

# Recombinant Advisory Committee Meeting December 4, 2008

- Update on Bone Marrow Transplantation for X-linked Severe Combined Immunodeficiency (X-SCID) at Duke University Medical Center

Rebecca H. Buckley, M.D.

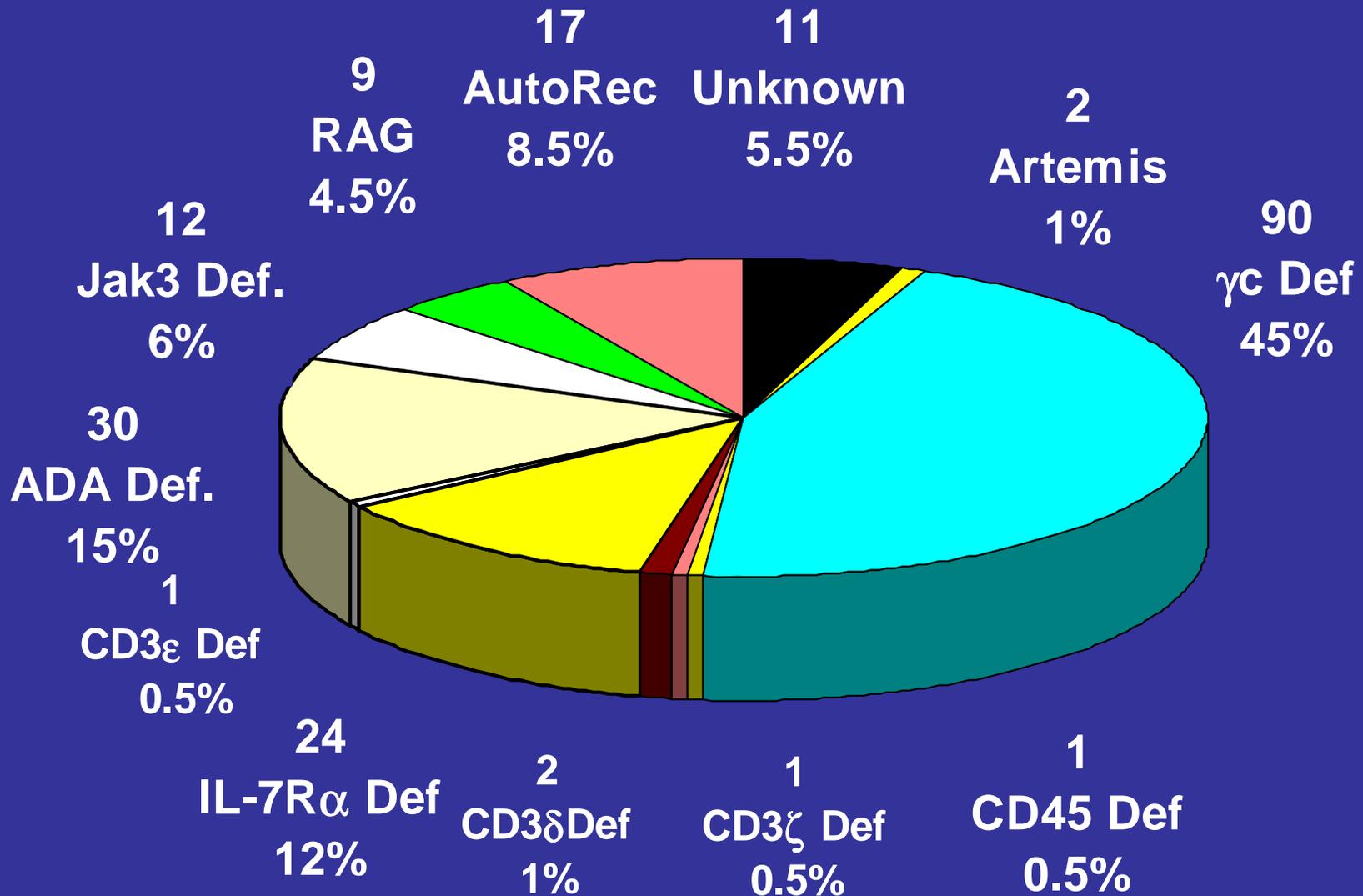
# Human Severe Combined Immunodeficiency (SCID)

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

# Twelve Abnormal Genes in SCID

- Cytokine Receptor Genes
  - *IL2RG*
  - *JAK3*
  - *IL7R $\alpha$*
- Antigen Receptor Genes
  - *RAG1*
  - *RAG2*
  - *Artemis*
  - *Ligase 4*
  - *CD3 $\delta$*
  - *CD3 $\epsilon$*
  - *CD3 $\zeta$*
- Other Genes
  - *ADA*
  - *CD45*

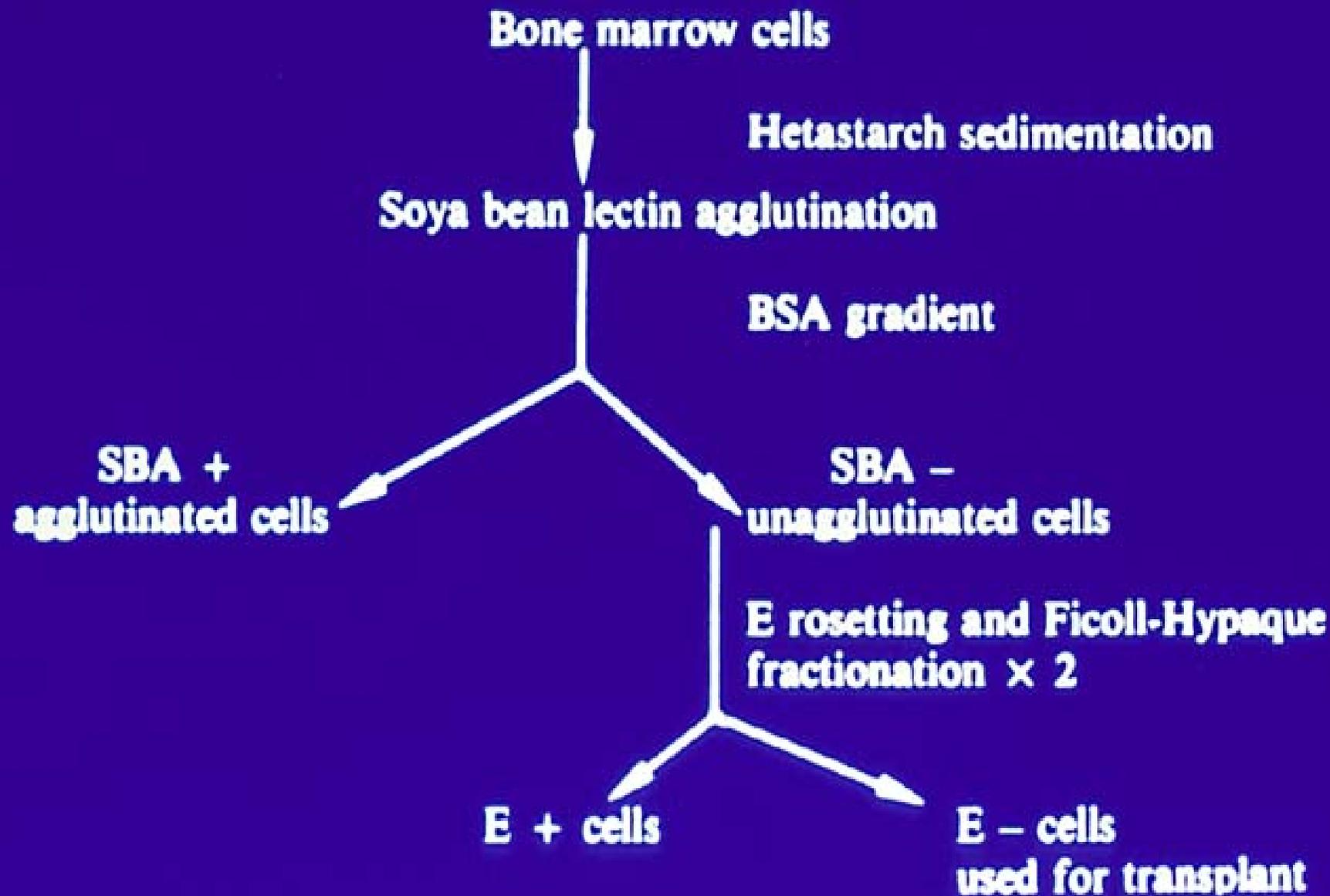
# 200 SCIDs: Genetic Types

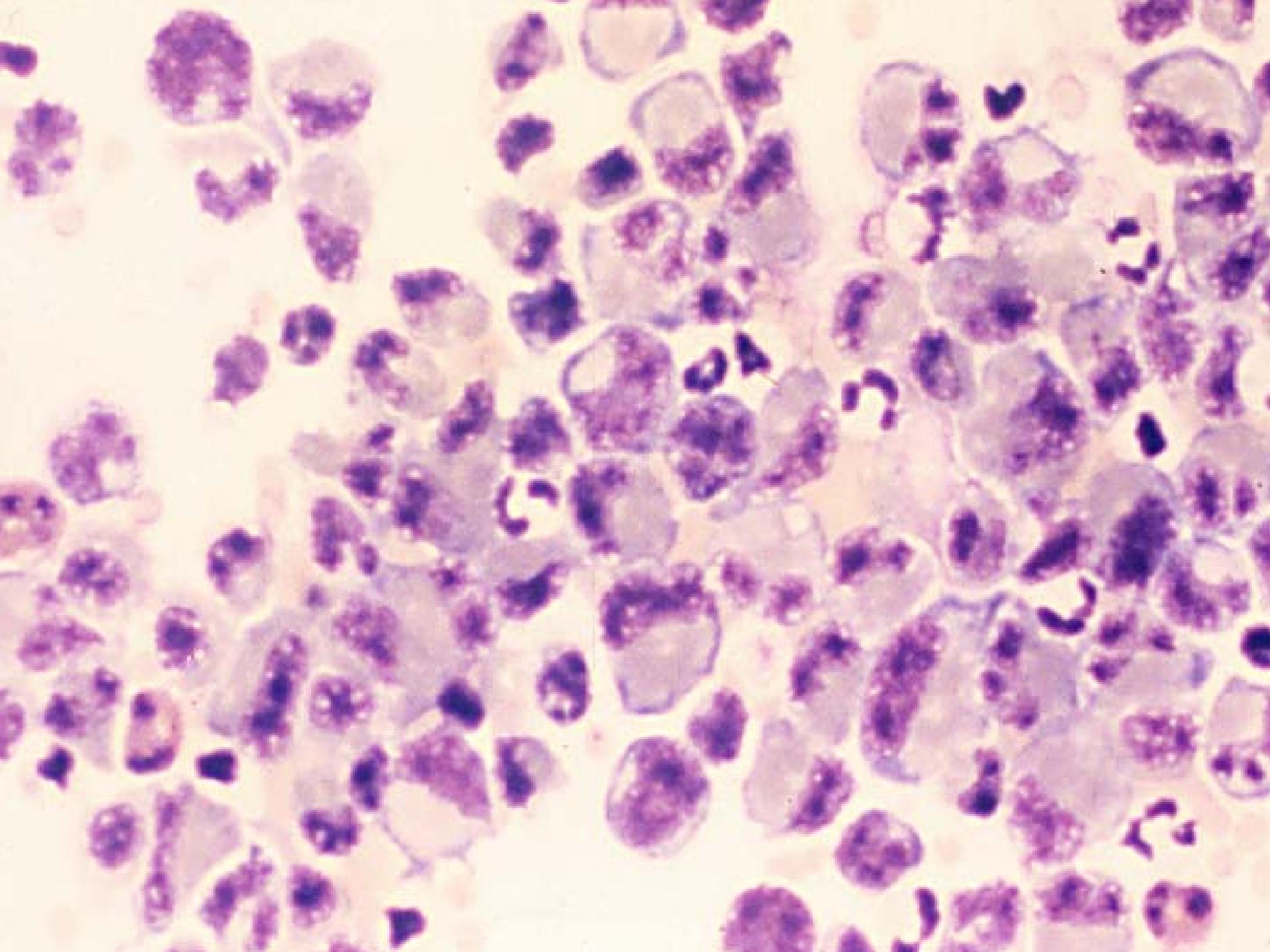


# SCID : Characteristics Common to All Types

- Known since 1968 that SCID can be treated successfully by bone marrow transplantation. They don't have any T cells, so there is no need for pre-transplant chemotherapy.
- Until 27 years ago this required strict HLA identity between donor and recipient to avoid lethal graft-versus-host disease (GVHD) .
- Now possible to avoid this by rigorous T cell depletion of the donor marrow, which allows use of half-matched parental donors and the omission of immunosuppressive GVHD prophylactic drugs.

