Hematopoietic Stem Cell Transplantation:

Evolution of a Peripheral Stem Cell Therapy

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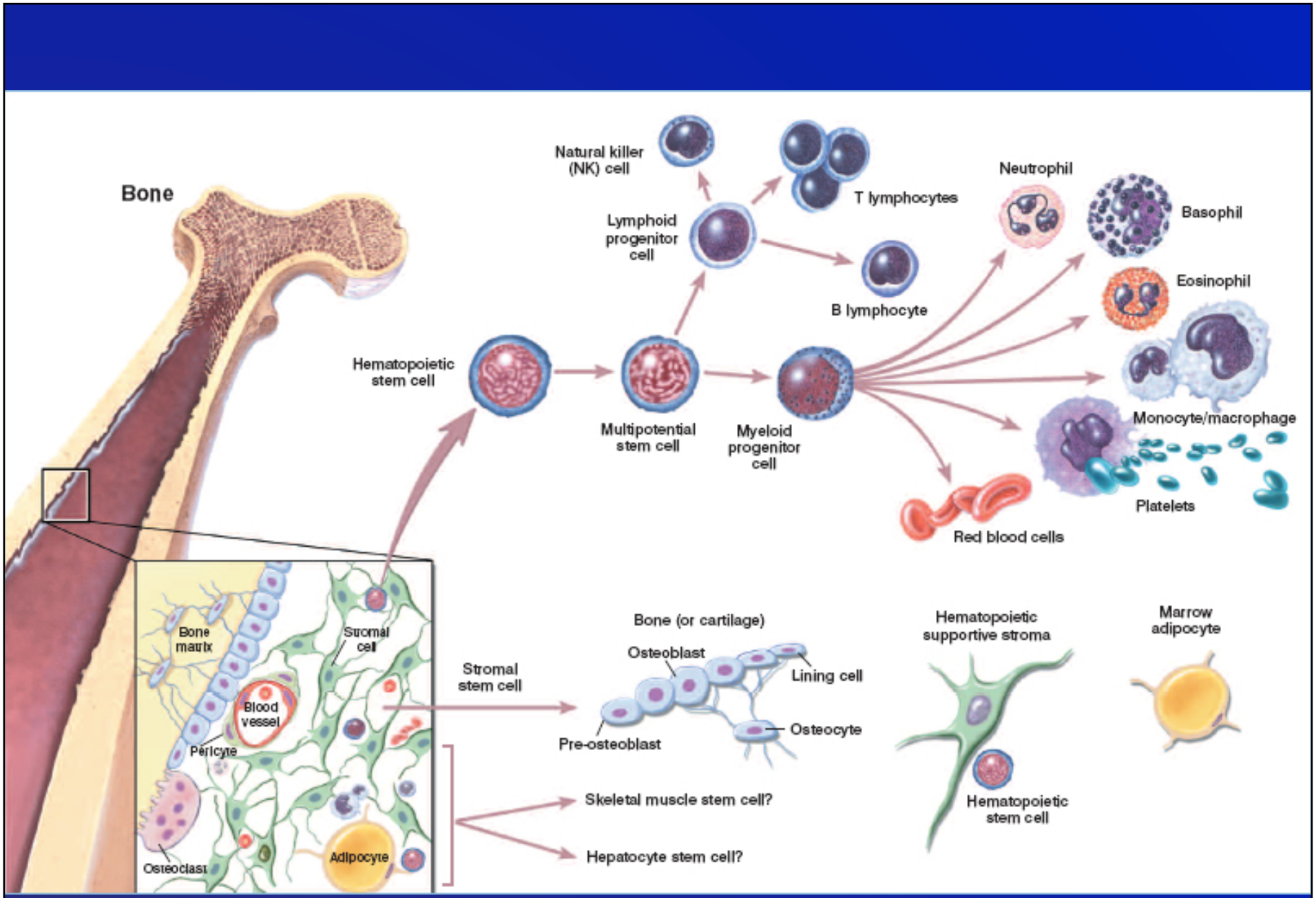
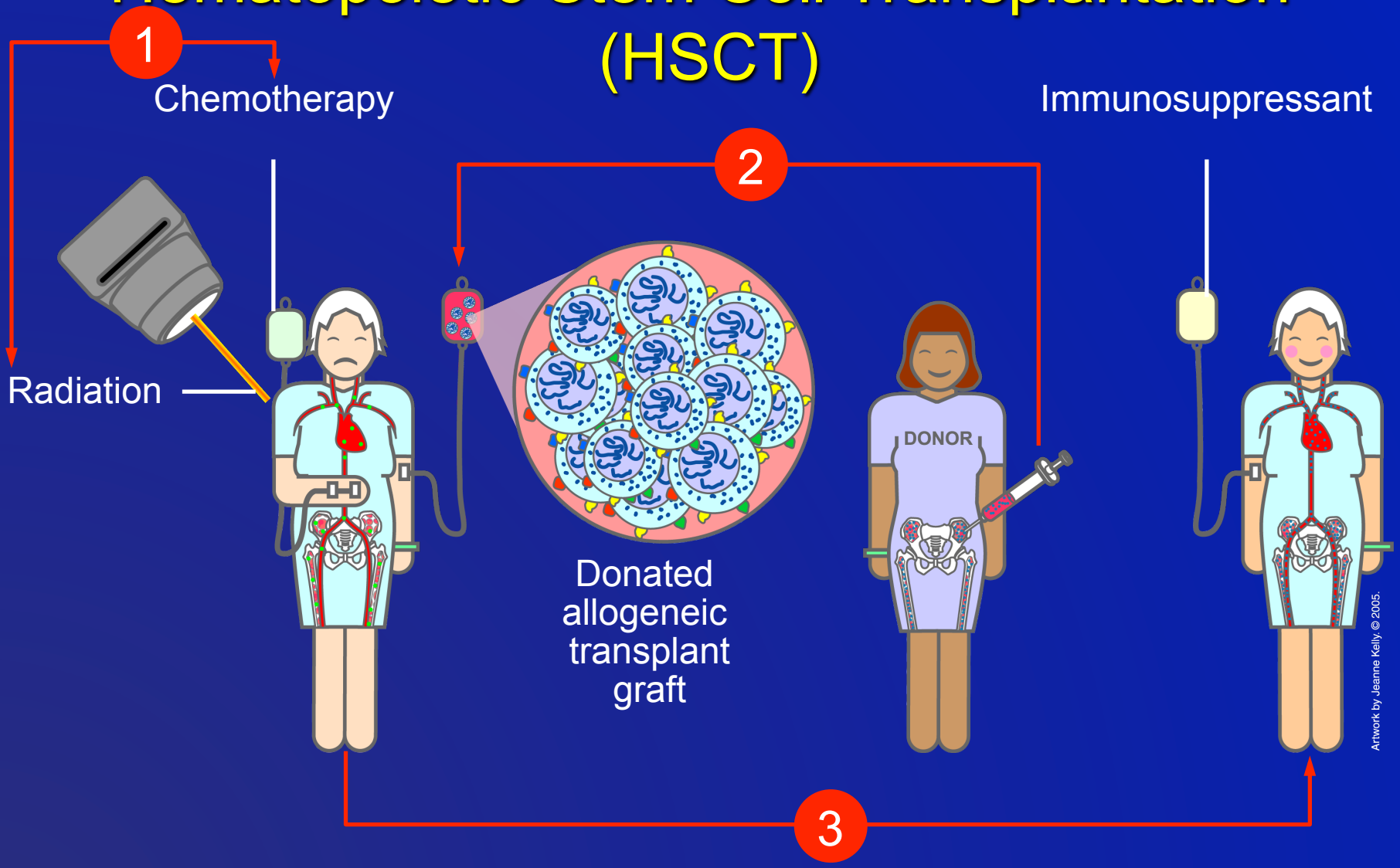


