Association of Public Health Laboratories (APHL) in Person Meeting on Severe Combined Immunodeficiency (SCID), Bethesda, MD

SCID: Treatment Plan/Long-term Outcomes/Quality of Life Data

11:25-12:00 a.m. July 31, 2015

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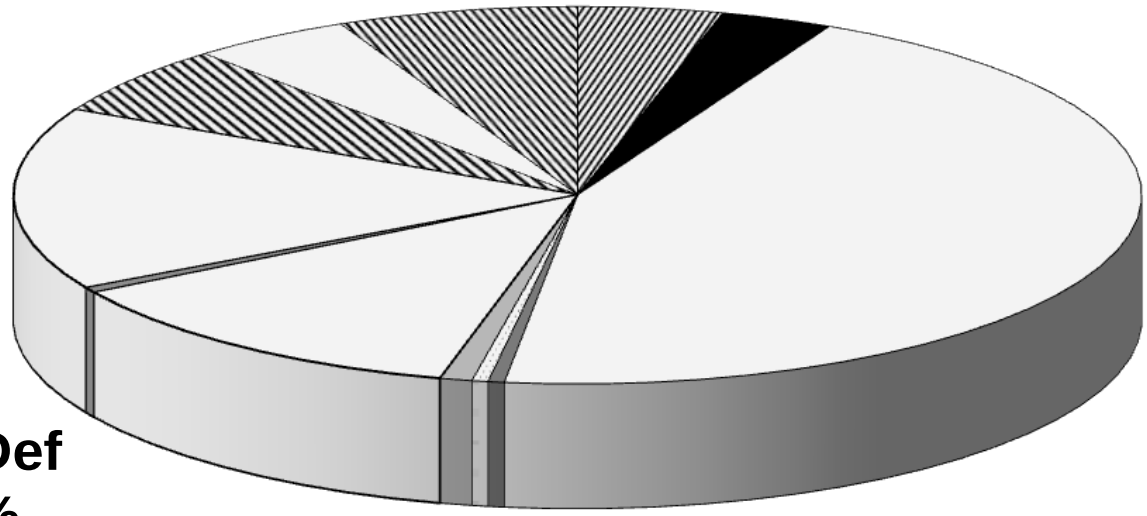
Human Severe Combined Immunodeficiency (SCID)

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

Thirteen SCID-Causing Mutated Genes

- Cytokine Receptor Genes
  - *IL2RG*
  - *JAK3*
  - *IL7R*a
- Antigen Receptor Genes
  - *RAG1*
  - *RAG2*
  - *Artemis*
  - *Ligase 4*
  - *DNA-PKcs*
  - *CD3*δ
  - *CD3*ε
  - *CD3*ζ
- Other Genes
  - *ADA*
  - *CD45*

217 SCIDS Seen at Duke: Genetic Types



10
RAG
4.6%

15
AutoRec
6.9%

9
Unknown
4.1%

7
Artemis
3.2%

13
Jak3 Def.
6%

34
ADA Def.
15.7%

97
γc Def
44.7%

1
CD3ε Def
0.5%

27
IL-7Rα Def
12.4%

2
CD3δDef
0.9%

1
CD3ζ Def
0.5%

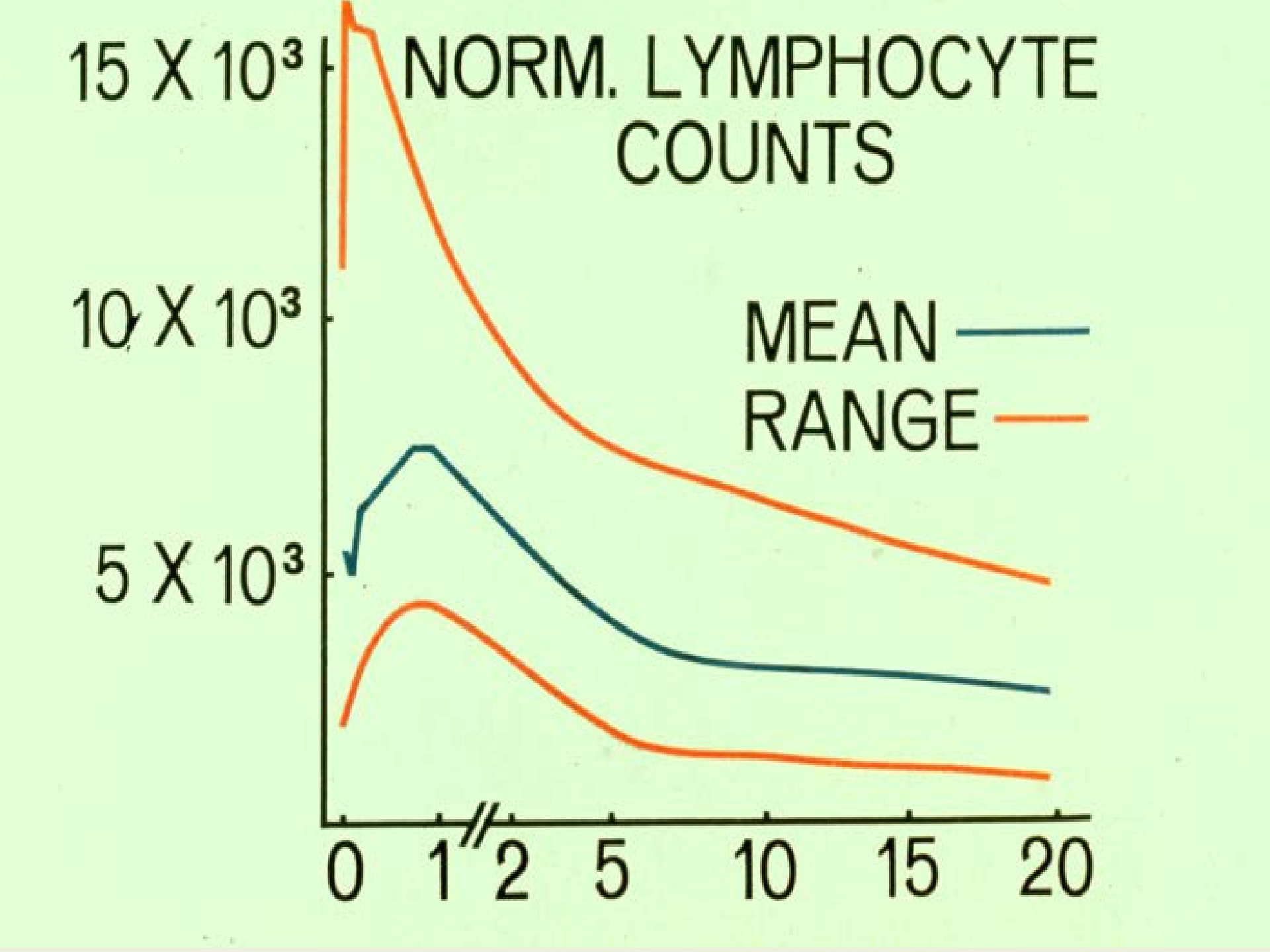
1
CD45 Def
0.5%

SCID Lymphocyte Phenotypes

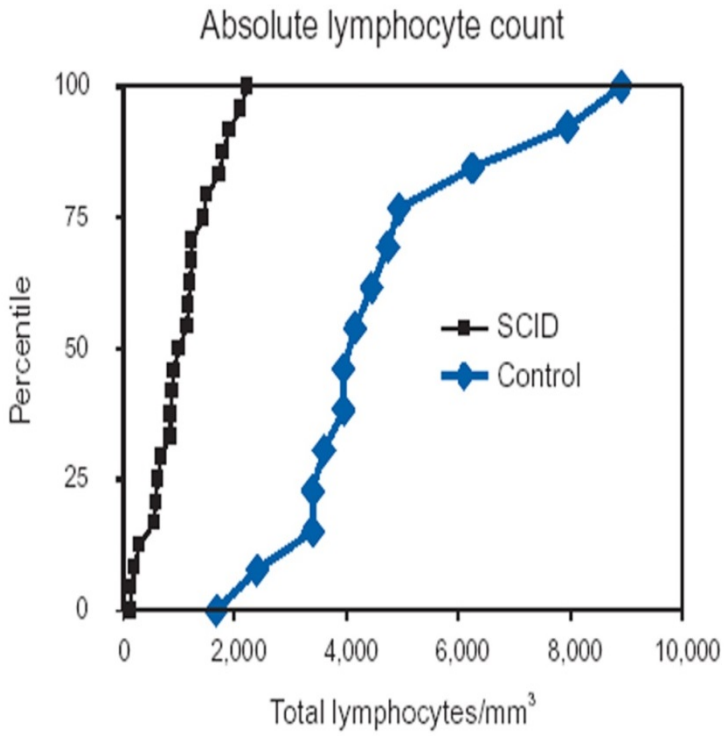
- T-B+NK- — γc-deficient (X-linked), Jak 3-deficient
- T-B+NK+ — IL-7Rα-deficient, CD3δ-deficient, CD3ε-deficient, CD3ζ-deficient, CD45-deficient
- T-B-NK- — ADA-deficient
- T-B-NK+ — RAG1/RAG2-deficient, Artemis-deficient, Ligase 4-deficient, DNA-PKcs

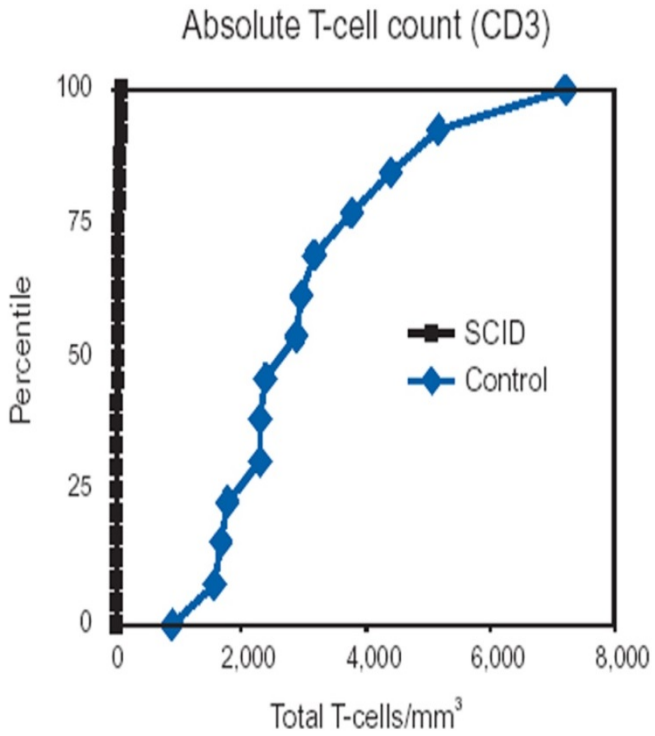
T Cells

- Comprise 70% of circulating lymphocytes in normal individuals.
- Since SCIDs have no T cells, they are lymphopenic.
- Some (but not nearly enough) SCIDs have been discovered because the physicians caring for them recognized their lymphopenia.
- The lower limit of normal for an absolute lymphocyte count at birth is 2000 and at 6 months is 4000/cmm.