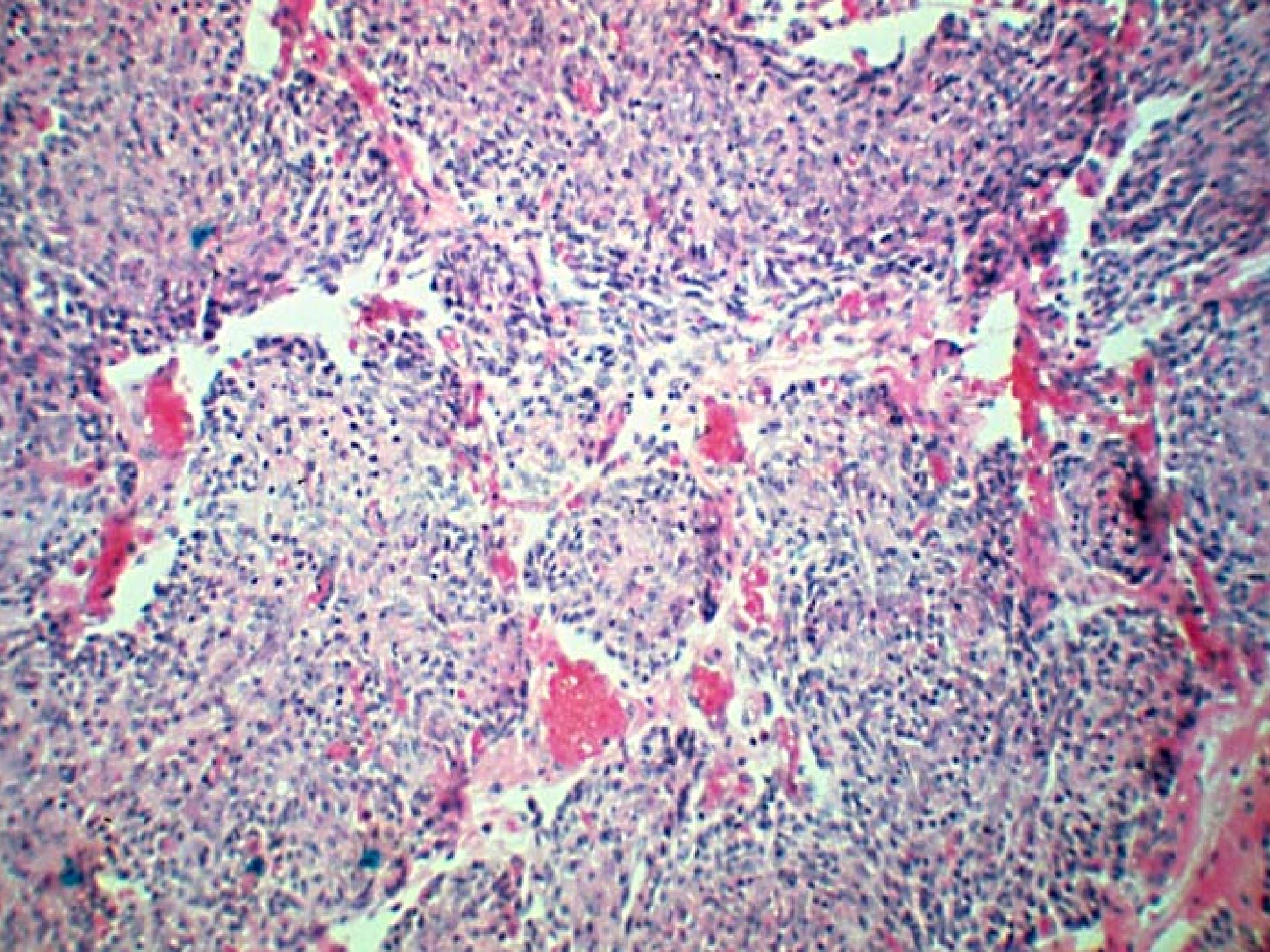




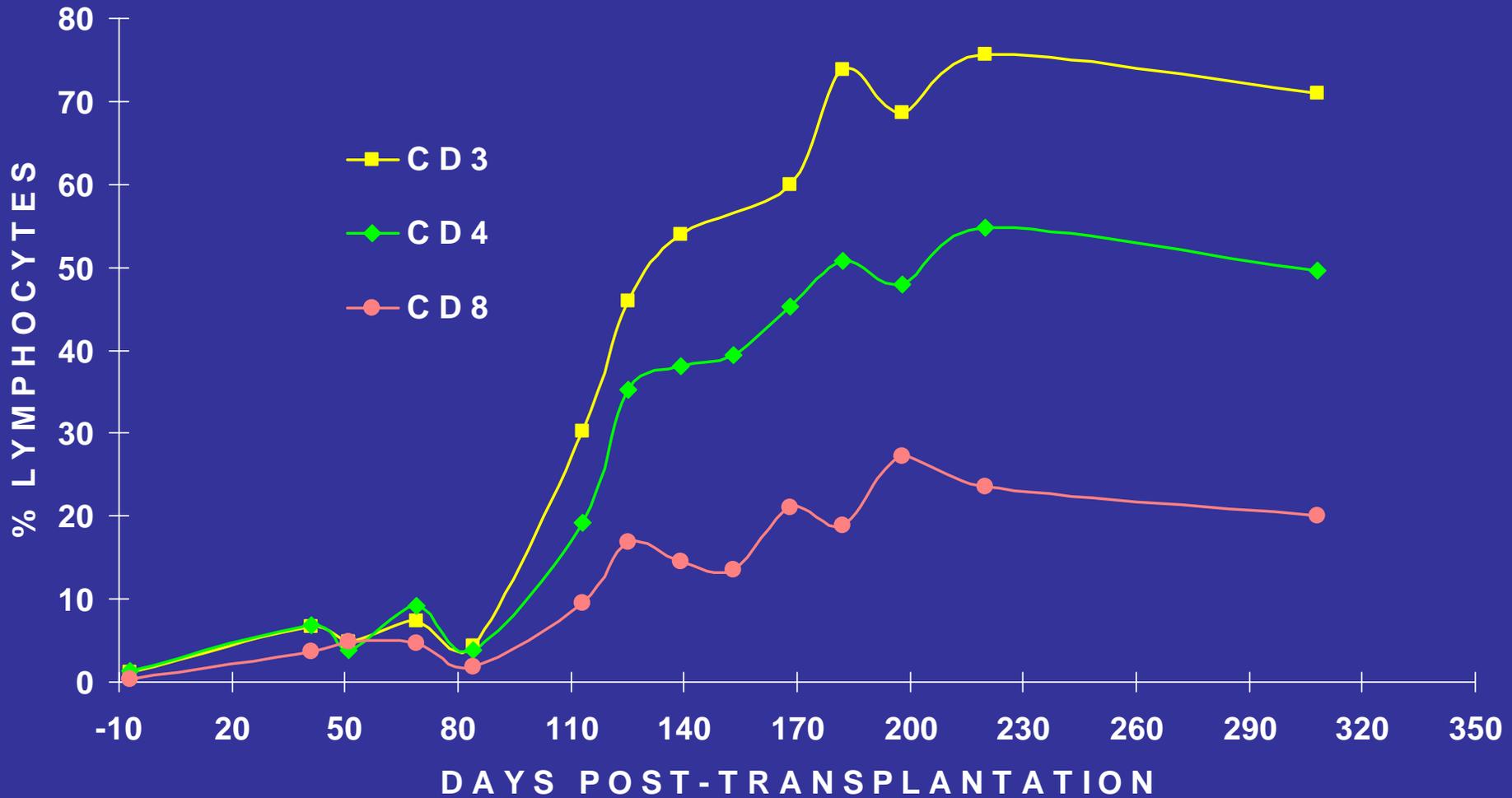


# SCID : Characteristics Common to All Types

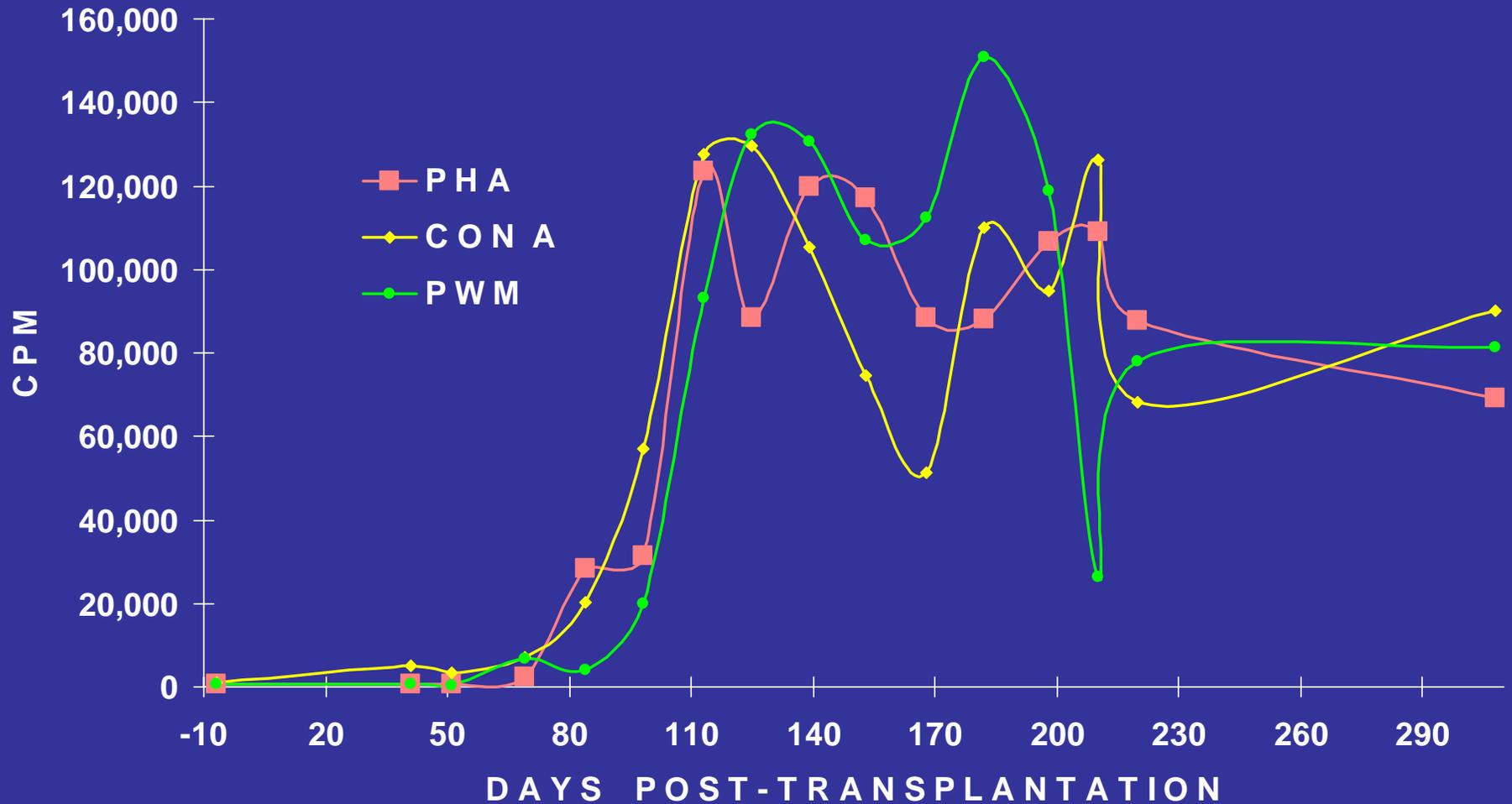
- Thymus is present but small (< 1 gram).
- Lacks corticomedullary distinction.
- Absence of thymocytes.
- Absence of Hassell's corpuscles.



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



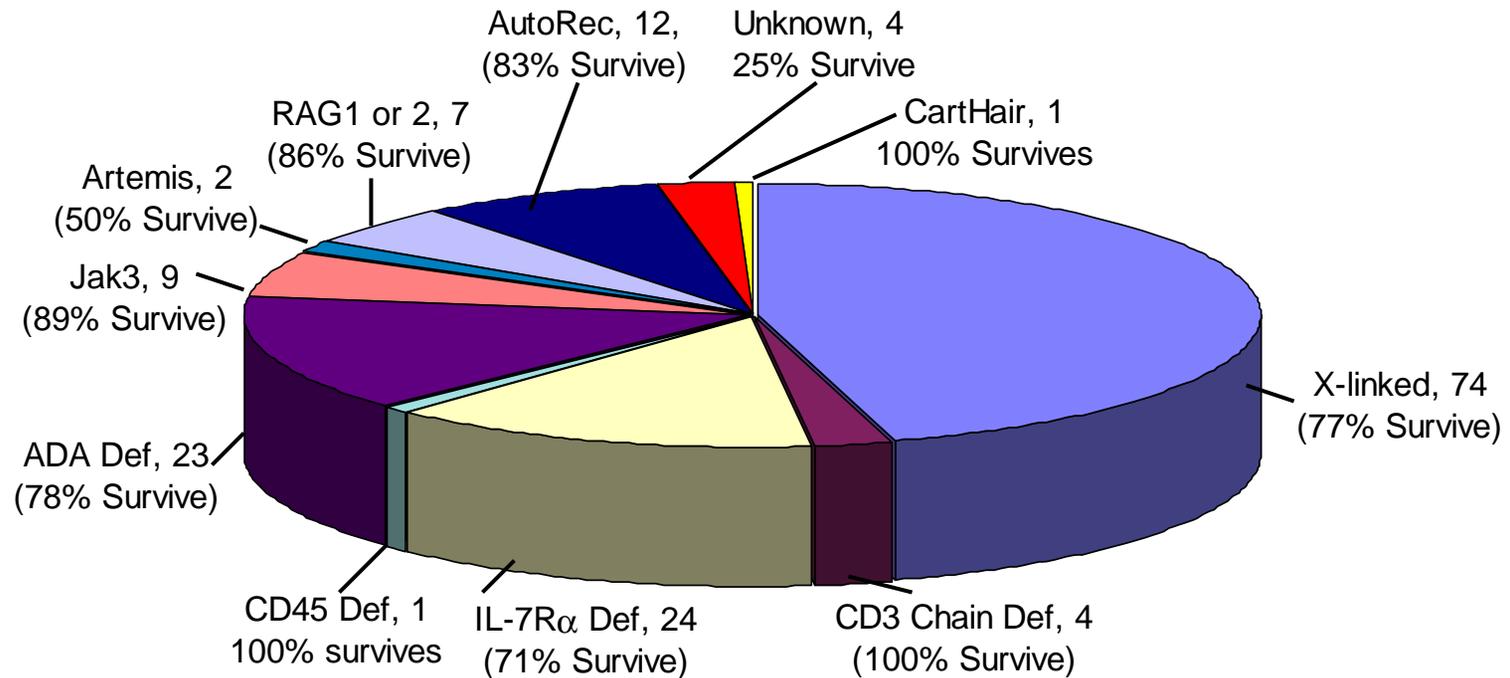
# Mitogen Responses in a Jak3 Def SCID after T Cell-Depleted Haploidentical Marrow Transplantation



# Bone Marrow Transplantation\* for Severe Combined Immunodeficiency at Duke University Medical Center 5/19/82-12/4/08

- Number surviving: 125 of 162 or 77%.
- Survivors range from 2 months to 26.5 years post-transplantation.
- HLA-identical: 16 of 16 or 100%.
- HLA haploidentical: 109 of 146 or 75%.
- When transplanted before 3.5 months of life, 45/48 (94%) survive up to 26.5 years.