Hematopoietic and stromal cell differentiation.

Available at <http://stemcells.nih.gov/info/2006report/2006chapter2>

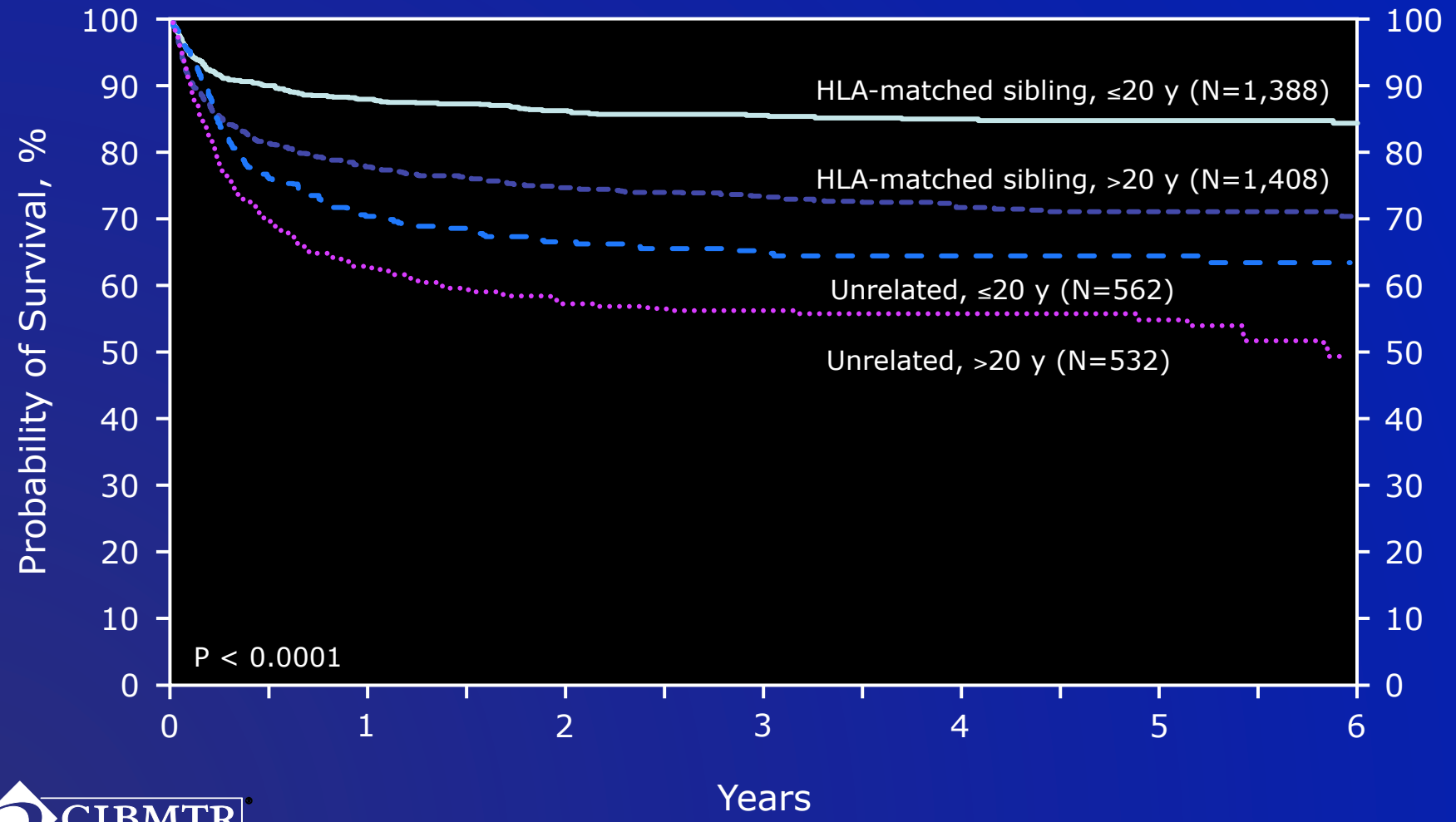
Hematopoietic Stem Cell Transplantation (HSCT)



Historical Perspective of Hematopoietic Stem Cell Transplantation (HSCT): Revolution in Practice

1950's	Rescue of radiation-induced marrow failure Transfer of marrow as therapy
1960 – 1990	Ablation of marrow – Eradication of hematopoietic malignancies • GVHD correlates with cure • Relapse is greater in absence of allogeneic differences between donors and patients (identical twins) • Relapse is greater if T cells are removed from donor inoculum • Infused T cells after transplant can treat relapsed disease
1990's – present	HSCT is an immunotherapy → non-myeloablative allogeneic HSCT • Hospitalization of 0 - 14 days • Ability to put in place an allogeneic immunotherapy with minimized toxicity • Limited to no neutropenia

Probability of Survival After Allogeneic Transplant for Severe Aplastic Anemia, by Donor Type and Age, 1998-2008