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

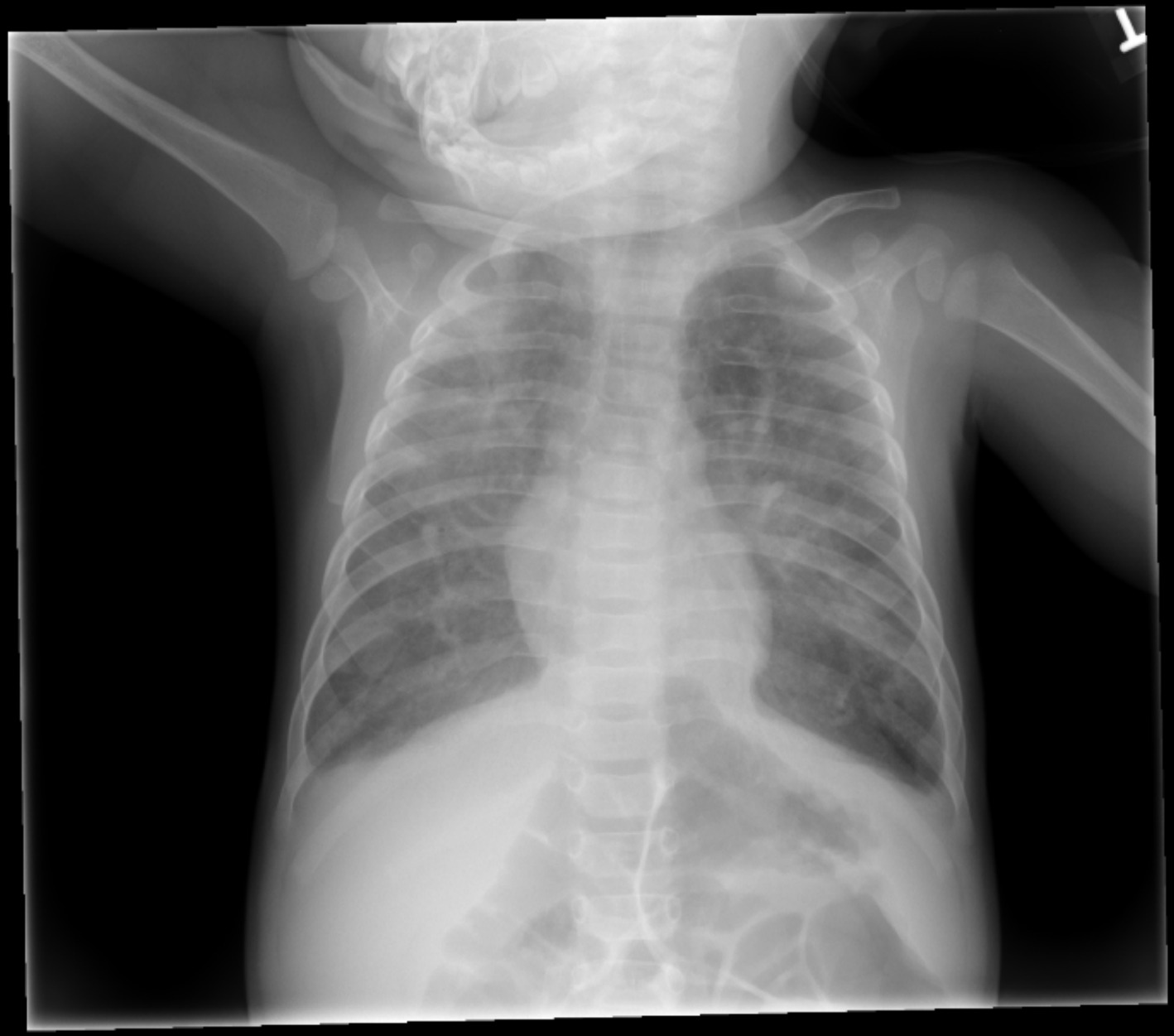
Absolute Lymphocyte Count Distributions in SCID: 25 SCID and 14 Healthy Newborns at Birth

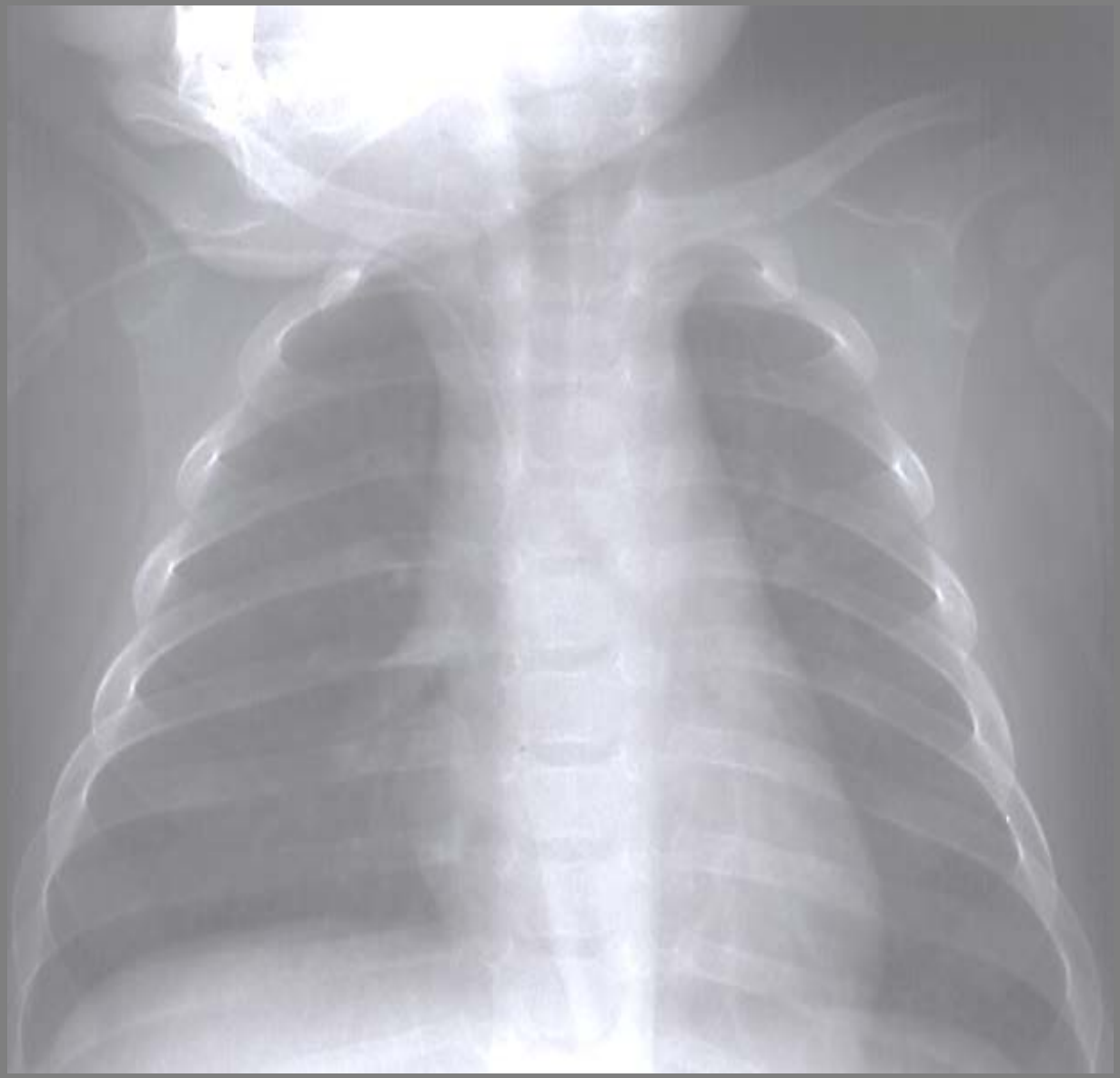




SCID : Characteristics Common to All Types

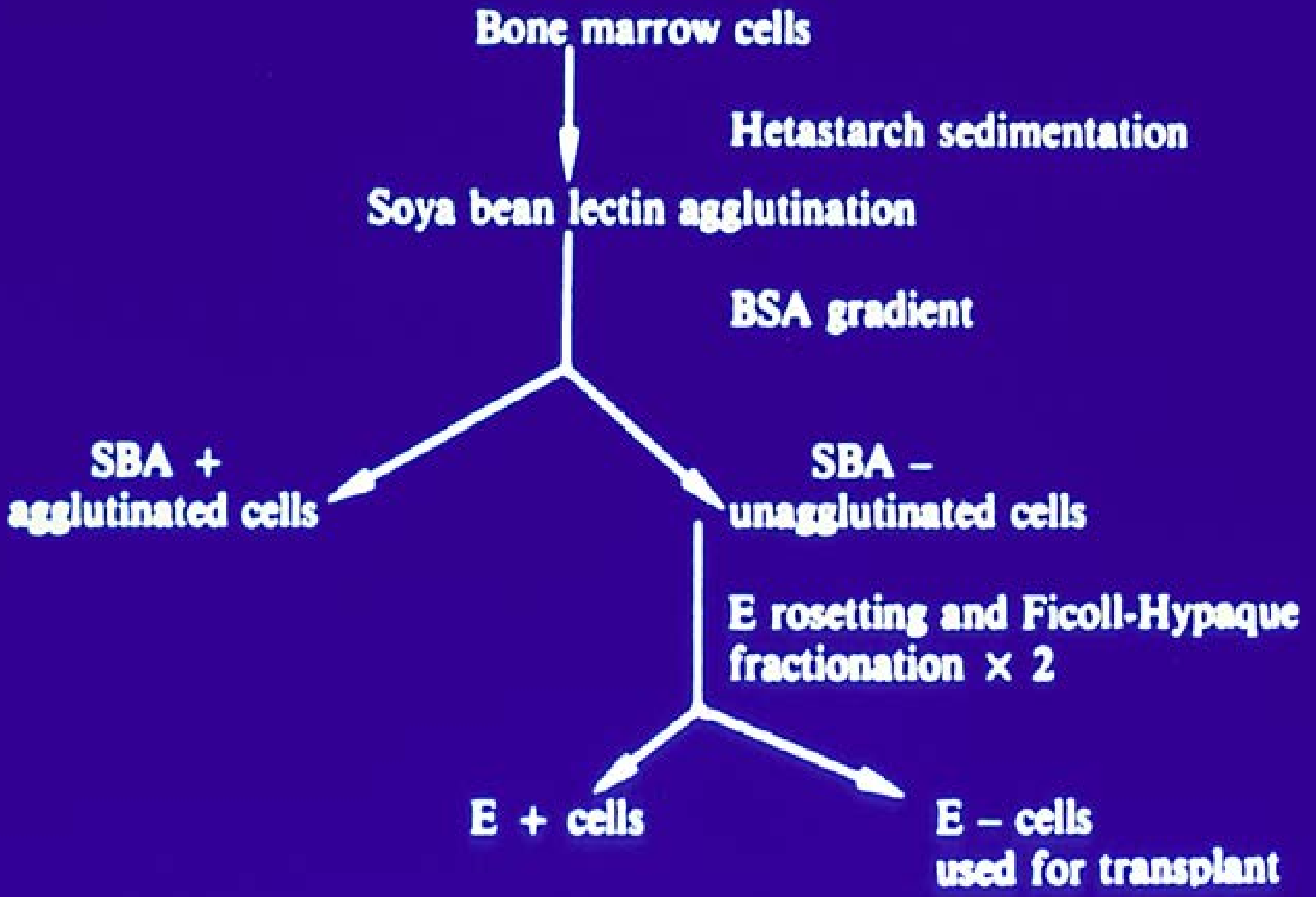
- Thymus is present but small (< 1 gram).
- Lacks corticomedullary distinction.
- Absence of thymocytes.
- Absence of Hassell's corpuscles.

