene therapy offered hope that the remaining defects in these chimeras could eventually be correctable by that means.


A
200
175
150
125
100
75
50
25
0
Proliferation (cpm x 10-3)
-15
0
45
60
75
90
105
120
135
150
165
180
240
270
Days after gene therapy