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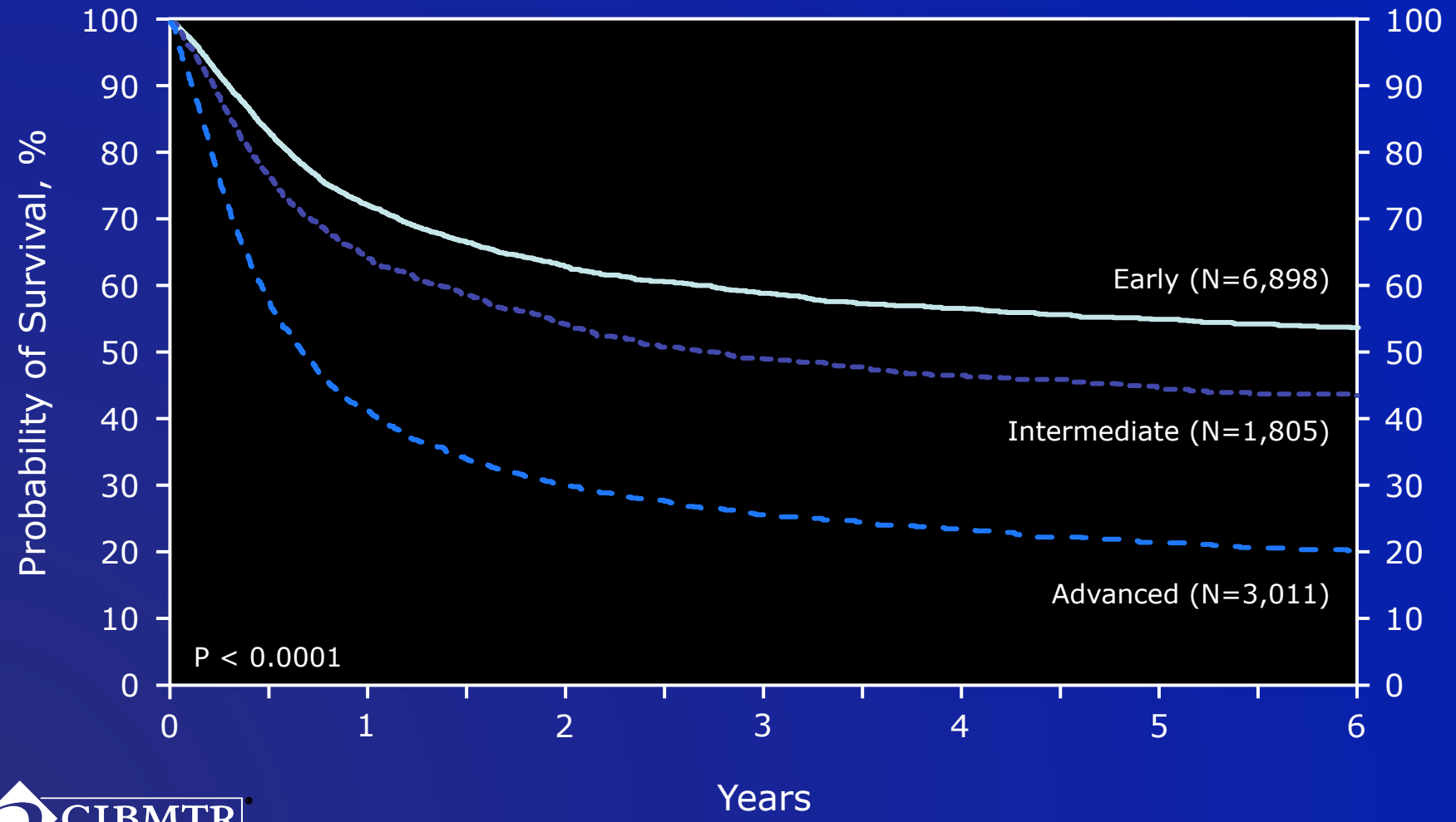
Probability of survival after HLA-matched sibling donor transplant for AML, by disease status, 1998-2008