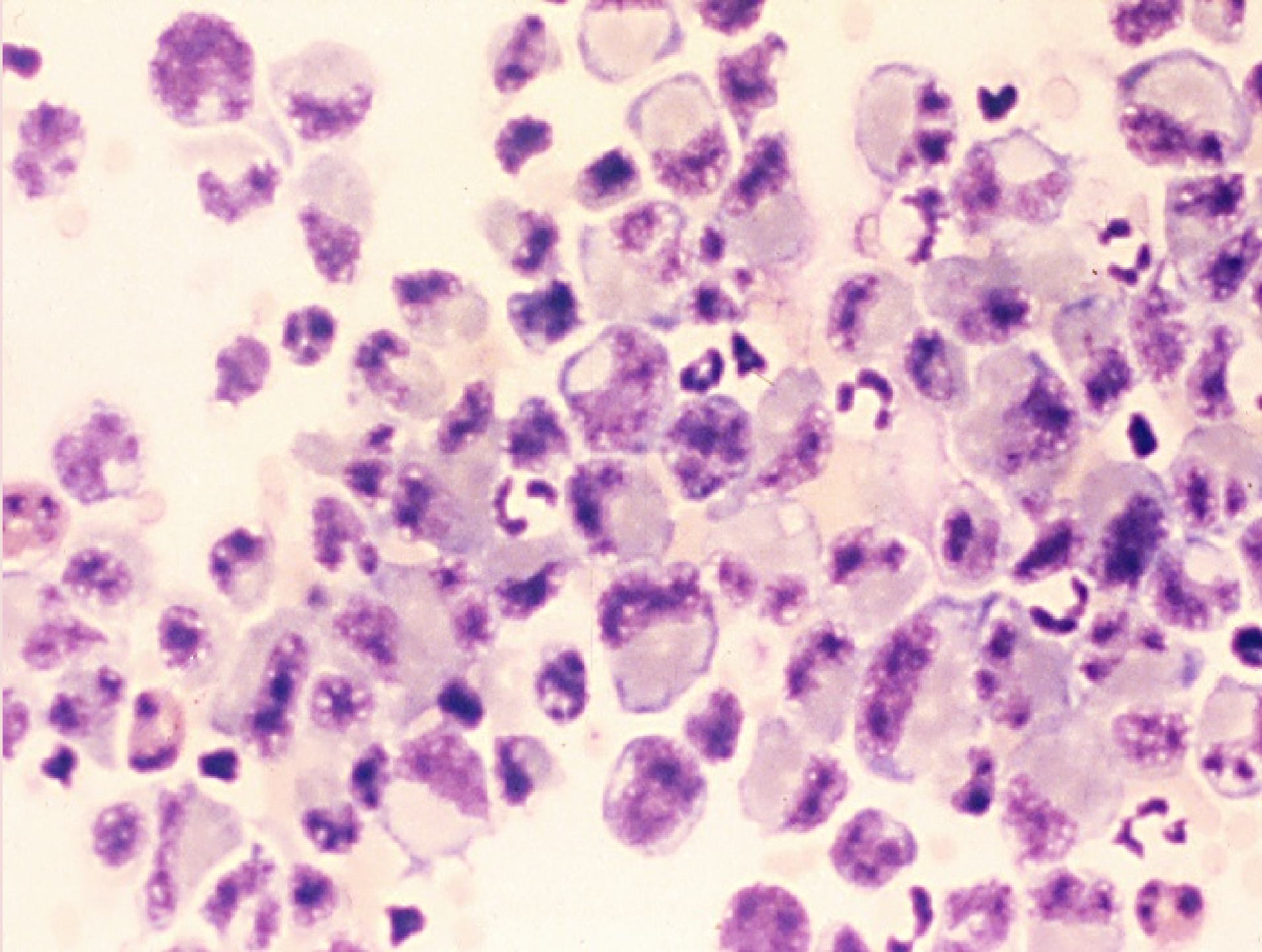


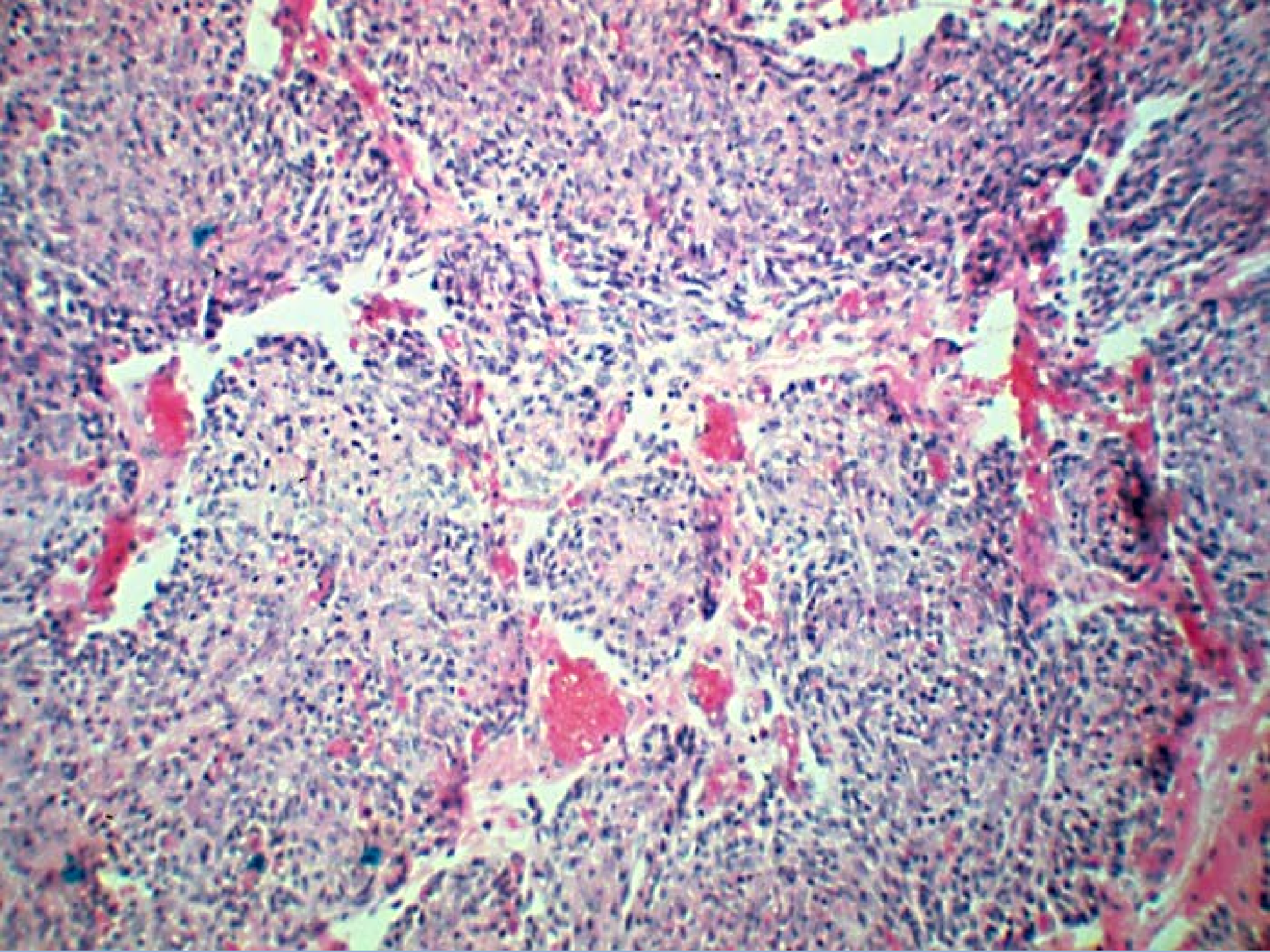


SCID : Characteristics Common to All Types

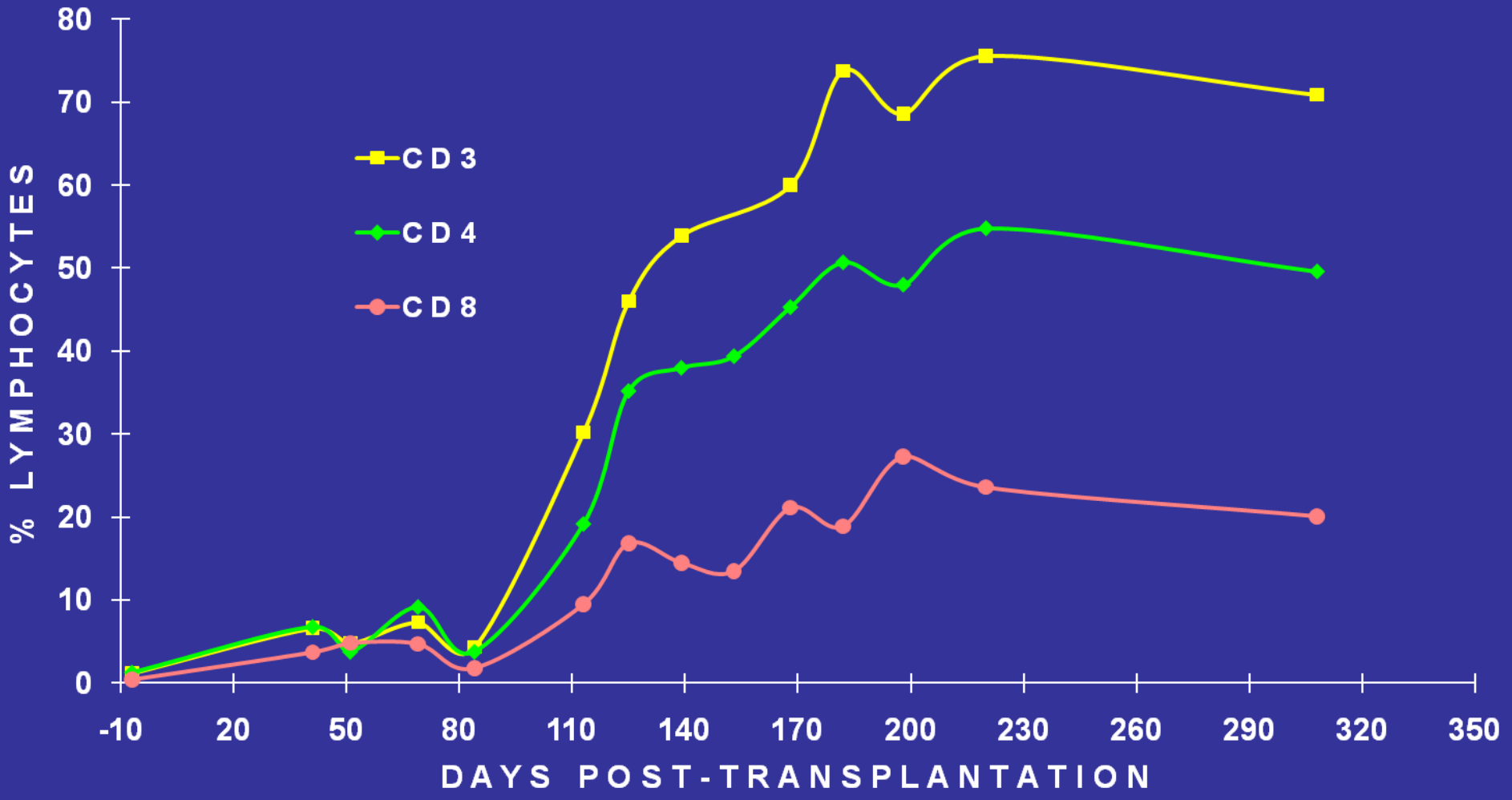
- Known since 1968 that all types can be treated successfully by bone marrow transplantation, without a need for pre-transplant chemotherapy, because they have no T cells to reject the transplant.
- Until 33 years ago this required strict HLA identity between donor and recipient to avoid lethal graft-versus-host 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.