\* Non-ablated; related donors.



Survival of 162 Transplanted SCIDs by Molecular Type,  
 1982-2008: 146 had HLA Haplo-identical Parental Donors,  
 16 Identical Donors, No Pre-Transplant Conditioning

# Causes of Death in 37 SCIDs After Marrow Transplantation

- CMV 8
- Adenovirus 8
- EBV /Lymphoma 6
- Enterovirus, Rotovirus 4
- Parainfluenza 3, Varicella 3, 2
- Herpes simplex/RSV 1 ea
- Pulmonary disease 4
- Candida sepsis 2
- Mitochondrial defect 1
- Nephrotic syndrome/chemo 1
- VOD 1
- GVHD 0

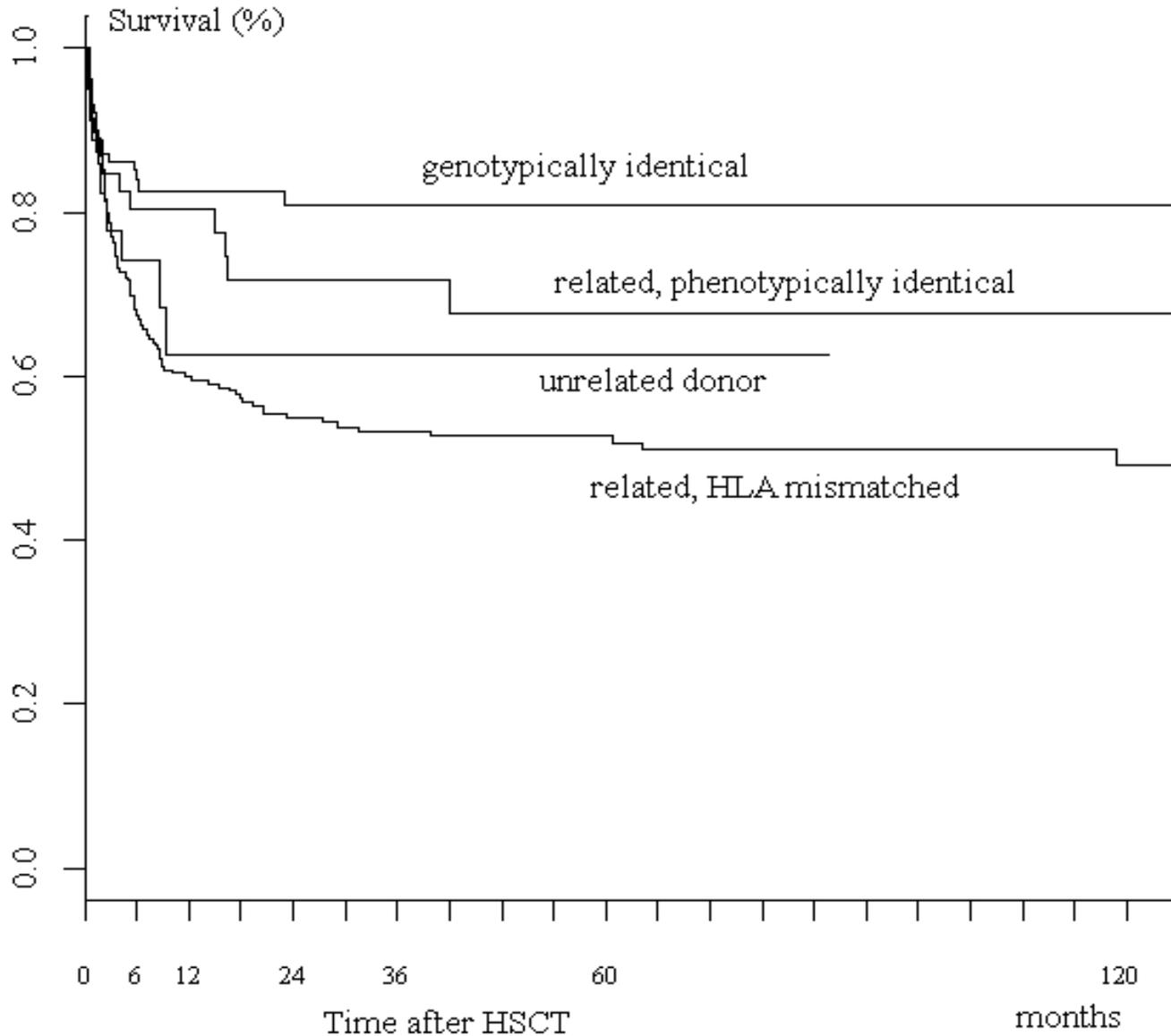
# Advantages of Rigorously T-Cell-Depleted Haploidentical Non-Ablated Parental Marrow Transplants

- Donor usually always immediately available.
- Don't have to wait for patient to get over infections or become stable.
- Can do in neonates.
- Can do essentially as an outpatient transplant if patient is well.
- Avoids the side effects of chemotherapy and GVHD prophylactic drugs.

# Survival Rates in SCID Transplants

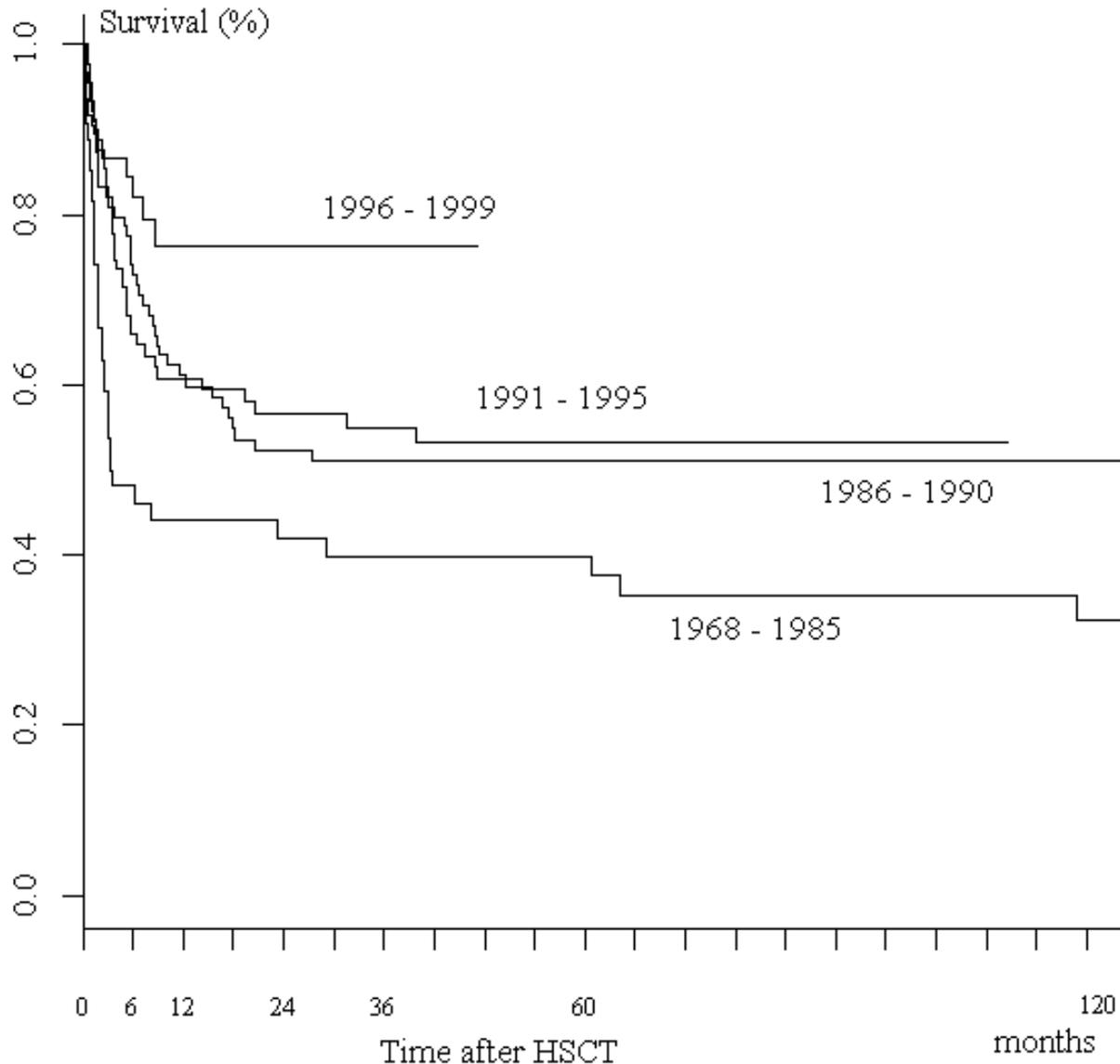
<b>Authors</b>	<b>Location</b>	<b>Total # SCIDs</b>	<b>Overall Survival</b>
Haddad et al. 1998	European Soc. ID	193	48%
Bertrand et al., 1999	European Soc. ID	178	52%
Smogorzewska et al.,2000	LA Childrens	48	58%
O'Marcaigh et al.2001	UCSF	16	75%
Buckley et al., 2008	Duke	162	77%