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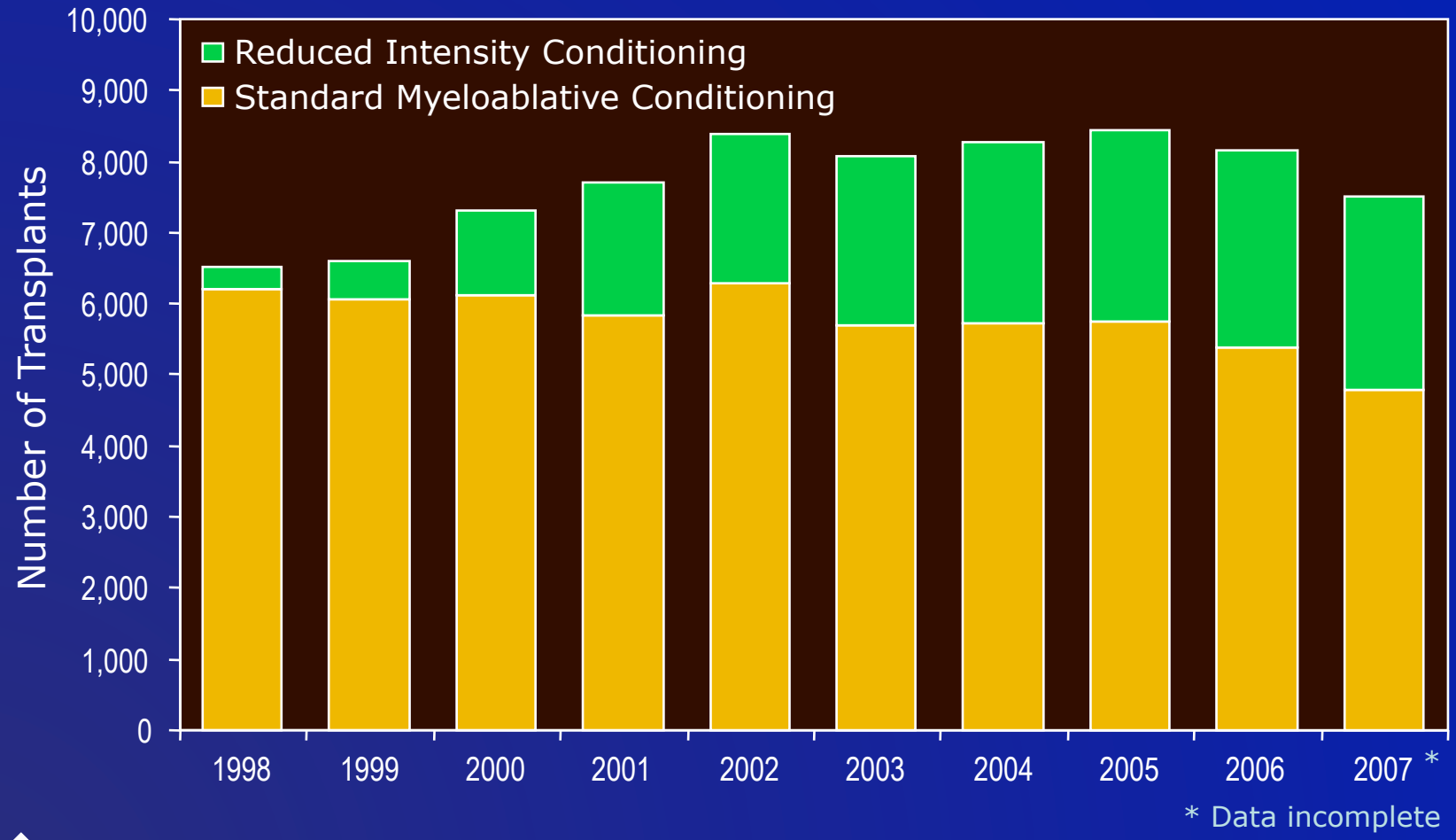
Allogeneic Transplantations by Conditioning Regimen Intensity, Registered with the CIBMTR, 1998-2007