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

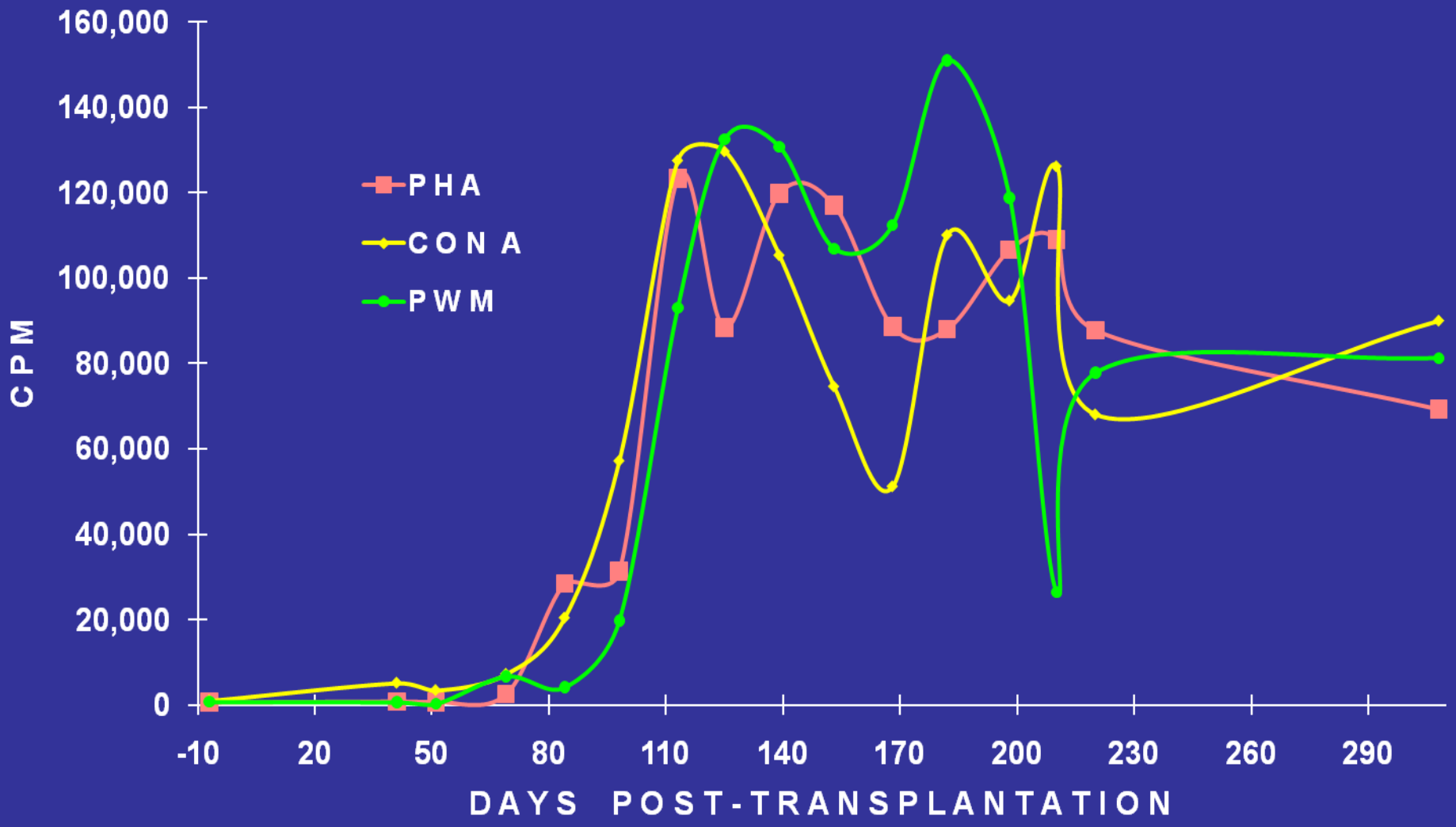




T Cell Development in a Jak3 Def SCID Patient after T Cell-Depleted Haploidentical Marrow Transplantation



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



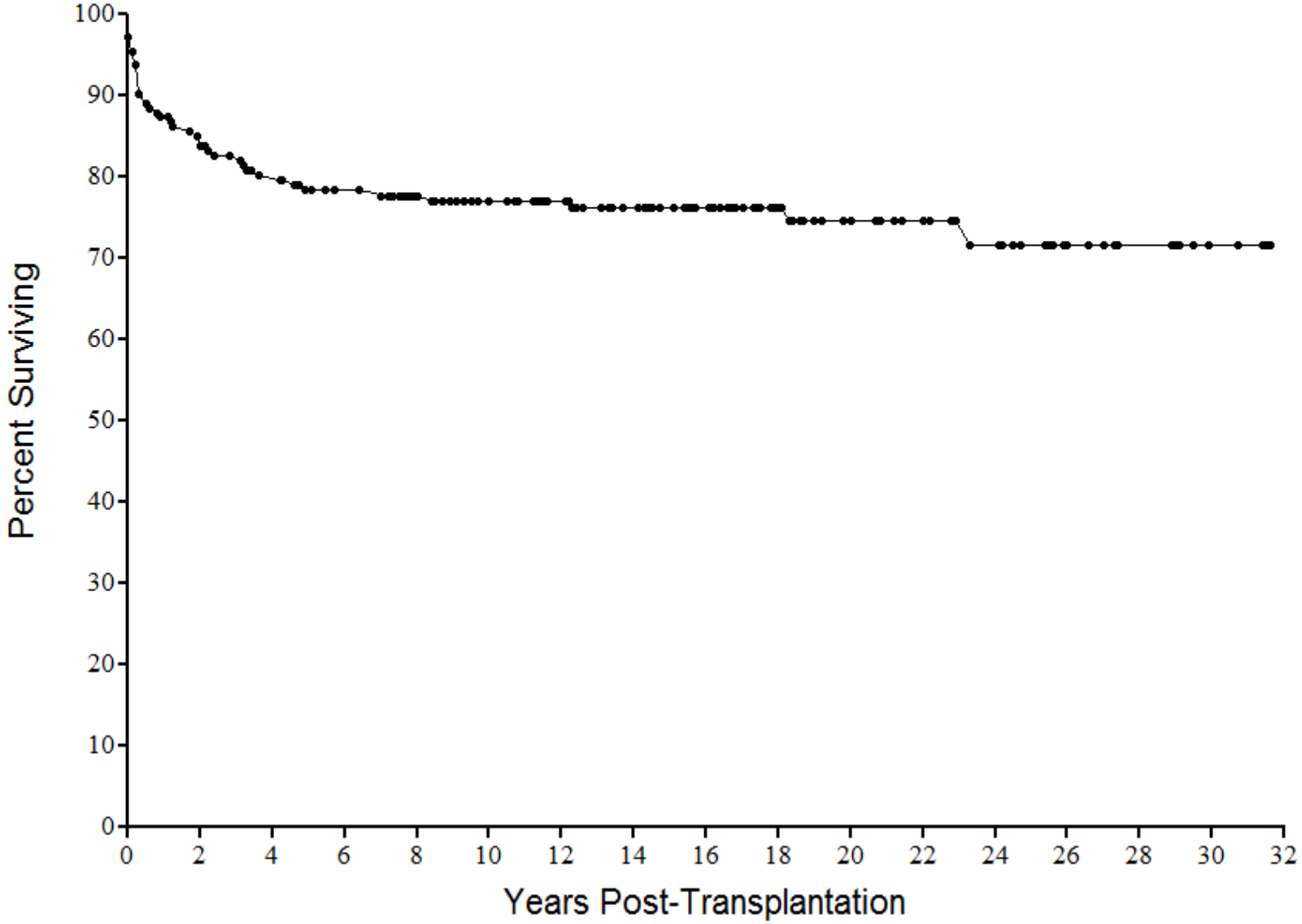
Bone Marrow Transplantation* for Severe Combined Immunodeficiency at Duke University Medical Center 5/19/82-7/31/15

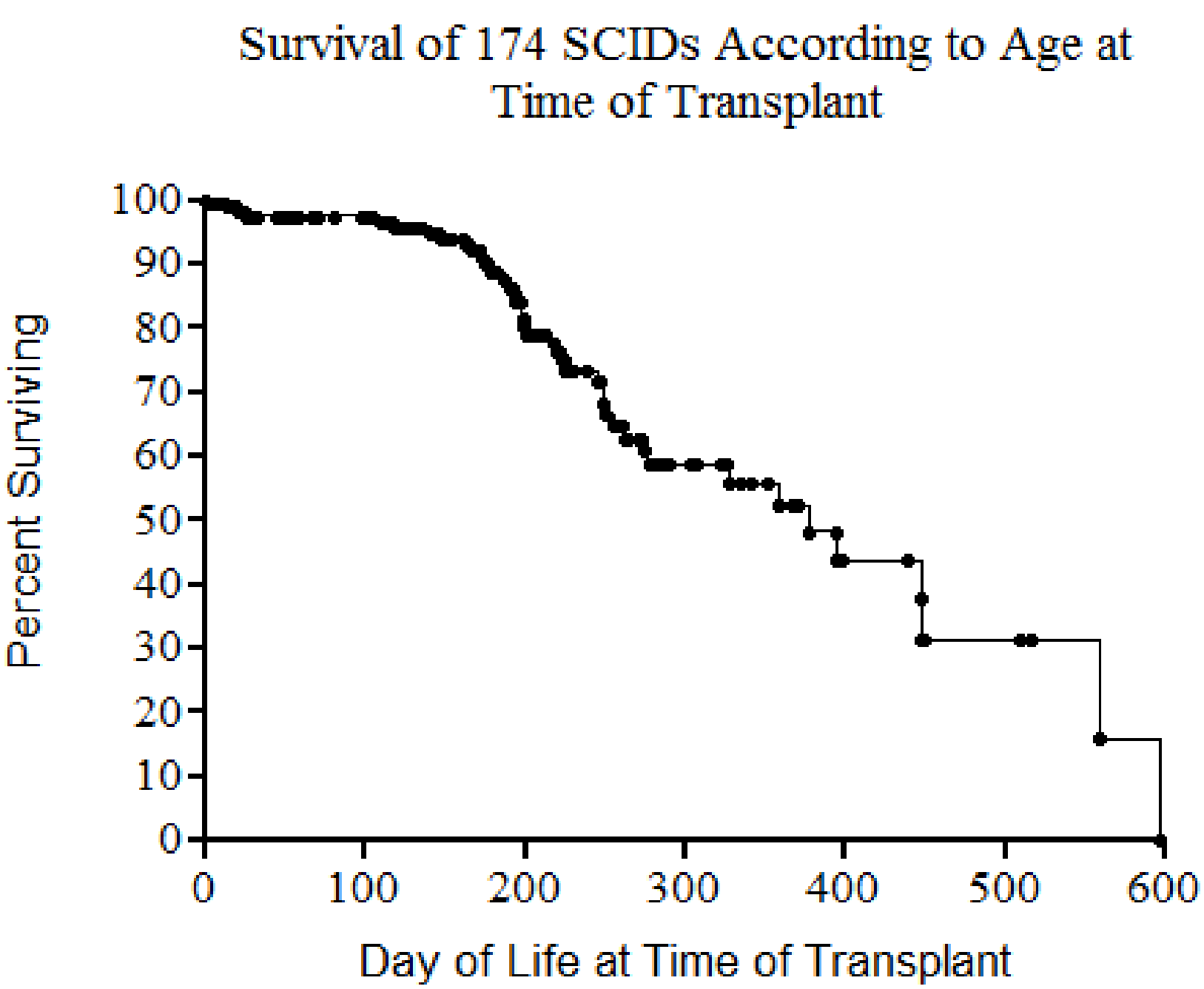
- Number surviving: 133 of 176 or 76%.
- Survivors range from 1 to 33 years post-transplantation.
- HLA-identical**: 18 of 18 or 100%.
- HLA haploidentical***: 115 of 158 or 73%.
- When transplanted before 3.5 months of life, 50/54 (**92.6%**) survive for up to 33 years.