# European Bone Marrow Transplants in SCID\*



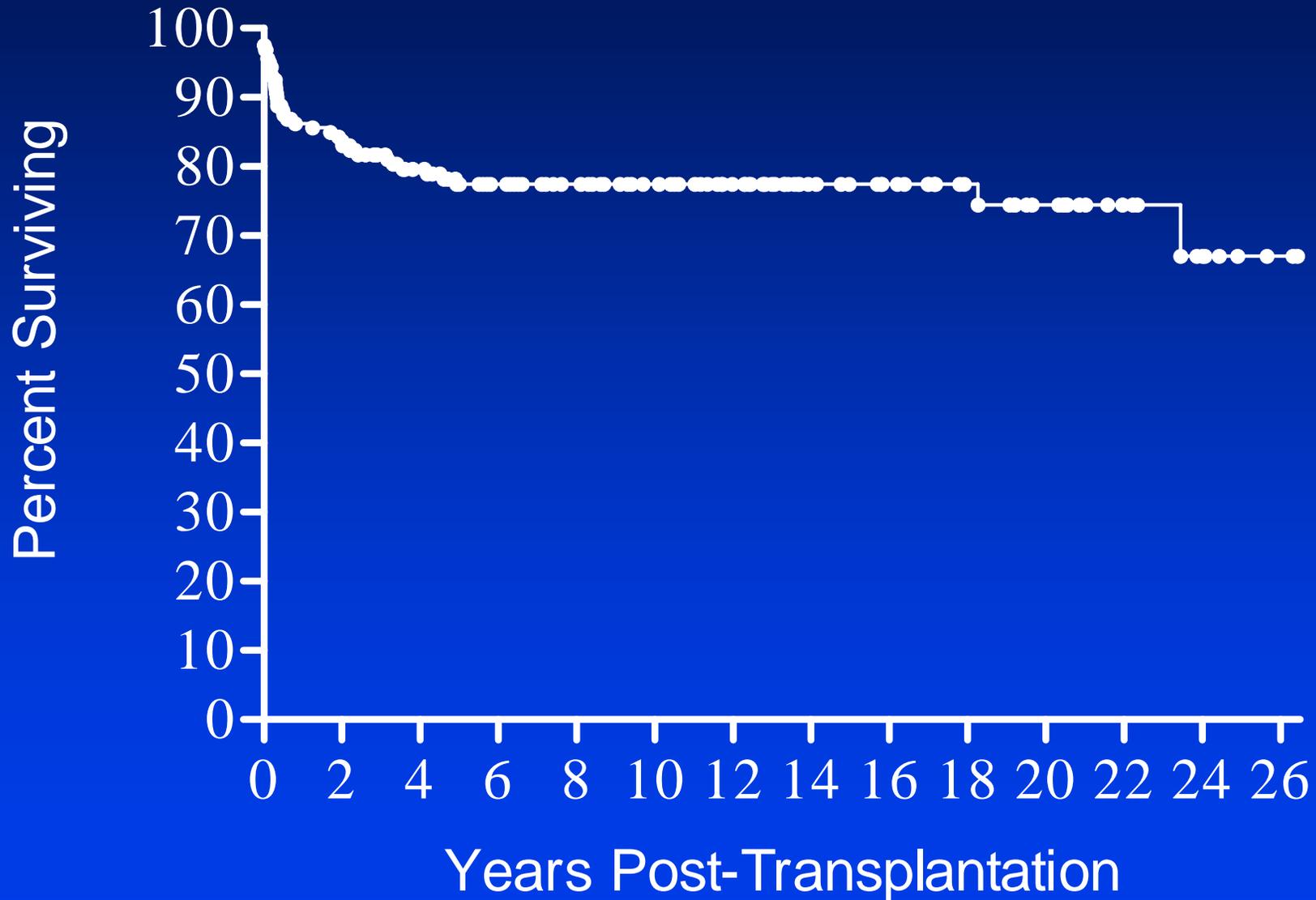
\*From: Antoine C.: Lancet, 361, 2003

# European Bone Marrow Transplants in SCID\*

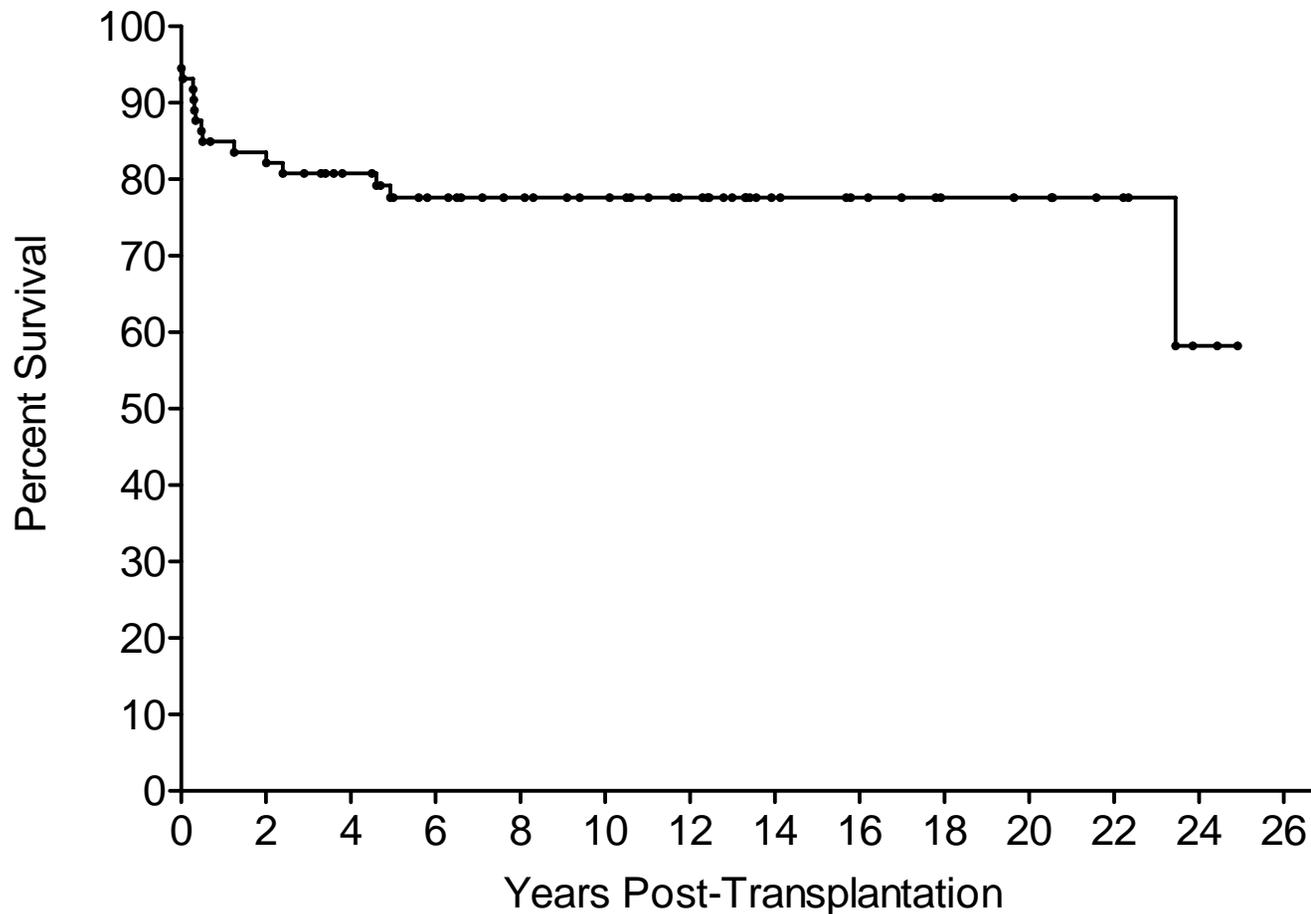


\*From: Antoine C.: Lancet, 361, 2003

# Kaplan Meier Plot of 162 SCIDs Transplanted over the Past 26.5 Years



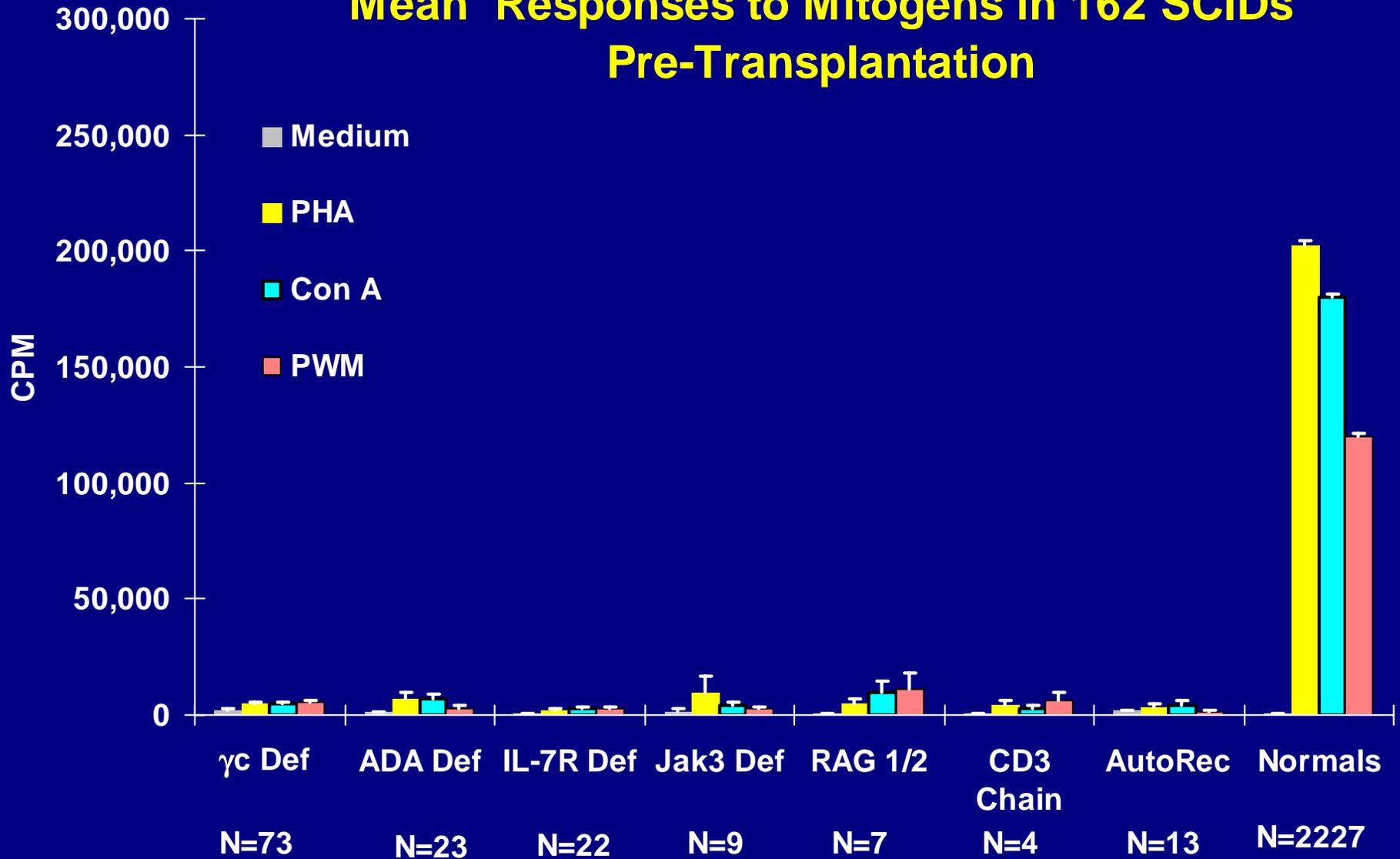
All (74) X-linked Severe Combined  
Immunodeficiency Patients Transplanted at  
Duke University Medical Center from May, 1982  
to December, 2008 (5 HLA-identical, 69  
Haploidentical)



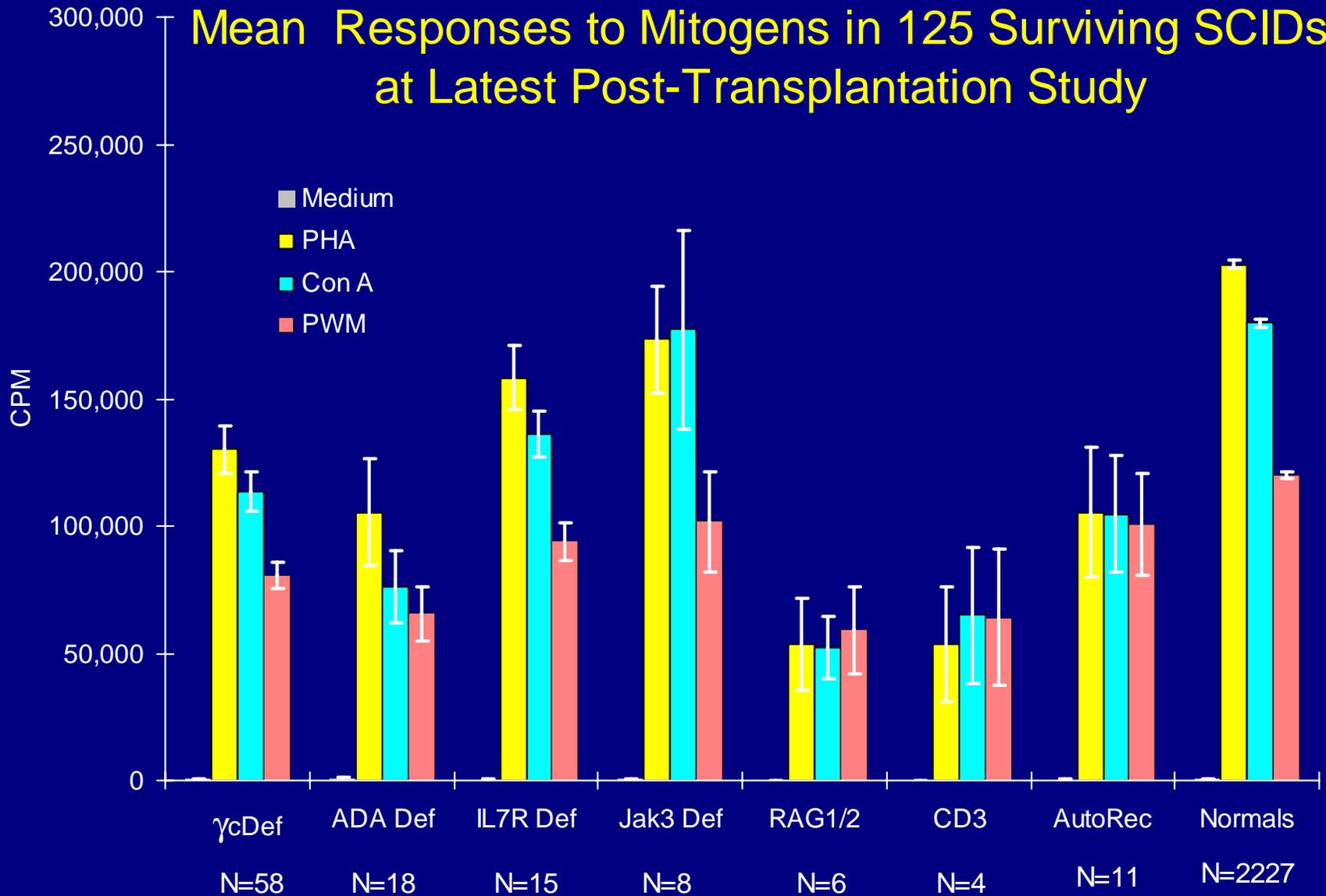
# Survival Rates in SCIDs Transplanted Before 3.5 Months of Life

<b>Authors</b>	<b>Location</b>	<b>Total # SCIDs</b>	<b>Overall Survival</b>
Kane et al., 2001	Newcastle	13	100%
Myers et al., 2002	Duke	24	95%
Buckley et al., 2008	Duke	48	94%