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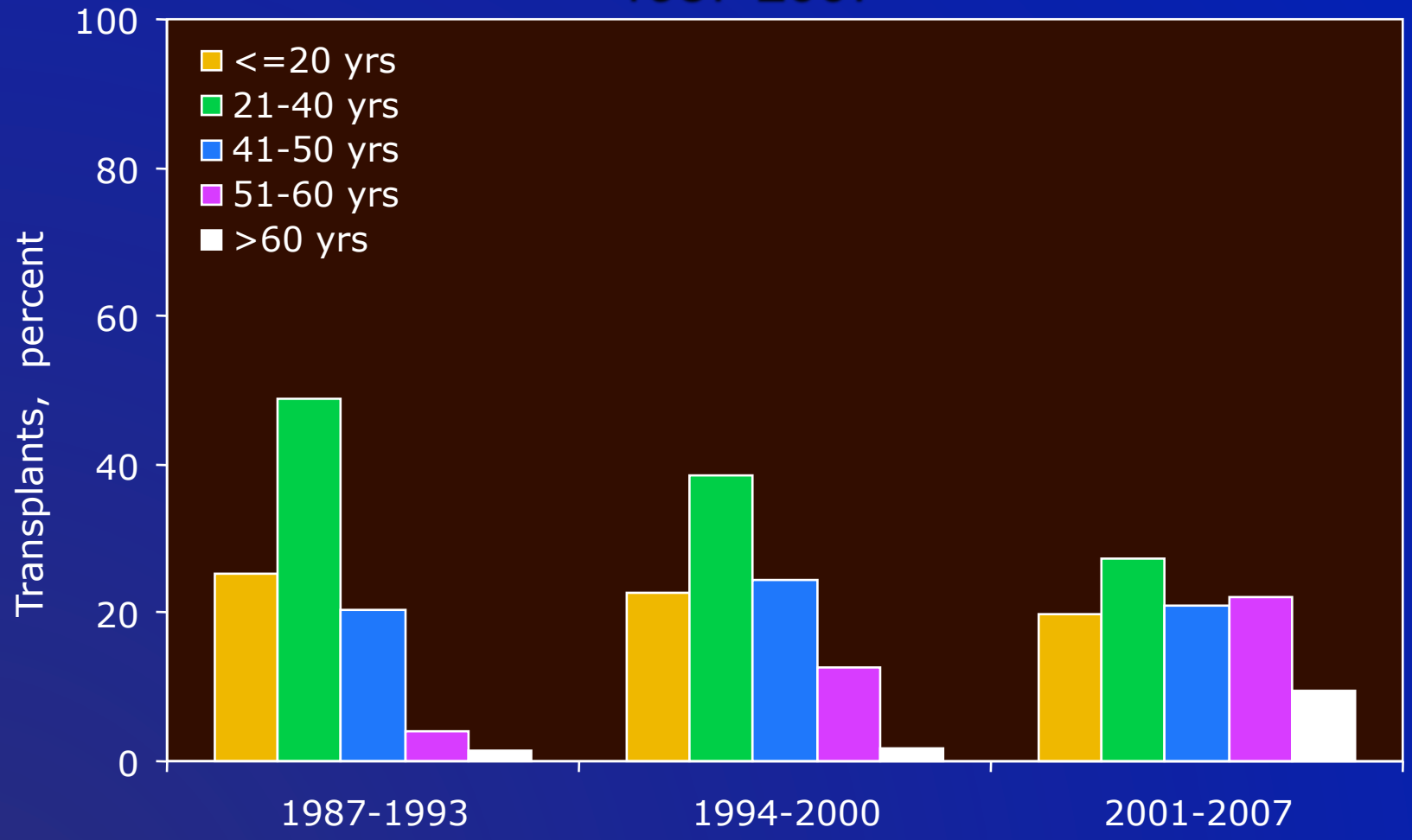
Trends in Allogeneic Transplantation by Recipient Age* 1987-2007