***Non-ablated; related donors**.

**10% of total ***90% of total

32.5 Year Survival (76%) of 176 SCID Patients Given Non-ablated, Related Donor Bone Marrow Transplants at Duke University Medical Center: 18 HLA-identical, 158 HLA Haploidentical



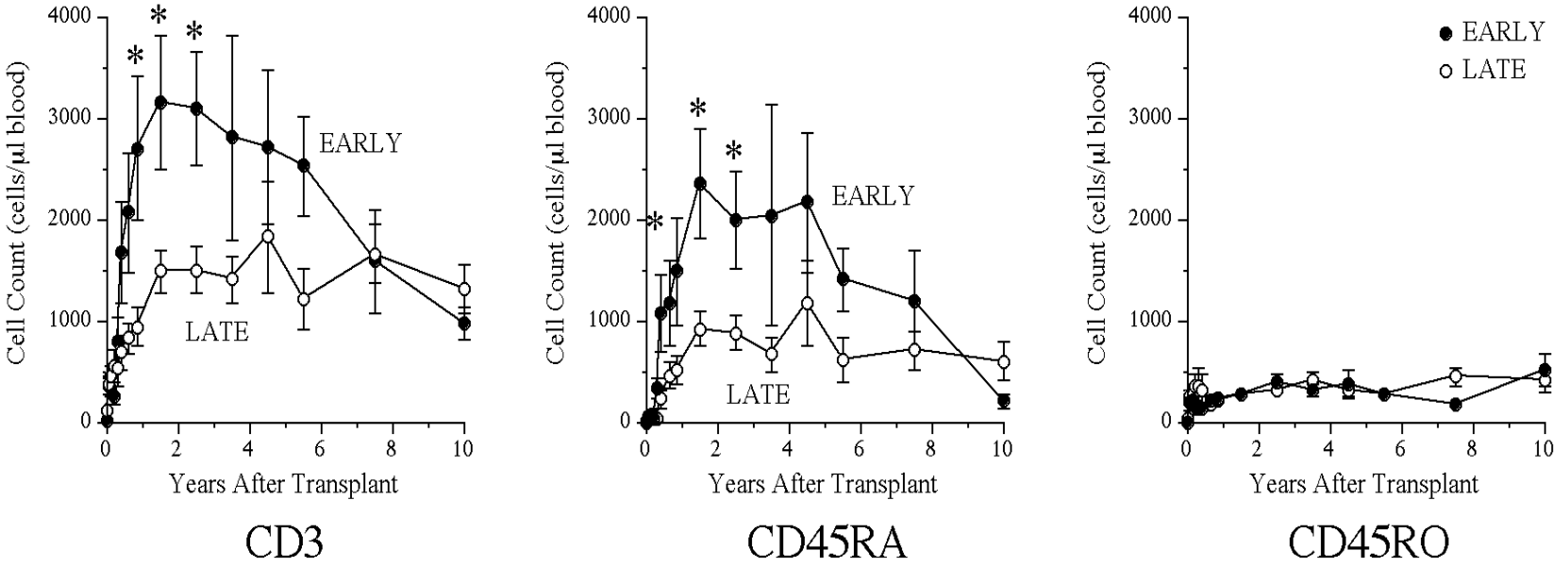

Survival of 174 SCIDs According to Age at Time of Transplant
Percent Surviving
100
90
80
70
60
50
40
30
20
10
0
0
100
200
300
400
500
600
Day of Life at Time of Transplant

Causes of Death in 43* SCIDs After Marrow Transplantation

CMV	9
Adenovirus	9
EBV /Lymphoma	6
Enterovirus, Rotovirus	4
Parainfluenza 3, Varicella	4, 2
Herpes simplex/RSV	1 ea
Pulmonary disease	4
Candida or bacterial sepsis	4
Nephrotic syndrome/chemo	2
Mitochondrial defect	1
CNS Infection	1
VOD	1
GVHD	0

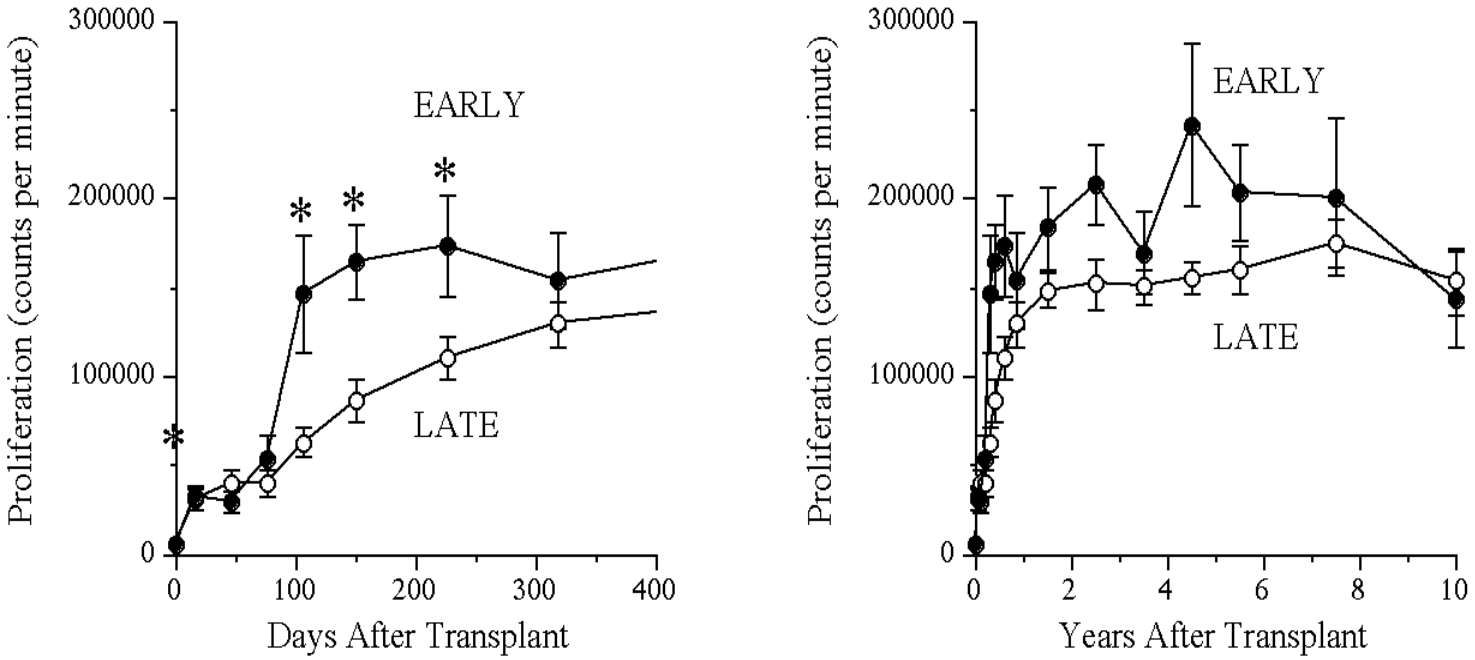
***32/43 (75%) died of viral infections they presented with.**

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)*



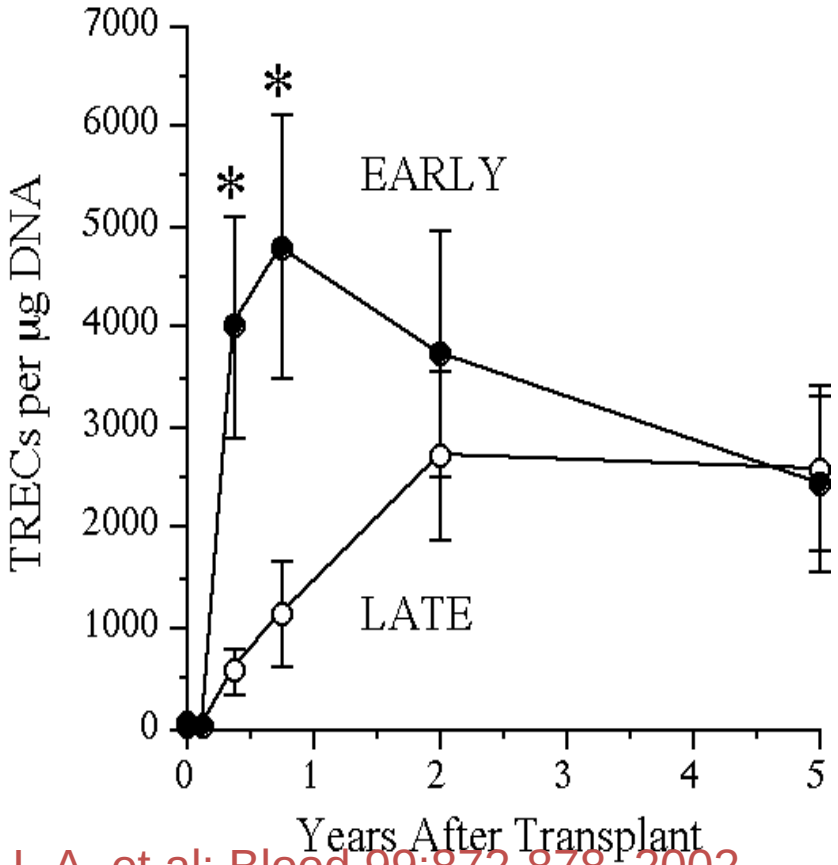
*Myers, L.A. et al: Blood 99:872-878, 2002