# Mean Responses to Mitogens in 162 SCIDs Pre-Transplantation

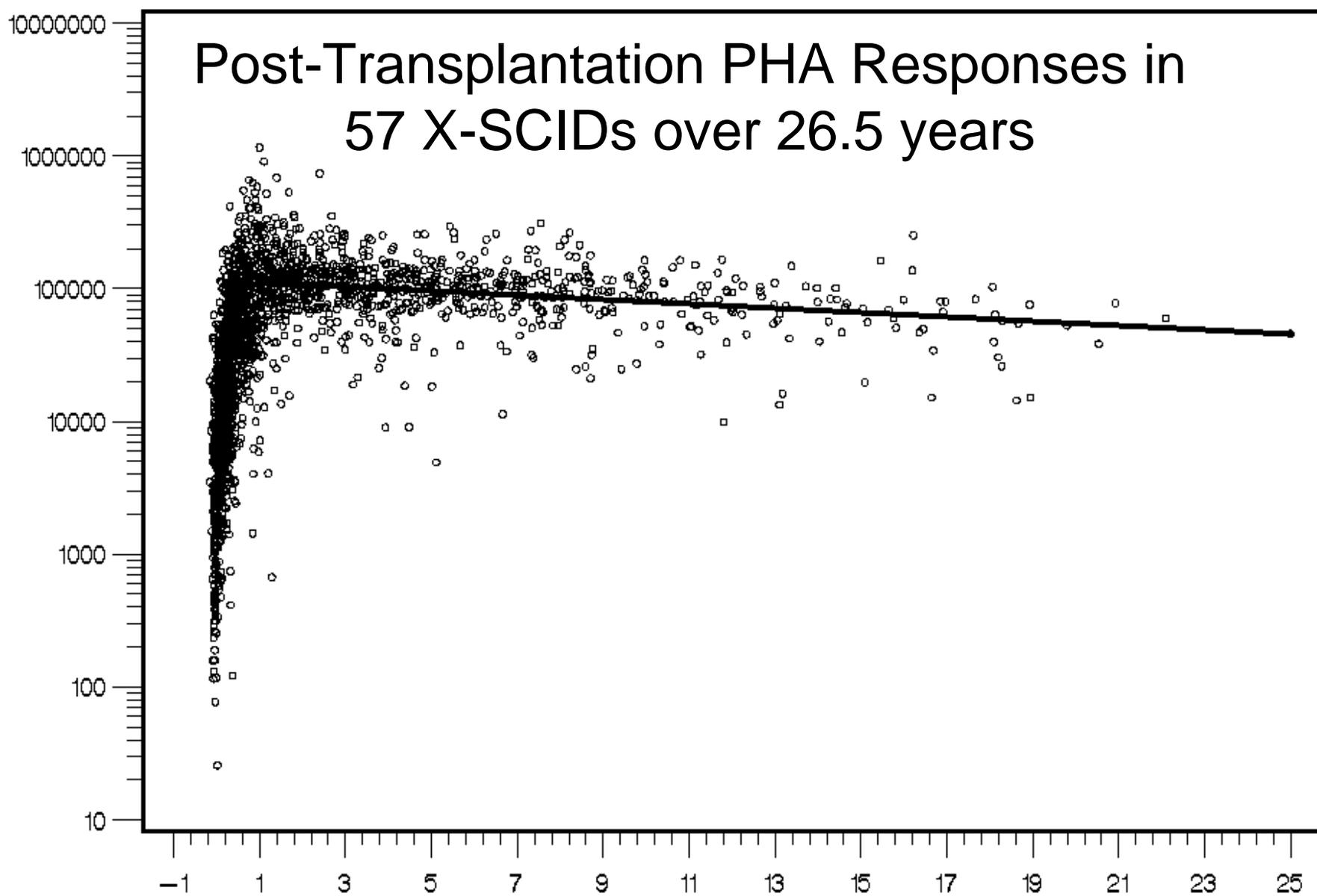


# Mean Responses to Mitogens in 125 Surviving SCIDs at Latest Post-Transplantation Study



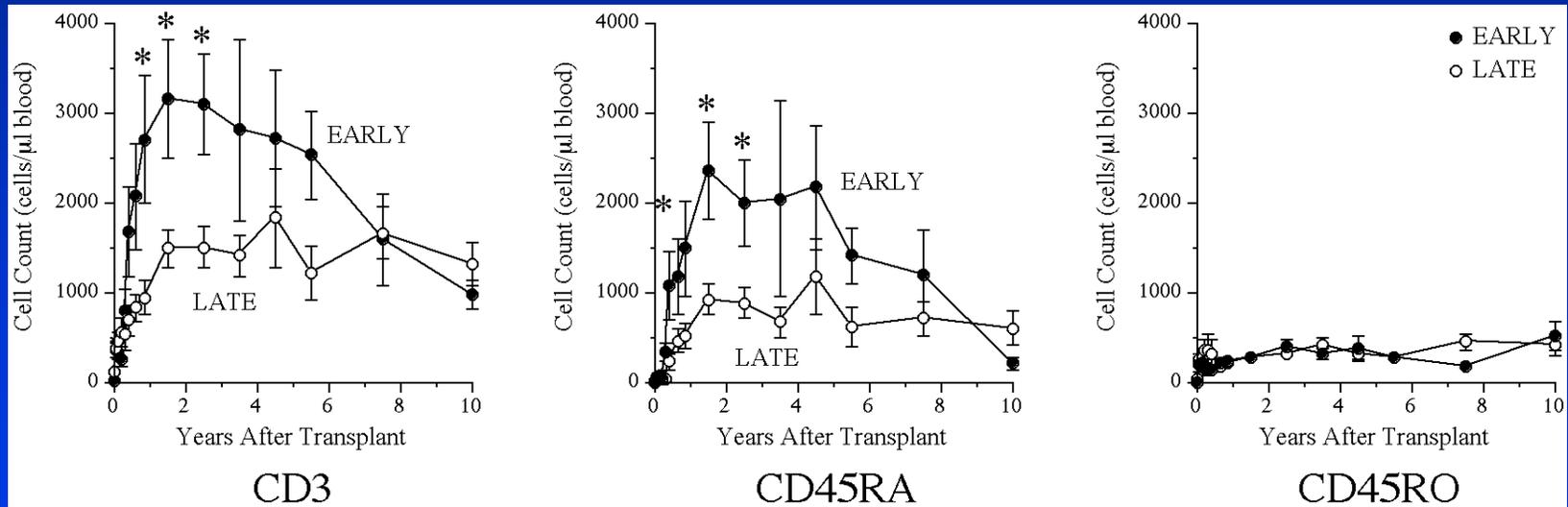
# Post-Transplantation PHA Responses in 57 X-SCIDs over 26.5 years

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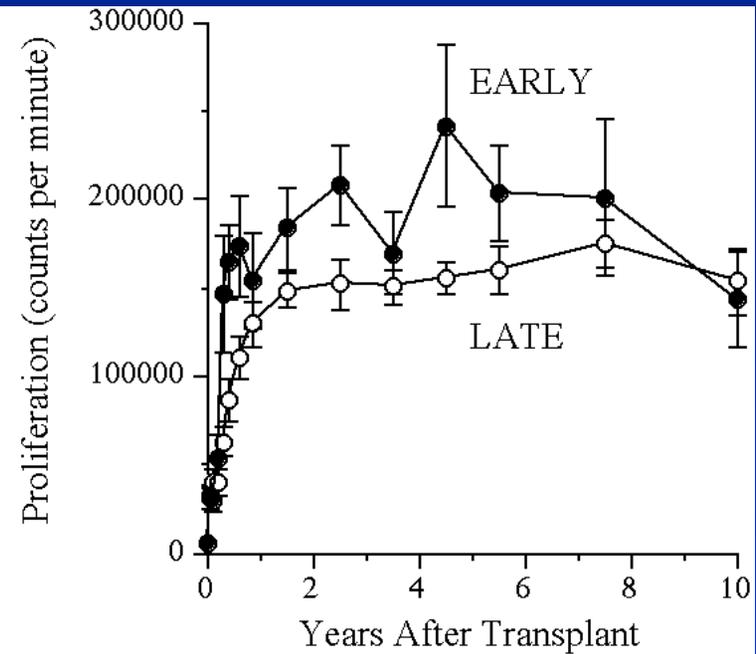
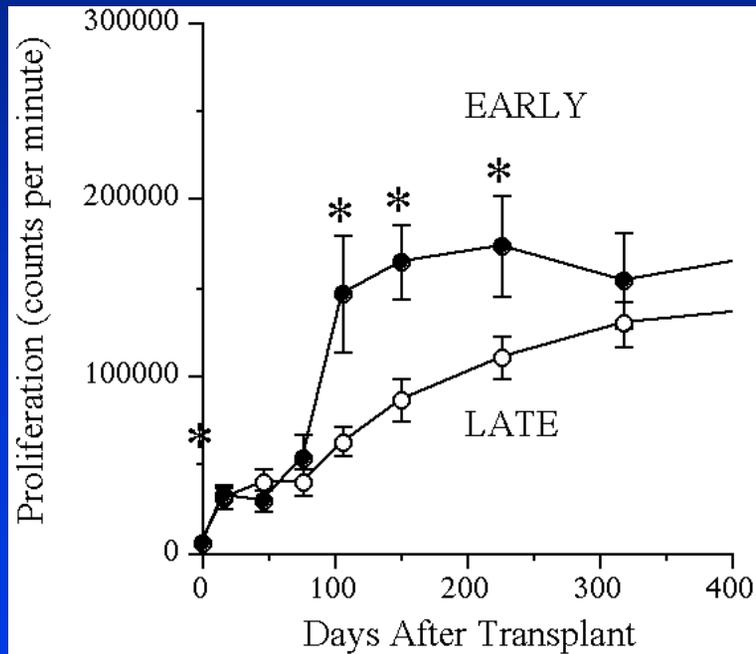


Years Post-Transplantation

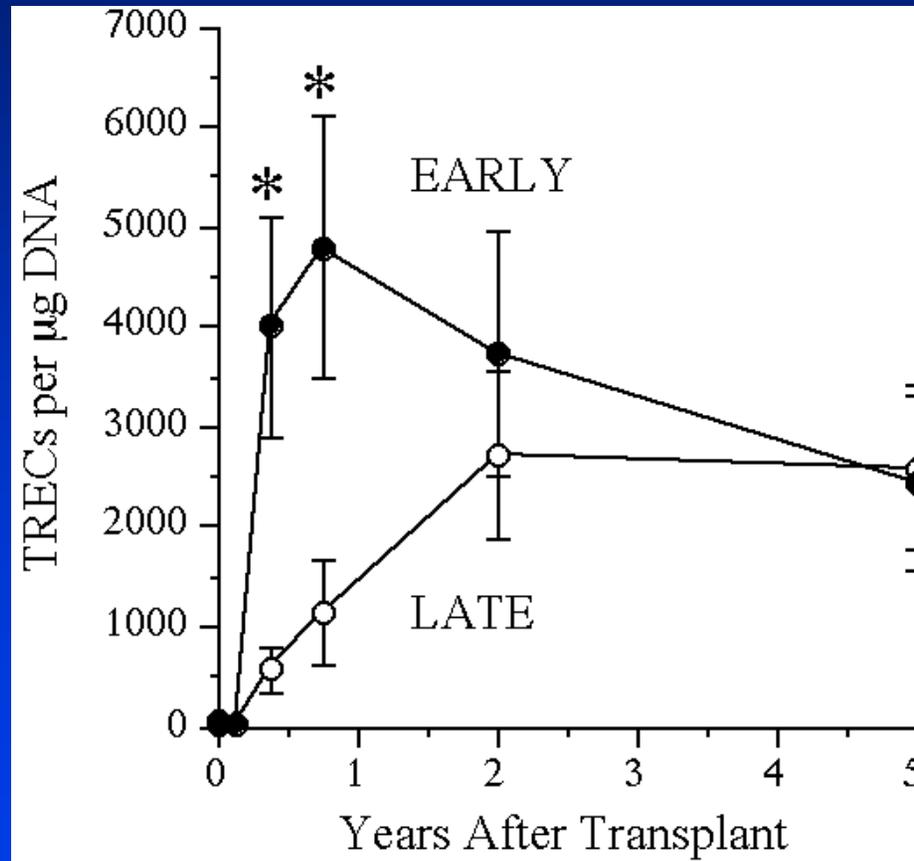
# Total (CD3+), Naïve (CD45RA+) and Memory (CD45RO+) T Cells of SCIDs Transplanted in the Neonatal Period (Early) Compared with Those Transplanted beyond that Period (Late)