* Transplants for AML, ALL, CML, MM, NHL, CLL, MDS

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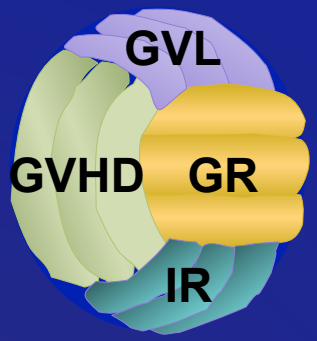
Major Obstacles to Allogeneic Stem Cell Transplantation

- Graft Rejection
- Immune Incompetence
- GVHD
- Relapse/GVL-GVT

Linked Biology of Graft Rejection (GR), GVHD, GVL and Immune Reconstitution (IR)

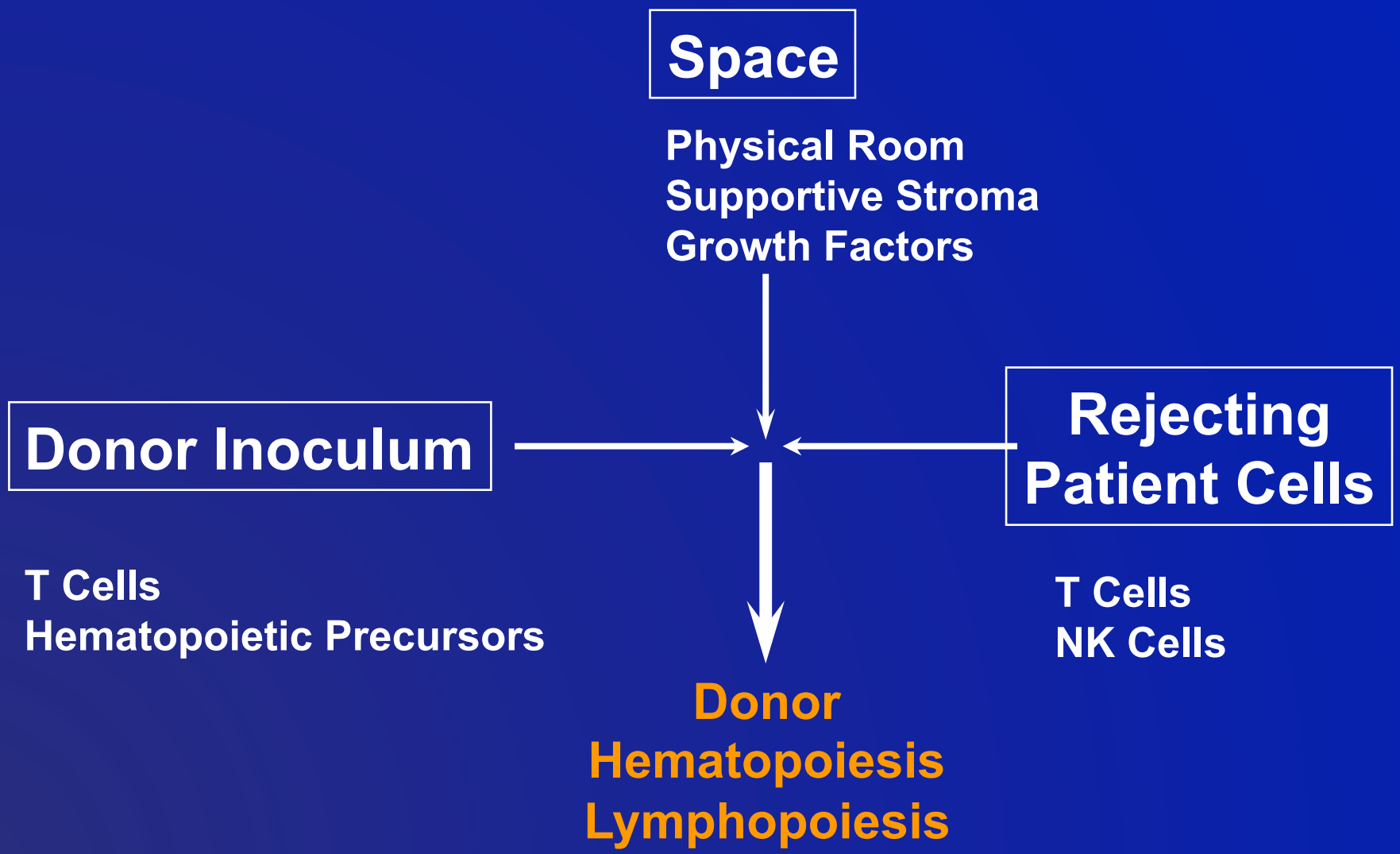


Barriers Are Donor-Recipient Dependent

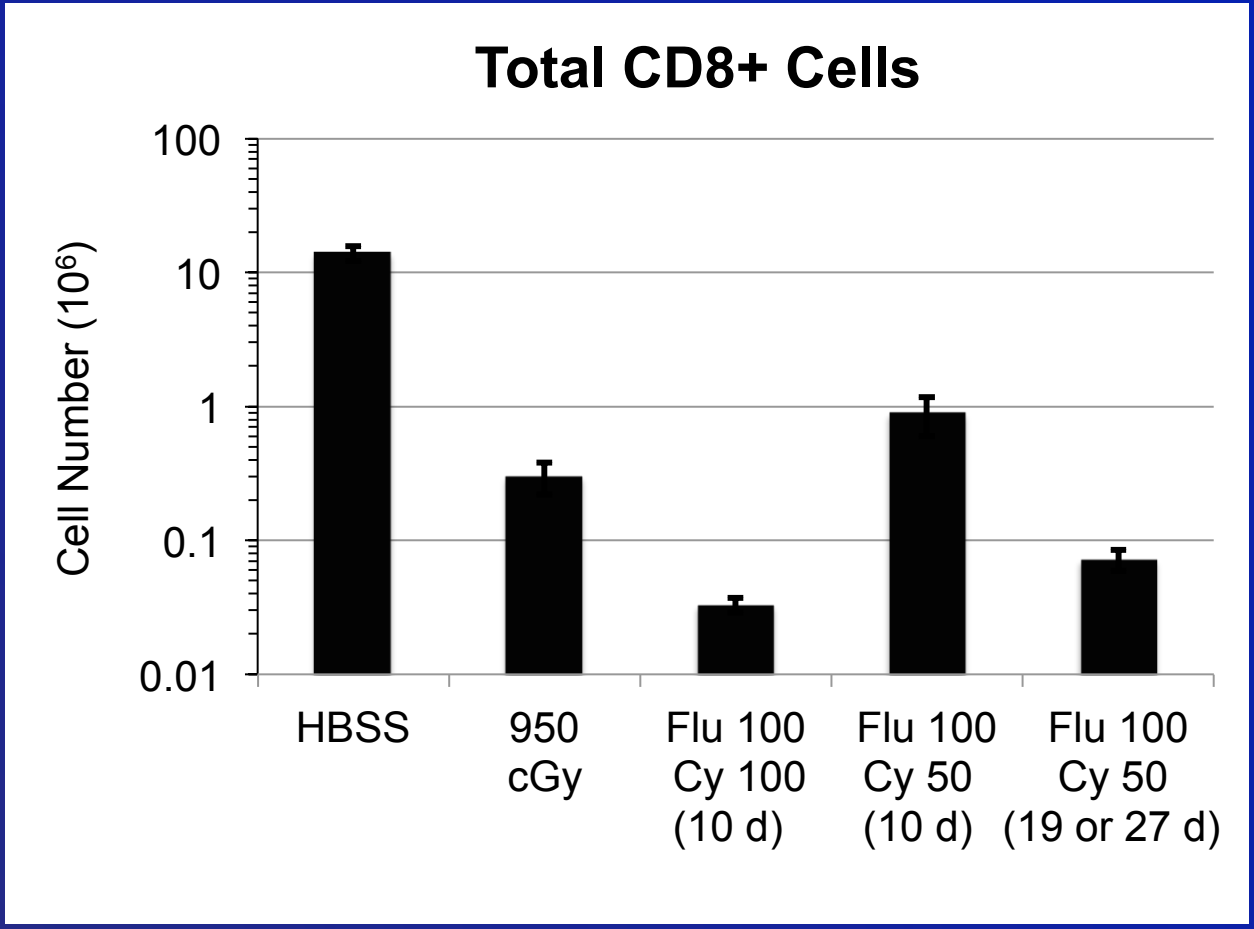
Barrier

Donor	Graft Rejection/ Failure	GVHD	Disease Relapse	Lack of Immune Reconstitution
Matched Sibling	+	+	++	+
Matched Unrelated	++	+	++	++
Cord Blood	+++	±	+/ ++	+++