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

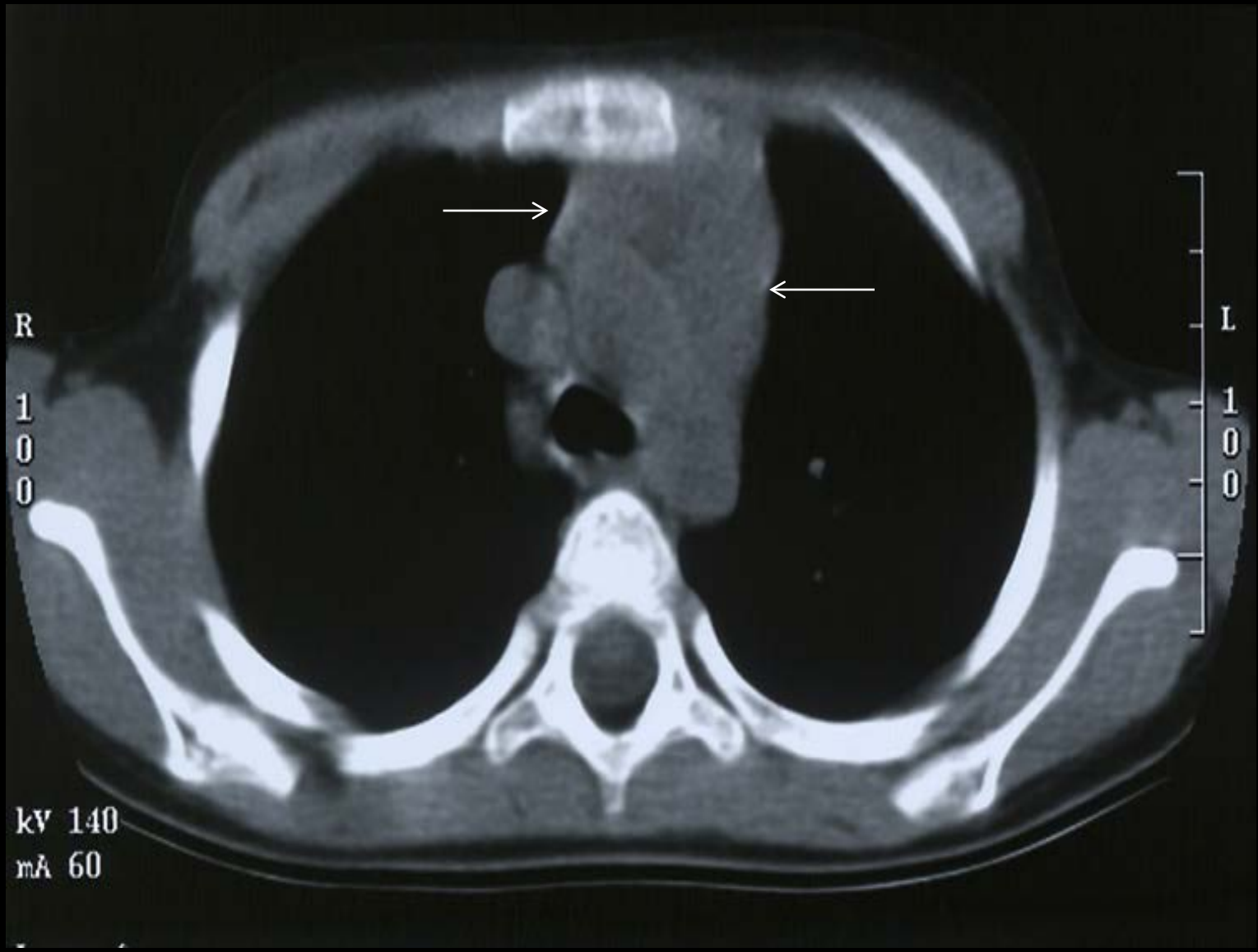


*Myers, L.A. et al: Blood 99:872-878, 2002

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

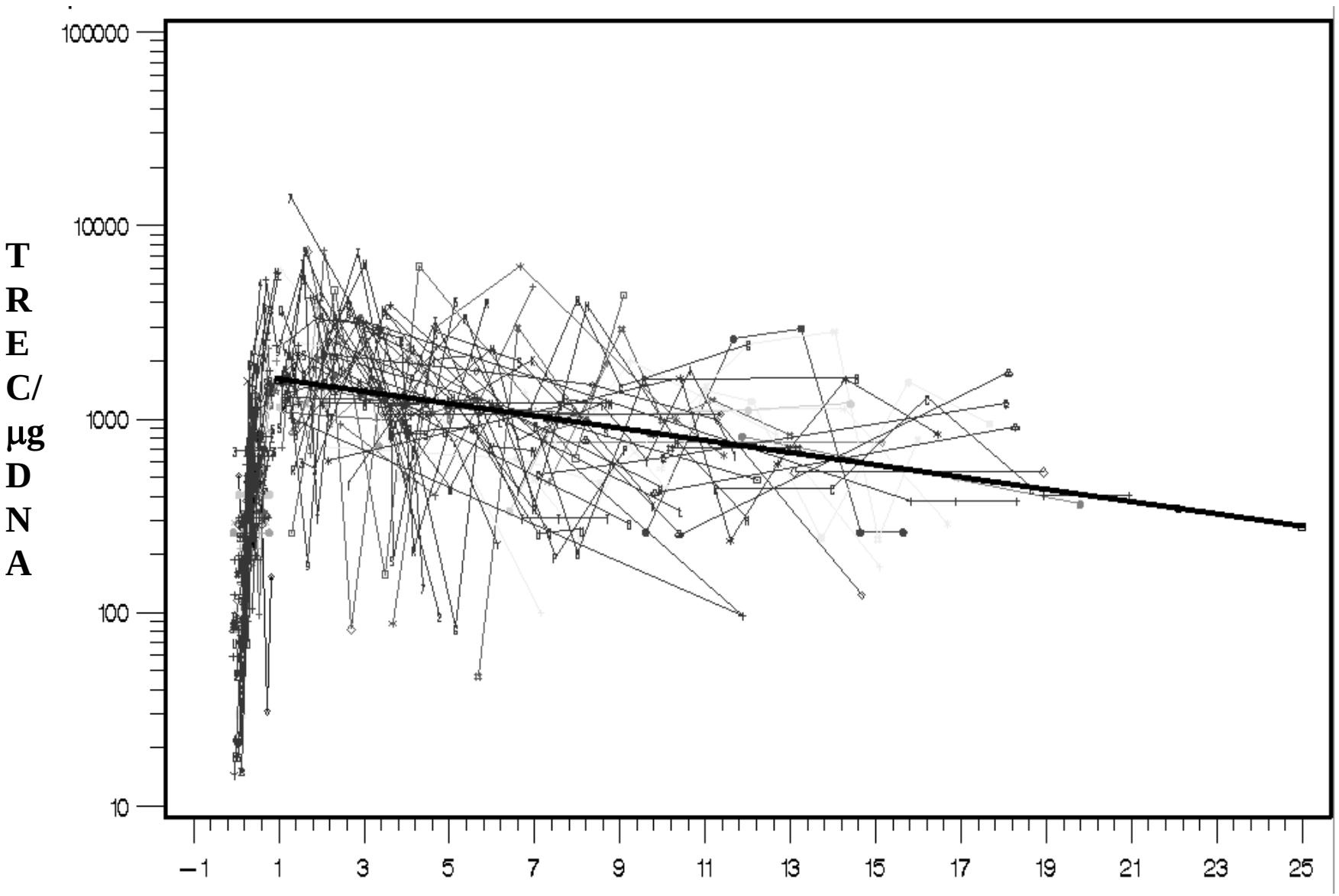


*Myers, L.A. et al: Blood 99:872-878, 2002



Myers, L.A. et al: Blood 99:872-878, 2002

All of the TREC Data on 128 SCIDs



Blood114: 1445-1453, 2009.

Summary and Conclusions Re B Cell Function*

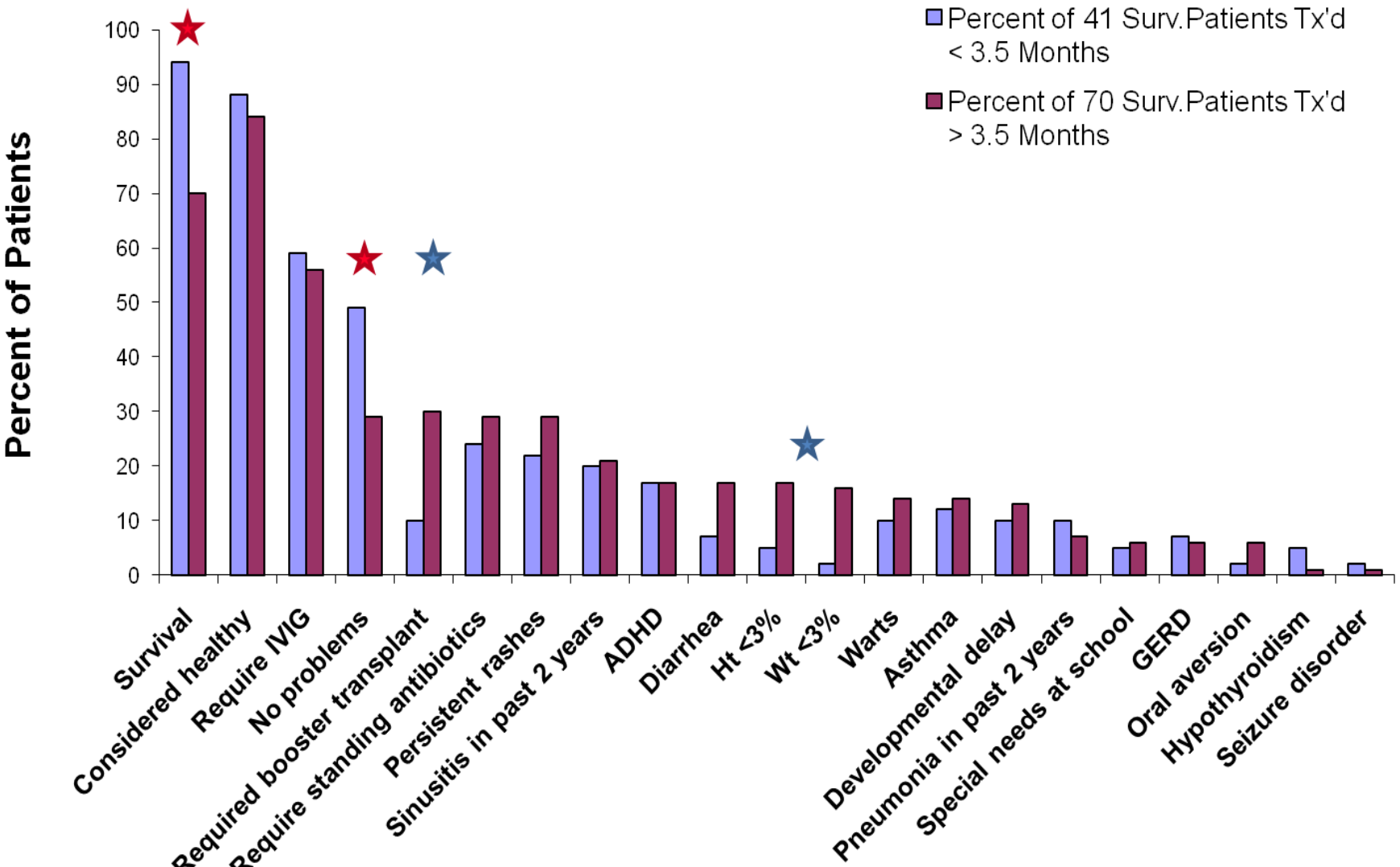
- The most important factor determining the development of normal B cell function post-transplantation in SCID appears to be the underlying molecular defect.

- Several genetic types of SCID (ADA deficient, CD3 chain deficient and IL-7Rα-deficient) develop normal B cell function after BMT despite having only their own B cells.

- Clearly, It is not necessary to use pre-transplant chemoablation to achieve B cell chimerism and function in the latter types of SCID.