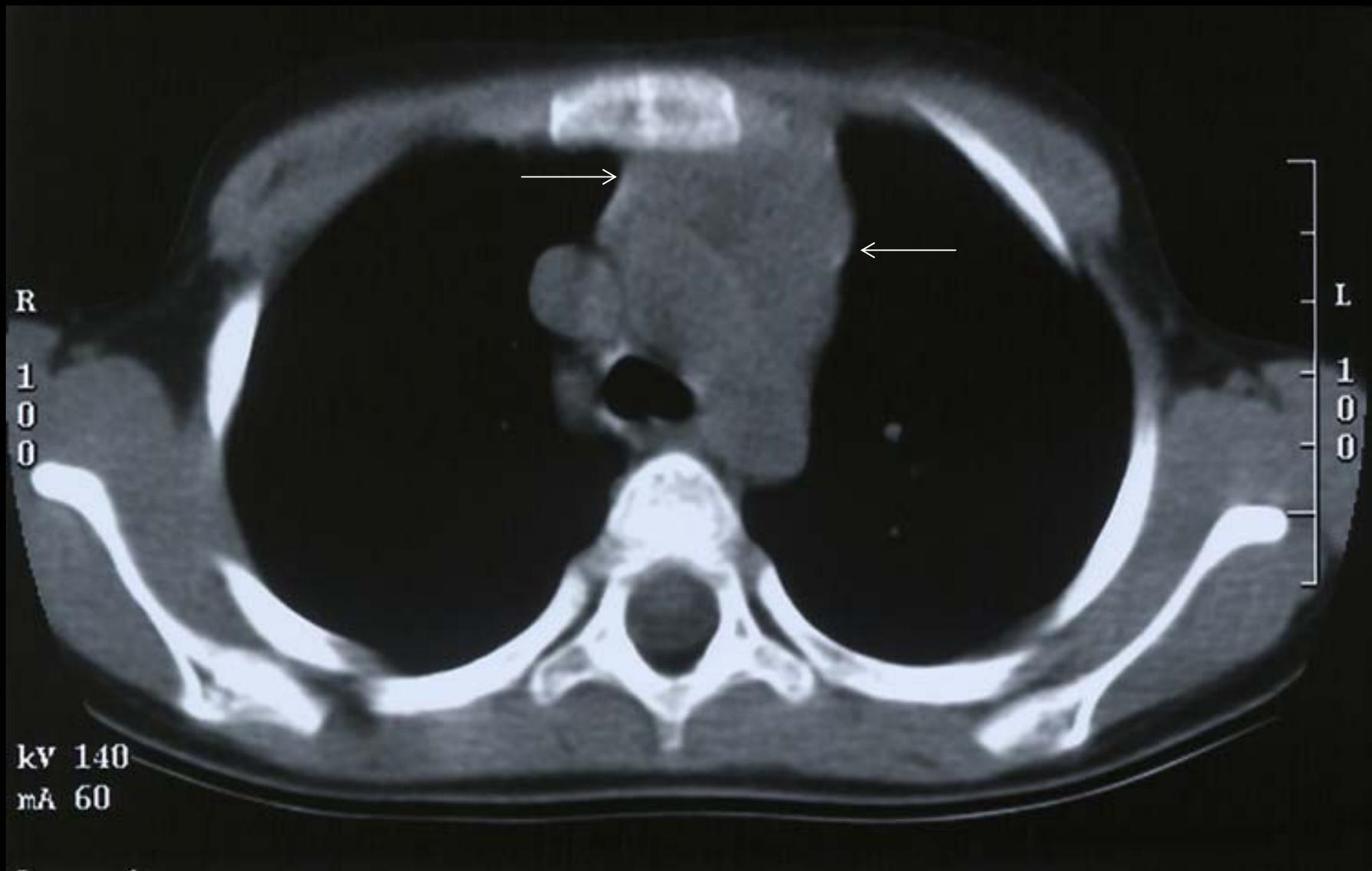


# Responses to PHA by Lymphocytes of SCIDs Transplanted in the Neonatal Period (Early) Compared with Those Transplanted beyond that Period (Late)

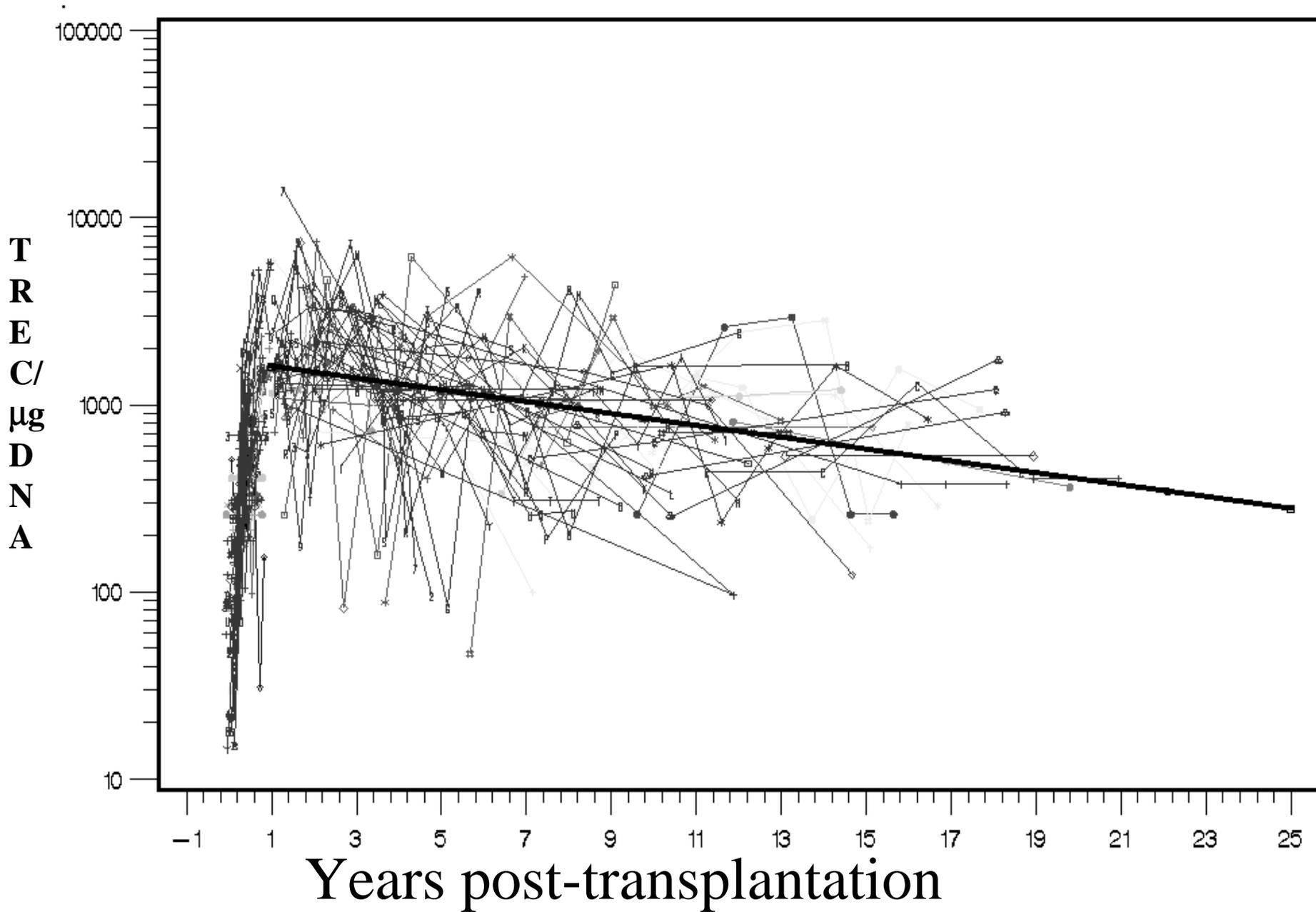


# Thymic Output of SCIDs Transplanted in the Neonatal Period (Early) Compared with Those Transplanted beyond that Period (Late)



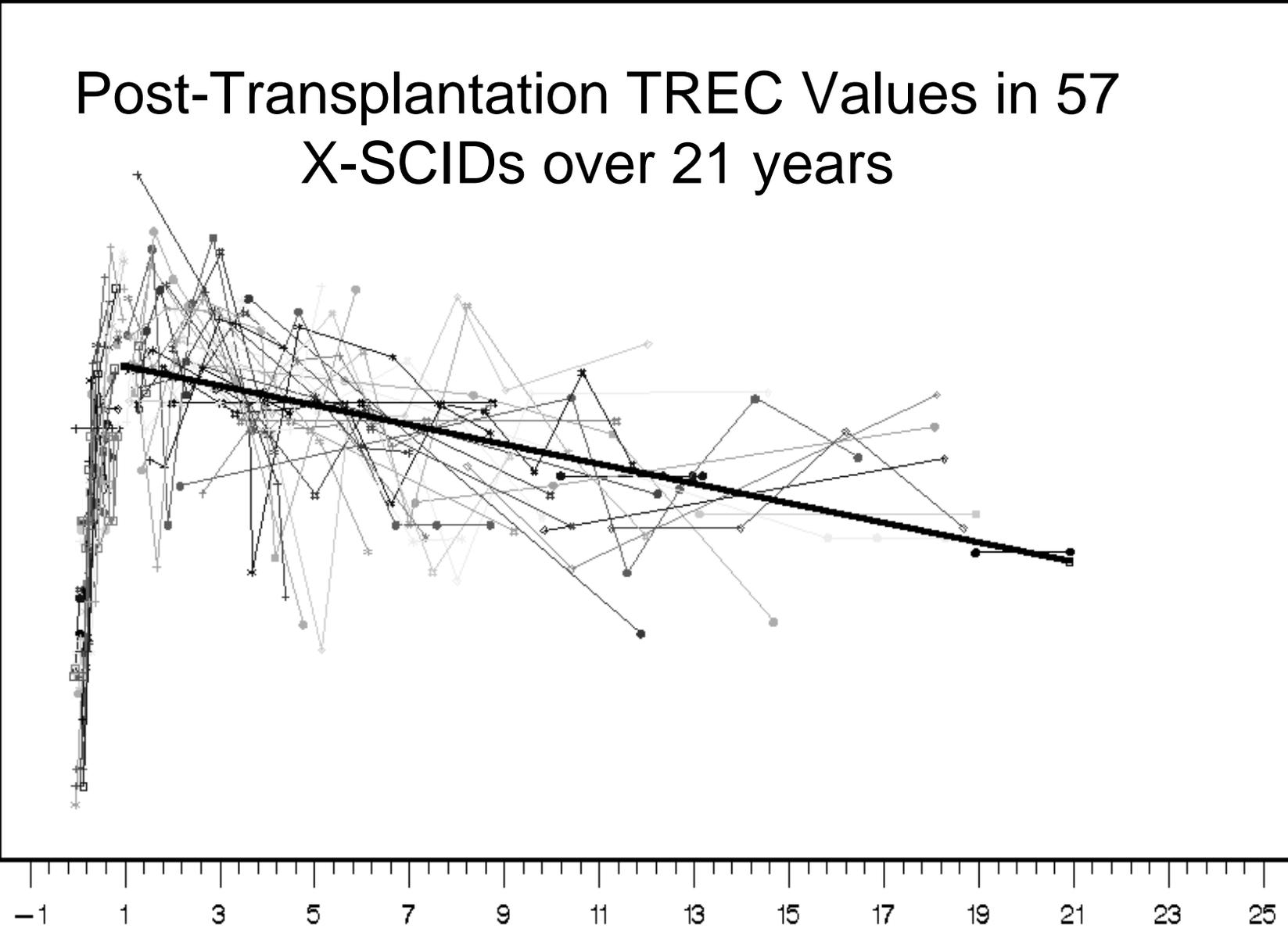


# All of the TREC Data on 128 SCIDs



# Post-Transplantation TREC Values in 57 X-SCIDs over 21 years

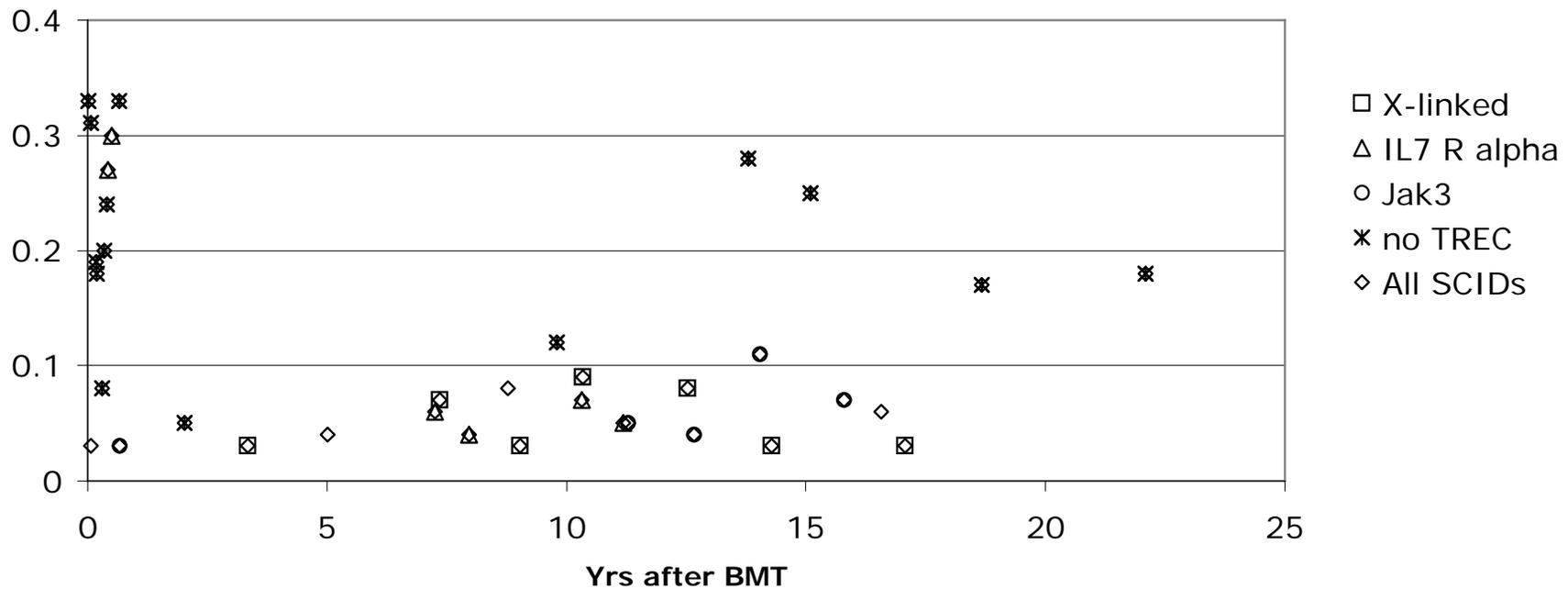
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**Years Post-Transplantation**