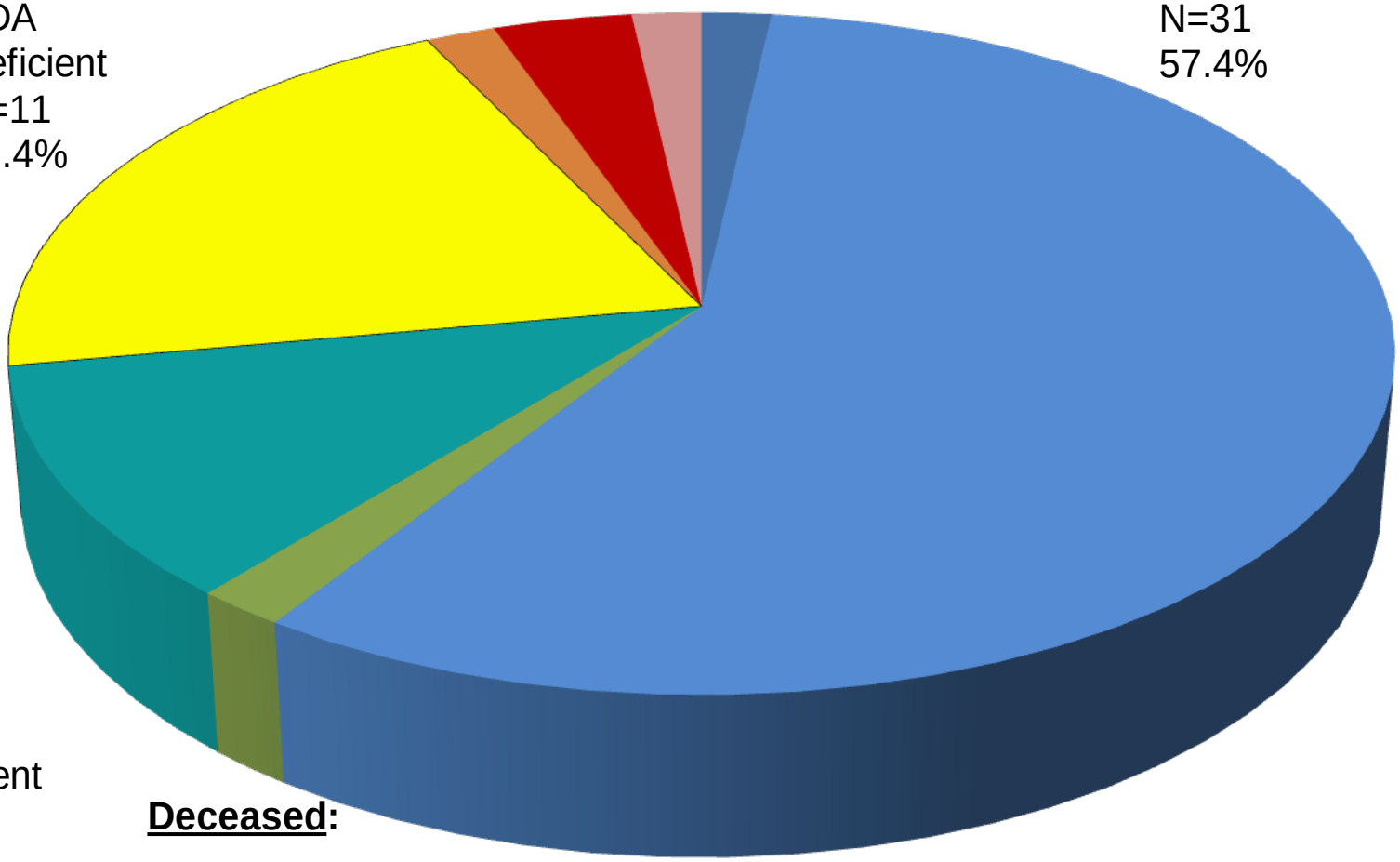
*Buckley et al J. Clin.Immunol, 33: 96-110, 2013.

Clinical Status Post-transplantation



*Railey MD J Pediatrics 155:834-840, 2009

54 SCIDs Transplanted at Duke in the First 3.5 Months of Life: 5 HLA-identical, 49 Haploidentical, <u>No Pre-Tx Chemo</u>. Only 4 required more than 1 transplant. 50 <u>(92.6%) Survive for up to 32.5 Years</u>



<u>Deceased</u>:

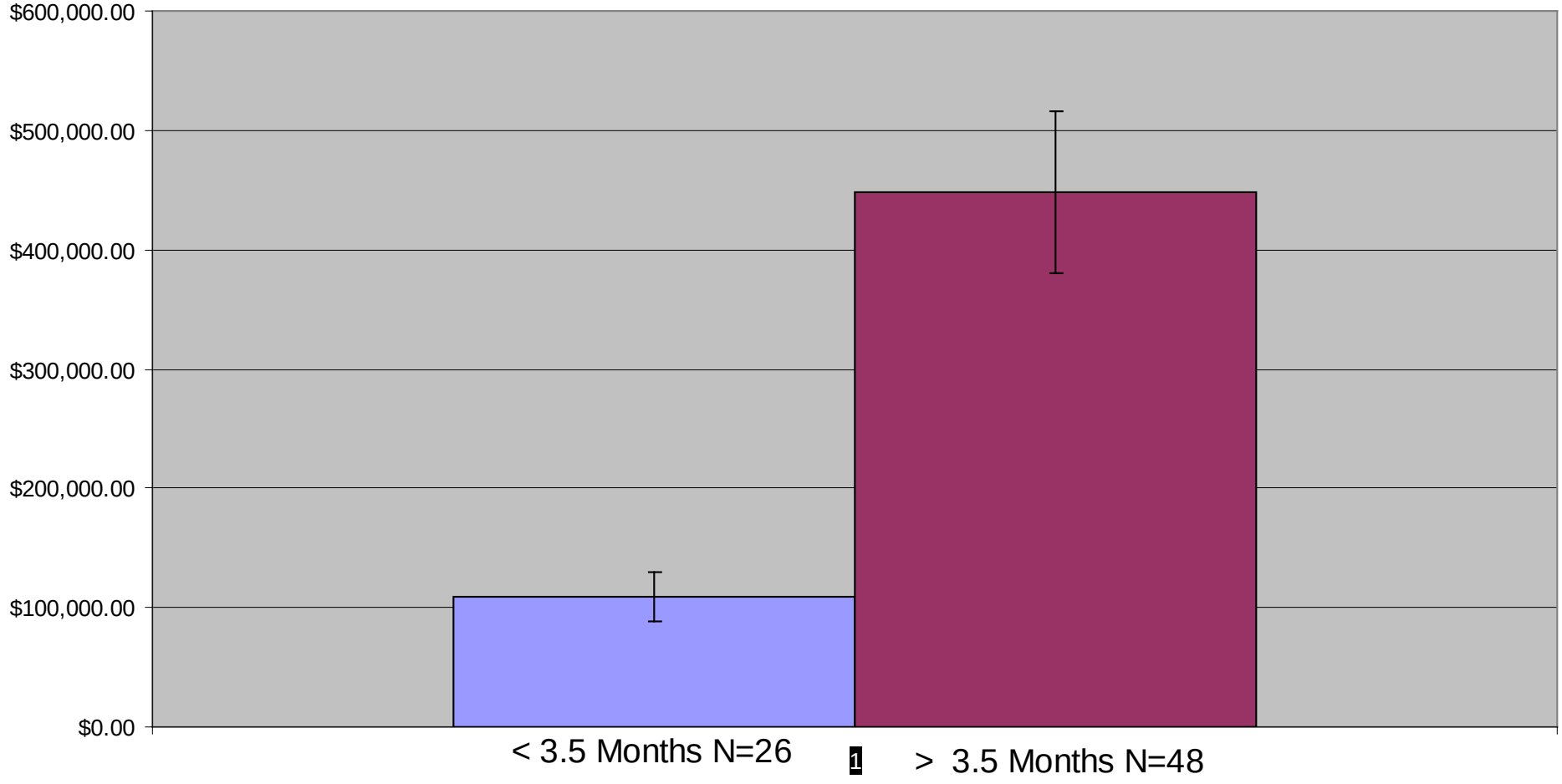
1 X-SCID
1 ADADef SCID
1 IL7Rα Def SCID
1 RAG2 Def SCID

Jak3=1, RAG=2, AutoRec=1,
CD3δ=1 Artemis=1

Neonatal Bone Marrow Transplants

- Of the 54 SCID infants transplanted early, 37 were neonates (i.e. less than a month of age) and 12 of them were 10 days of age or less (earliest 7 days of age). Donors were mothers (10), fathers (2) or siblings (1). None were infected at the time of transplant.
- Except for the marrow cell infusion, the infants were outpatients. They were admitted overnight for the cell infusion, then discharged to an apartment and followed in the clinic every 1-2 weeks until T cell function developed. They did not have central lines and a majority were breastfed.

Mean Total Costs of SCID Bone Marrow Transplants According to Age of the Patient at Transplantation (N=74)

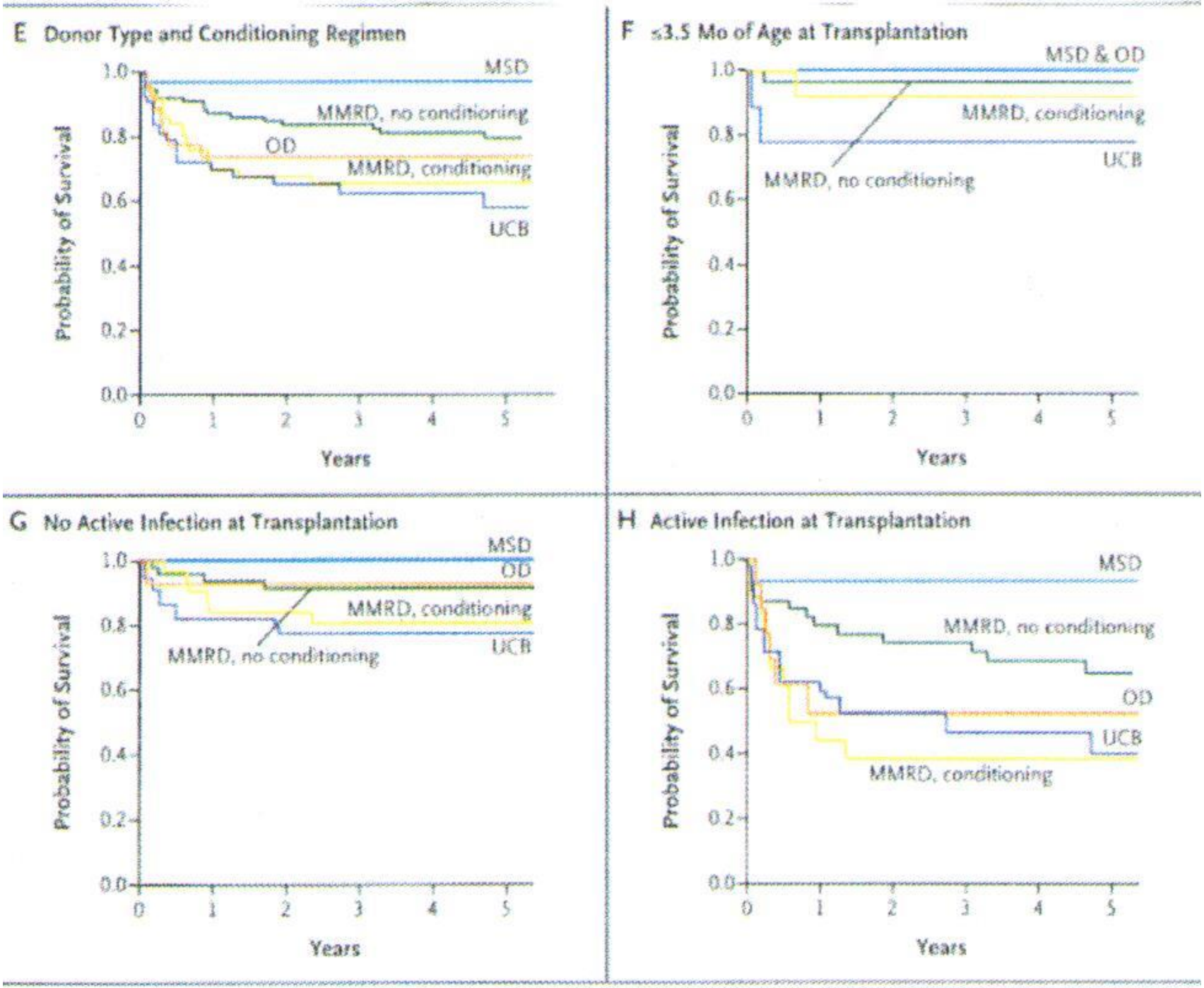


Concerns for the Future

- How can we ensure that screen-positive infants are evaluated by an immunologist first to determine that the diagnosis is correct?
- How many screen-positive infants will receive unnecessary transplants?
- Who will be transplanting these infants? Do they have experience in treating SCID?
- How many SCIDs will receive unnecessary pre-transplant conditioning?

NIAID Primary Immunodeficiency Treatment Consortium (PIDTC) Retrospective Study Transplantation Outcomes for 240 Severe Combined Immunodeficiency Patients, 2000–2009. New England Journal of Medicine 371: 434-446, 2014. PMID: 25075835.

- Survival at 5 years, freedom from immunoglobulin substitution, and CD3+ T-cell and IgA recovery were more likely among recipients of grafts from matched sibling donors than among recipients of grafts from alternative donors.
- However, the survival rate was high regardless of donor type among infants who received transplants at 3.5 months of age or younger (94%) and among older infants without prior infection (90%) or with infection that had resolved (82%).
- **Among actively infected infants without a matched sibling donor, survival was best among recipients of haploidentical T-cell–depleted transplants in the absence of any pretransplantation conditioning.**
- Among survivors, reduced-intensity or myeloablative pretransplantation conditioning was associated with an increased likelihood of a CD3+ T-cell count of more than 1000 per cubic millimeter, freedom from immunoglobulin substitution, and IgA recovery but did not significantly affect CD4+ T-cell recovery or recovery of phytohemagglutinin-induced T-cell proliferation.
- The genetic subtype of SCID affected the quality of CD3+ T-cell recovery but not survival.


E Donor Type and Conditioning Regimen
MSD
MMRD, no conditioning
OD
MMRD, conditioning
UCB
Probability of Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Years
F ≤3.5 Mo of Age at Transplantation
MSD & OD
MMRD, conditioning
UCB
MMRD, no conditioning
Probability of Survival
Years
G No Active Infection at Transplantation
MSD
OD
MMRD, conditioning
UCB
MMRD, no conditioning
Probability of Survival
Years
H Active Infection at Transplantation
MSD
MMRD, no conditioning
OD
UCB
MMRD, conditioning
Probability of Survival
Years

Adverse Events from Pre-Transplant Chemotherapy

Early

- Neutropenia, diminishing innate immunity
- thrombocytopenia, bleeding
- anemia
- mucositis
- nausea, vomiting, diarrhea
- hair loss
- hemorrhagic cystitis
- **Veno-occlusive disease**

Adverse Events from Pre-transplant Chemotherapy (cont'd)

- Late
  - kidneys, liver, heart, lungs
  - poor growth
  - poor tooth development
  - delayed puberty, **sterility**
  - malignancy

Effects of Chemotherapy on Neurodevelopment and Neurocognition

- Lin M. Long-term neurocognitive function of pediatric patients with severe combined immunodeficiency (SCID): pre- and post-hematopoietic stem cell transplant (HSCT). J Clin Immunol 2009;29(2):231-7.
- Titman P. Cognitive and behavioral abnormalities in children after hematopoietic stem cell transplantation for severe congenital immunodeficiencies. Blood 2008;112(9)3907-3913.

Conclusions

- 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 (92.6 percent) probability of longterm success.
- T cell-depleted haploidentical marrow transplantation provides life-saving therapy for all forms of SCID, but it, like other forms of treatment, is not a perfect treatment.

Collaborators

Co-Investigators

- Joseph L. Roberts, MD/PhD
- Marcella Sarzotti-Kelsoe, PhD
- Talal Mousallem, MD

Duke Clinicians

- M. Louise Markert, MD/PhD
- Suhag Parikh, MD

Co-ordinators and Care

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

Duke Technicians

- Roberta Parrott, BS
- Steve Showalter, CMT
- Jean Rundquist, CMT

Conditions with Low or Absent T Cells Detected by TREC Screening

Multisystem syndromes with variable T cell deficiency

57% DiGeorge/chromosome 22q11.2 deletion
15% Trisomy 21
3% Ataxia telangiectasia
2% CHARGE syndrome

Secondary T lymphopenia

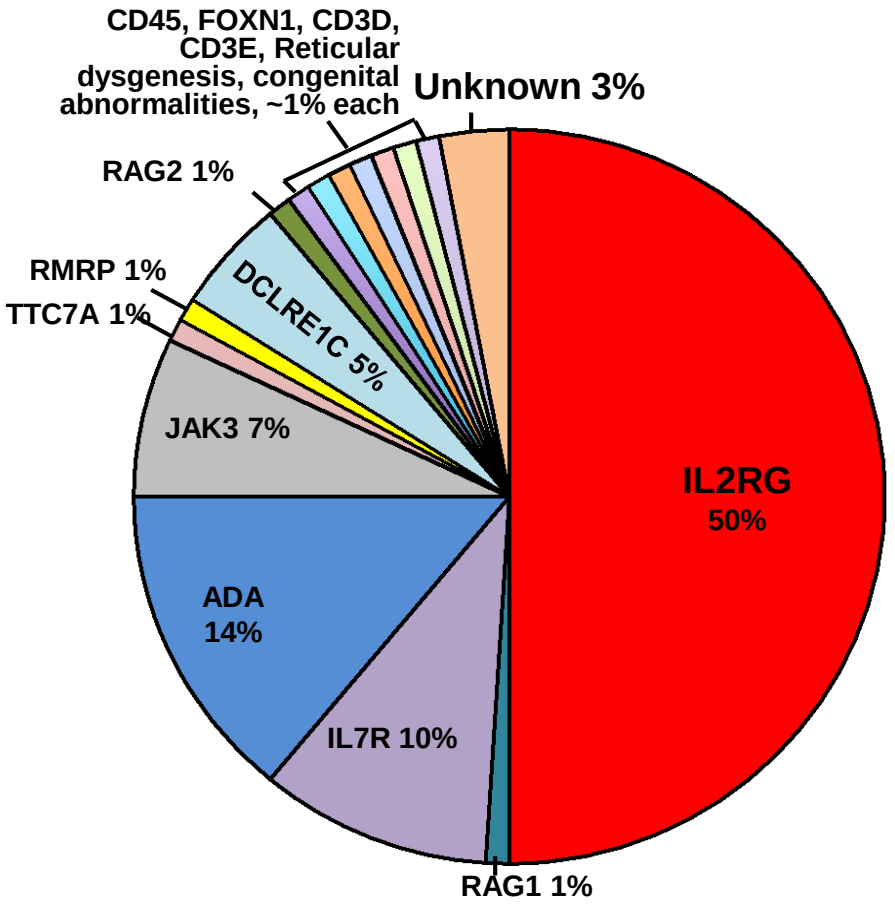
25% Congenital cardiac anomalies
38% Other congenital anomalies
13% Vascular leakage, third spacing, hydrops
3% Neonatal leukemia

Extreme preterm birth alone—T cells become normal over time

"Variant SCID" or Idiopathic T lymphopenia—Low T cells and TRECs, low naïve CD45RA T cells, no maternal engraftment, impaired T cell or antibody responses, no known gene defect

SCID Cases reported from Transplant Centers

Incidence 1 per 100,000



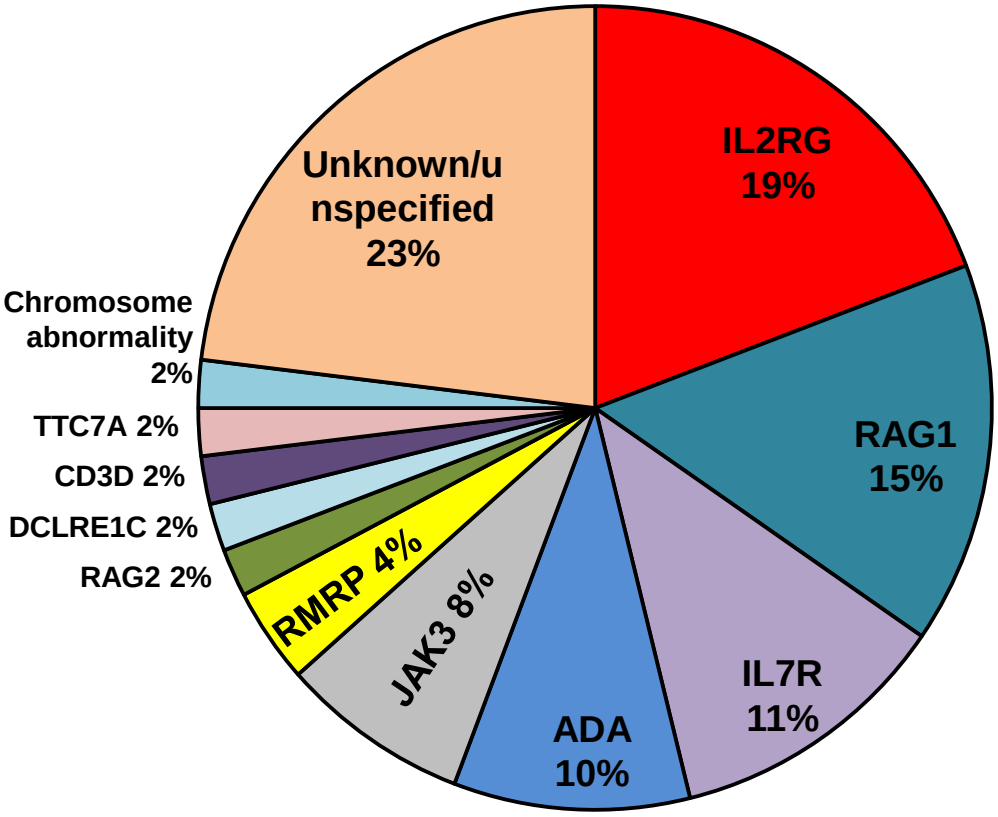
Combined estimates from published series (Duke, European, PIDTC)

SCID Cases found by Newborn Screening

52 cases in 3 Million Infants

1.715 per 100,000, or 1/58,000

Survival 92%



Kwan et al., Manuscript published, 2014

Implementation Status