# T Cell Diversity by Spectratyping

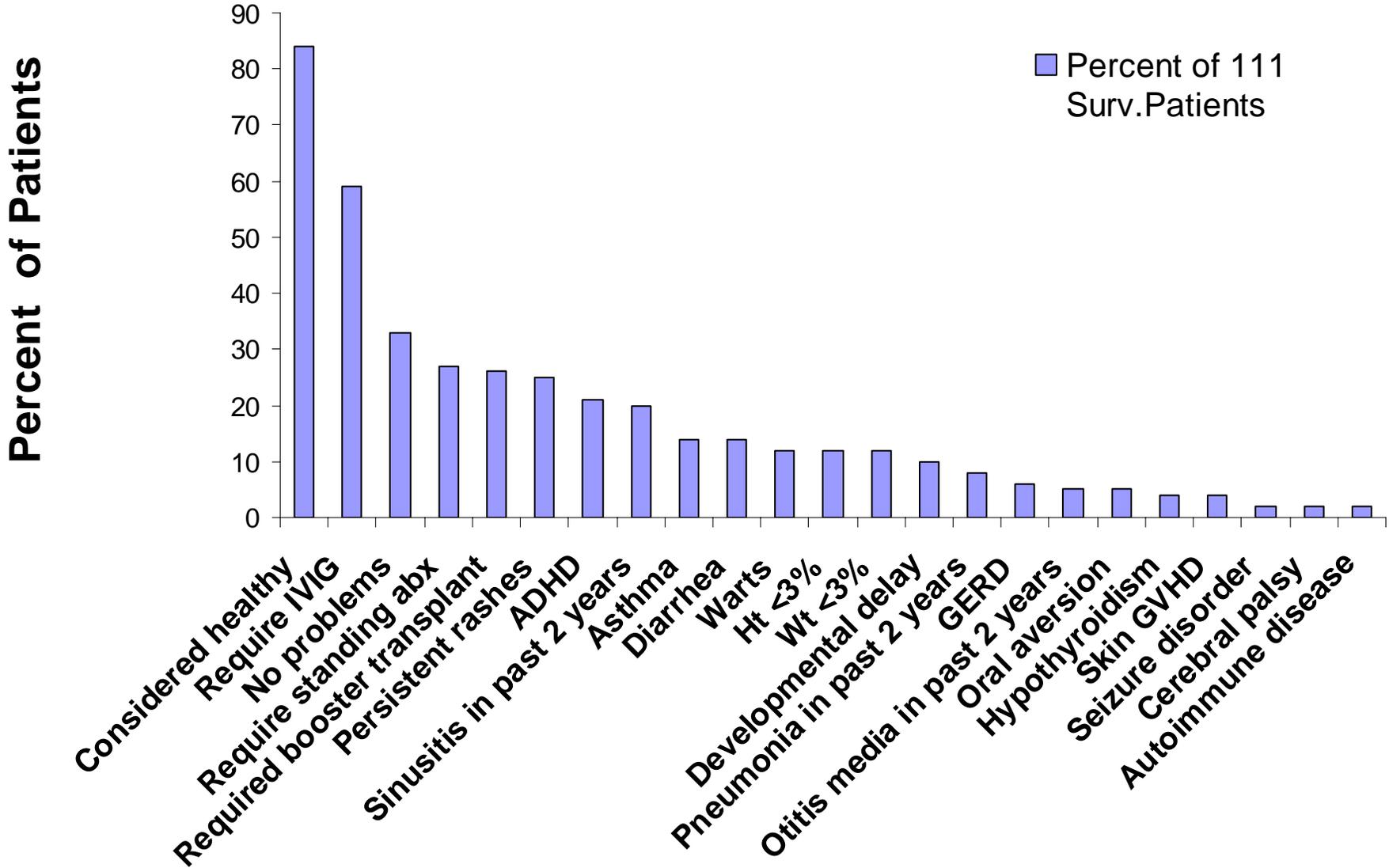
DKL vs yrs post TX



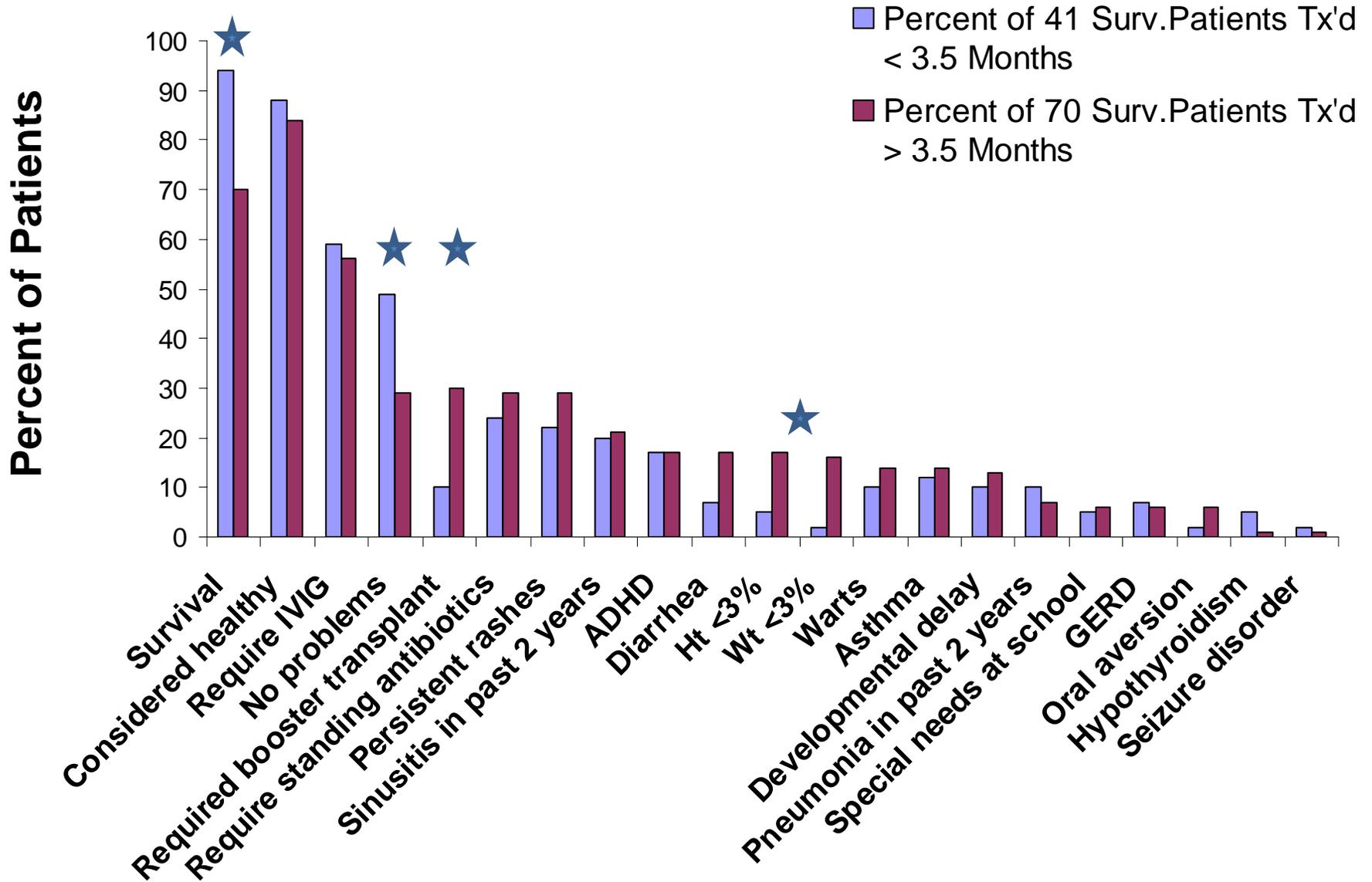
# Chimerism and B Cell Function After Bone Marrow Transplantation

- 115/125 surviving patients transplanted at Duke are T cell chimeras. 1 is too soon to know.
- 9 patients (7 ADA Def and 2 X-SCID) did not become chimeric.
  - 7/22 ADA deficient SCIDs; 2 later underwent successful gene therapy in Italy, 4 are on PEG-ADA and 1 received a MUD transplant.
  - 2 X-linked received gene therapy, 1 successful. The unsuccessful one received a MUD transplant.
- 33/125 (26%) have donor B cells; 65/125 (59%) on IVIG or SQIG. 19/57 (33%) X-linked have donor B. 38/57 (67%) X-SCID on IVIG or SQIG.

# Clinical Features of SCIDs Longterm



# Clinical Status Post-transplantation



# Factors Affecting Stem Cell Therapy in SCID

- Viral Infections.
- Age at transplantation: first 3.5 months of life best.
- Presence of transplacentally-transferred maternal T cells.
- Genetic types of SCID: Resistance to engraftment in ADA-deficient and RAG SCIDs.
- B cell function best in IL-7R $\alpha$  CD45-deficient, ADA-deficient and CD3 chain deficient SCIDs, less good in X-linked, Jak3, and RAG-deficient.
- Pre-transplant NK cells in IL-7R $\alpha$ -deficient, CD3 chain deficient and CD45-deficient SCIDs do not interfere with engraftment.
- Donor-derived NK cells disappear in X-linked and Jak3-deficient SCIDs post-transplantation.

# Conclusions

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- SCID is a pediatric emergency, and the potential exists to diagnose this condition routinely at birth.
- If a rigorously T cell depleted stem cell transplant from a relative can be done in the first 3.5 months of life without pre-transplant chemotherapy or post-transplant GVHD prophylaxis, before infections develop, there is a high (94 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.

# Collaborators

## Duke Co-Investigators

- Joseph L. Roberts, MD/PhD
- Marcella Sarzotti-Kelsoe, PhD
- Dongfeng Chen, Ph.D.
- Michael Keller, M.D.
- Mary Dell Railey, M.D.

## Duke Clinicians

- Wesley Burks, MD
- Laurie M. Lee, MD
- M. Louise Markert, MD/PhD
- Larry W. Williams, MD

## Other Investigators

- Jennifer M. Puck, MD
- John O'Shea, MD
- Warren J. Leonard, MD

## Co-ordinators and Care

- Referring Physicians
- Debra Sedlak, CPNP
- A/I Fellows
- Pediatric Residents

## Duke Technicians

- Roberta Parrott, BS
- S. Myriah Cooney, BS
- Chan M. Win, BS
- Zermeena Marshall, BS

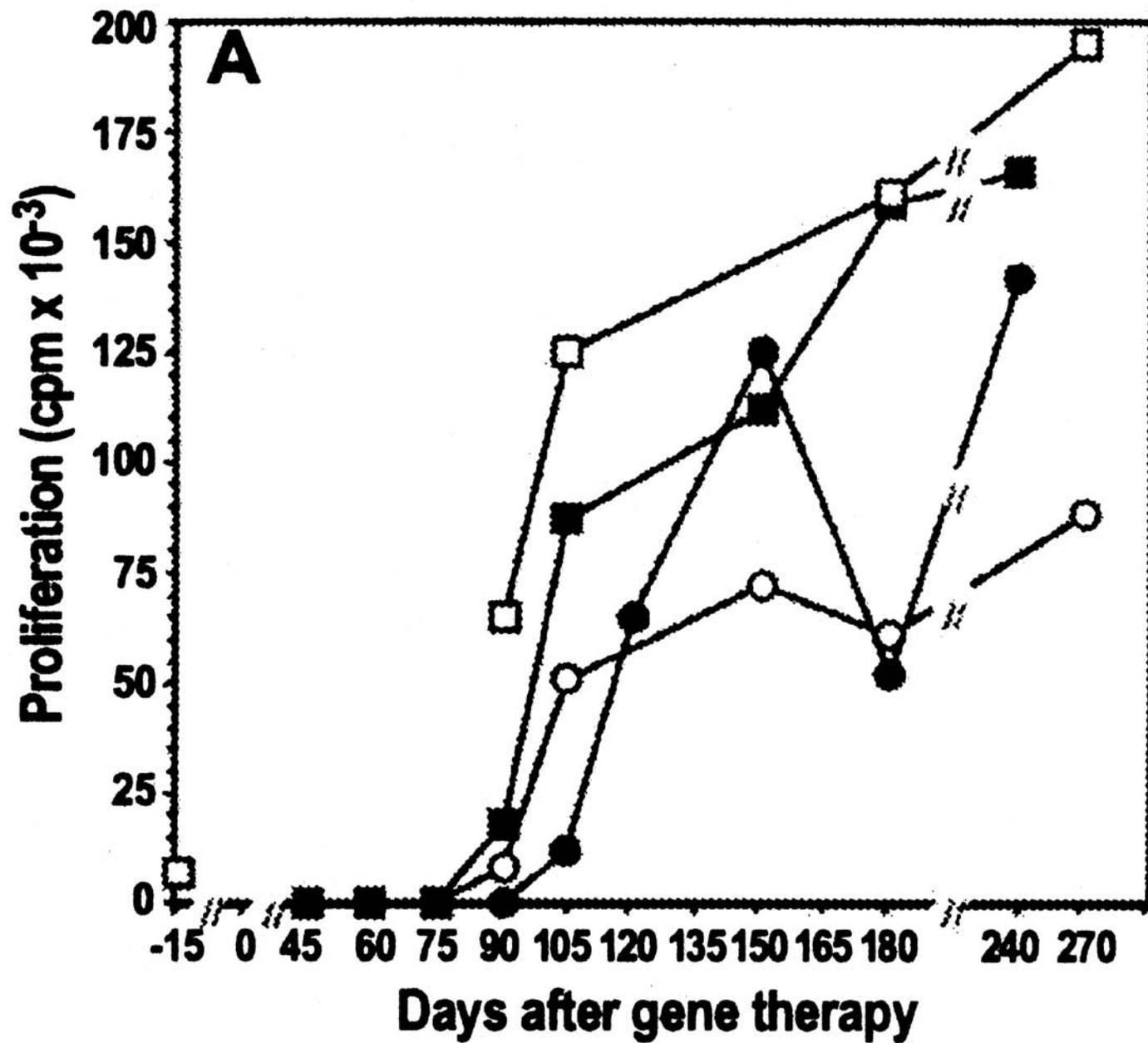




# Lymphoproliferative Disorders in SCID\*

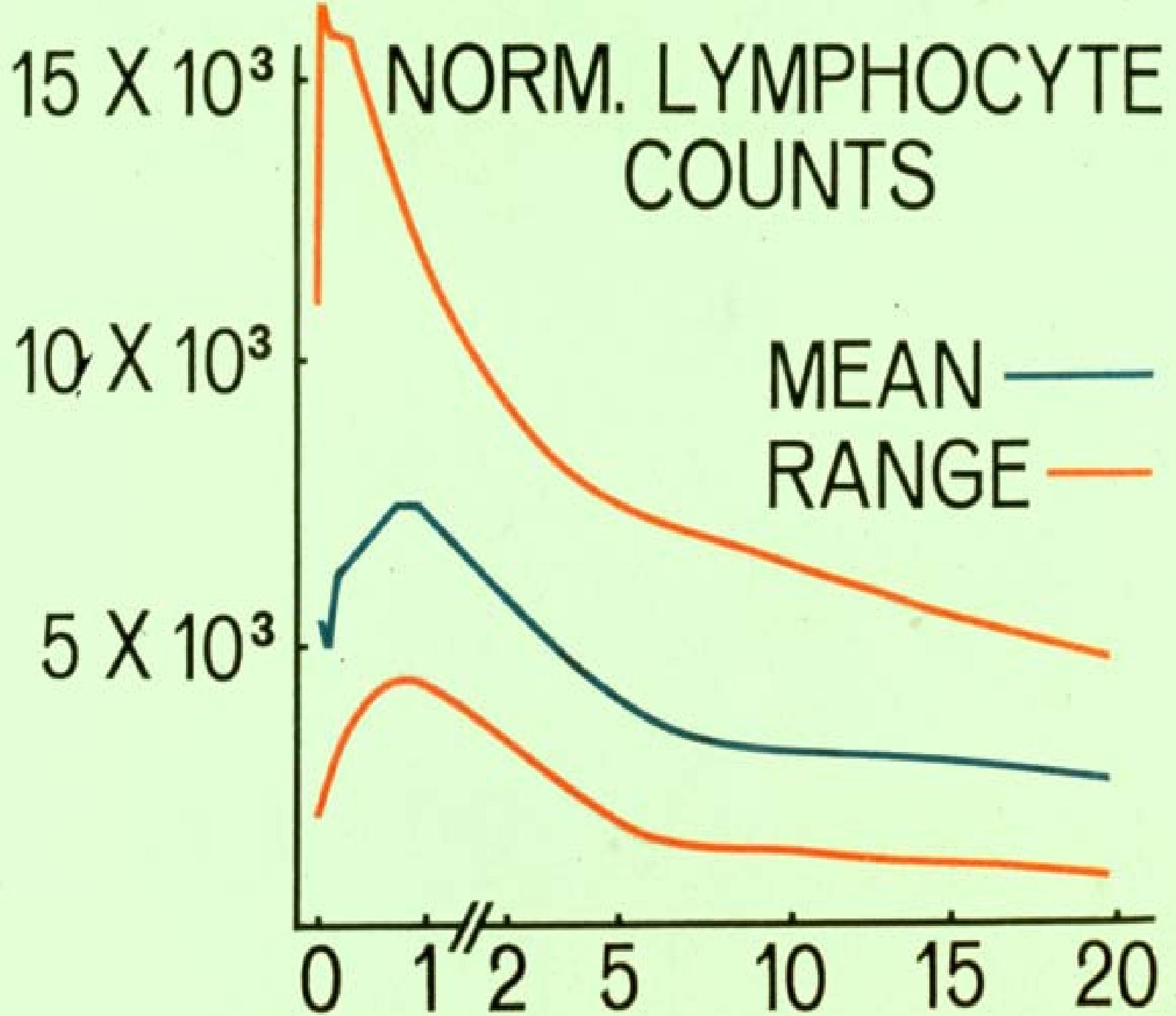
- Incidence estimated at 1-5%. (6/162 or 3.7% EBV lymphoproliferative disease at Duke: 4 x-linked, 2 IL7R $\alpha$ ).
- Mean age at diagnosis: 1.6 years; M:F =3.3:1
- Approximately 74% non-Hodgkin's lymphoma
- 9.5% Hodgkin's disease
- Carcinomas much less frequent
- Not always EBV +

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

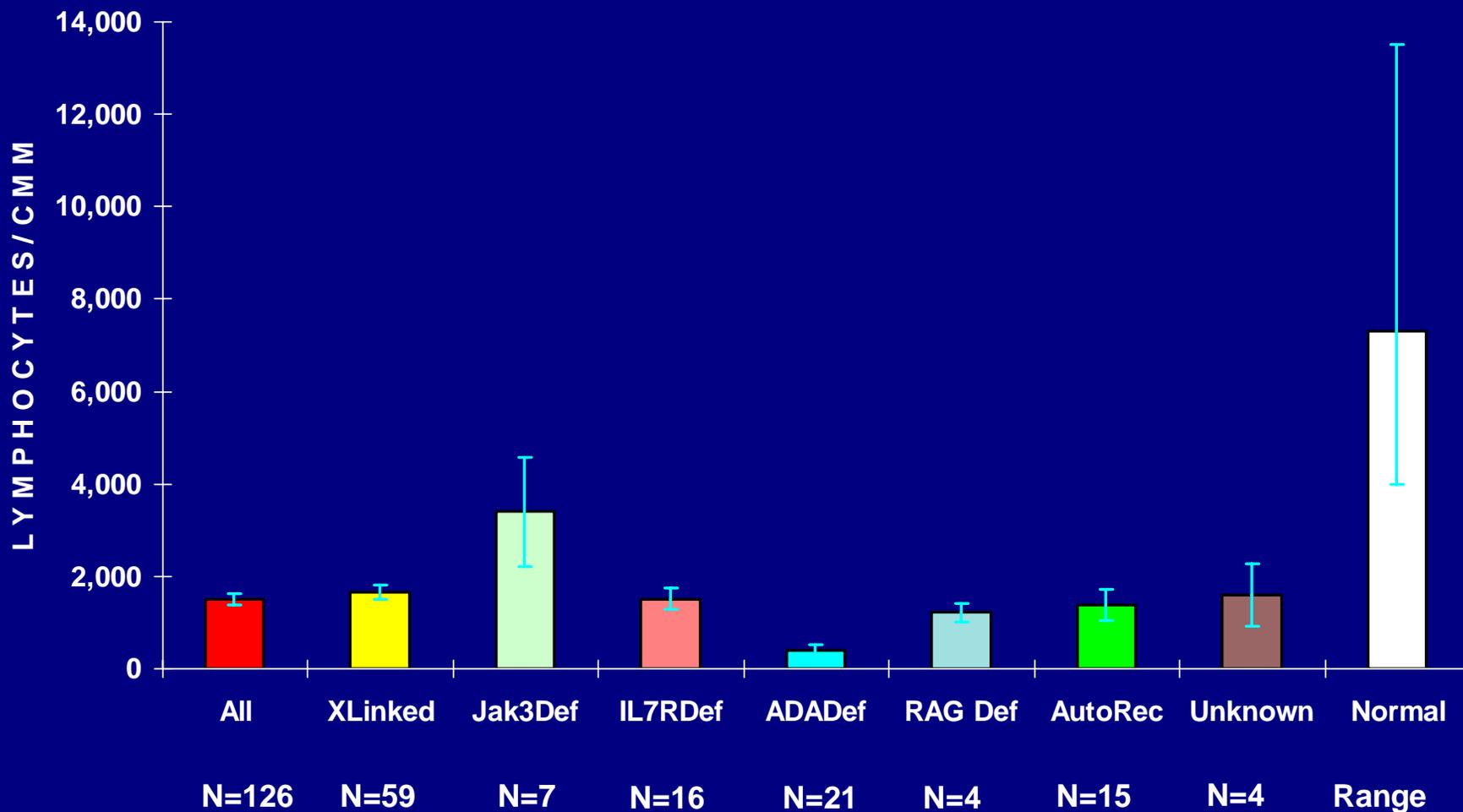


# SCID : Characteristics Common to All Types

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



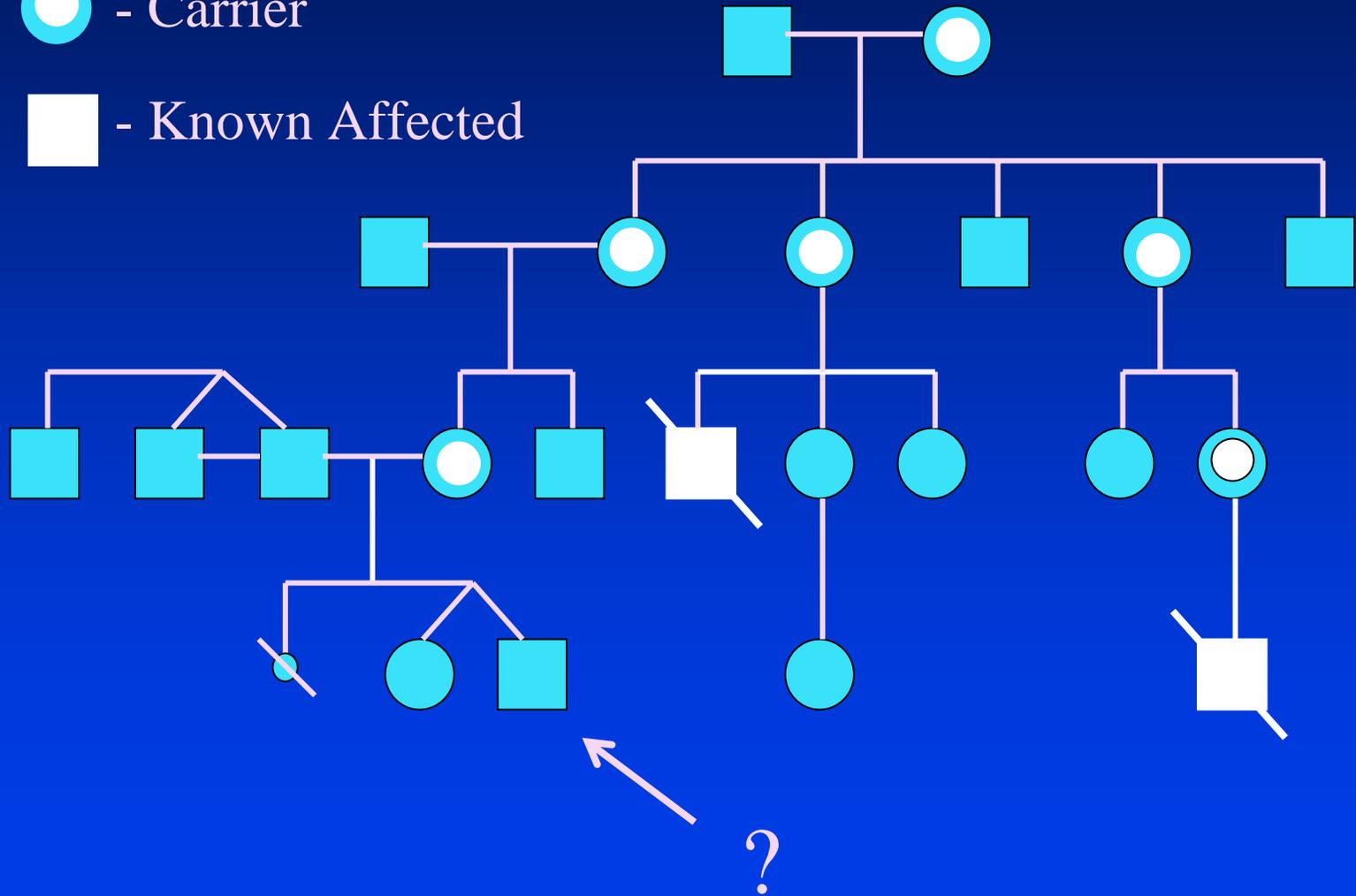
# Mean Absolute Lymphocyte Counts in 126 SCIDs Pre-Transplantation



# XSCID Pedigree

● - Carrier

■ - Known Affected



# Cord Blood White Cells

<u>Parameter</u>	<u>Boy</u>	<u>Girl</u>	<u>Normal</u>
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<sup>3</sup>)

<u>Subtype</u>	<u>Boy</u>	<u>Girl</u>	<u>Normal</u>
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)