Determinants of Engraftment

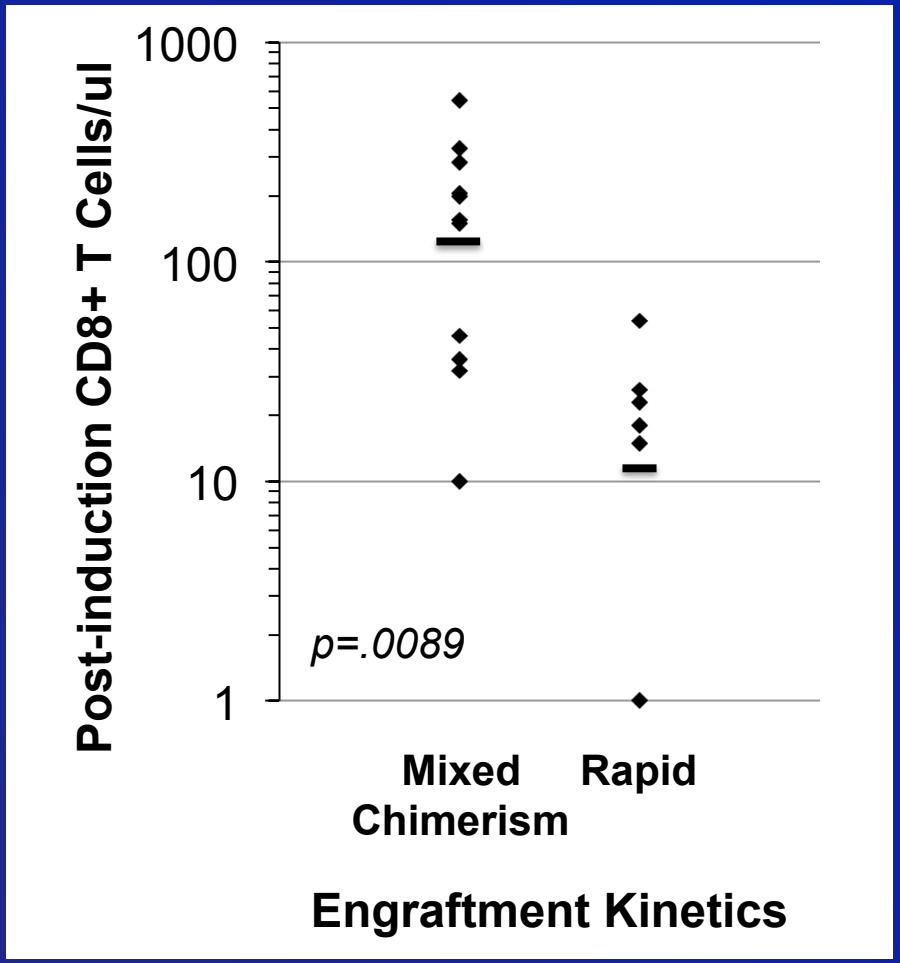


Achieving Optimal Recipient T Cell Depletion



Petrus MJ et al Biology of Blood and Marrow Transplantation; 6: 182 (2000).

Pretreatment T Cell Number Determines Engraftment Rate



Hardy NM et al Biol Blood Marrow Transplant ; 13:1022 (2007).

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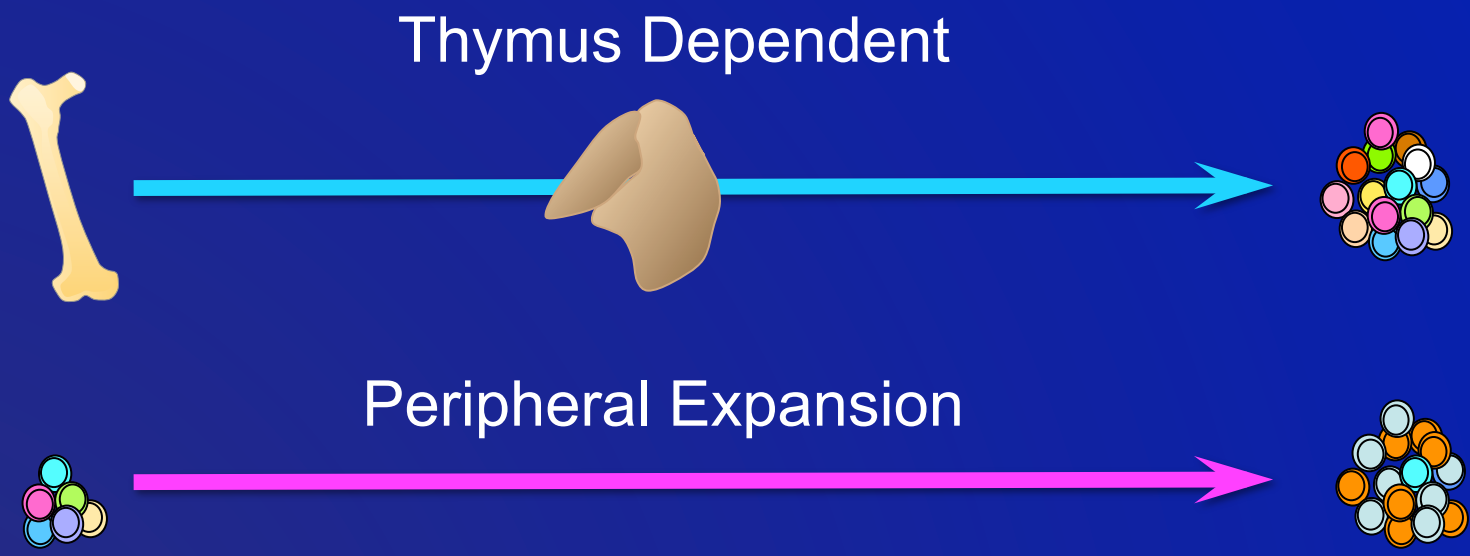
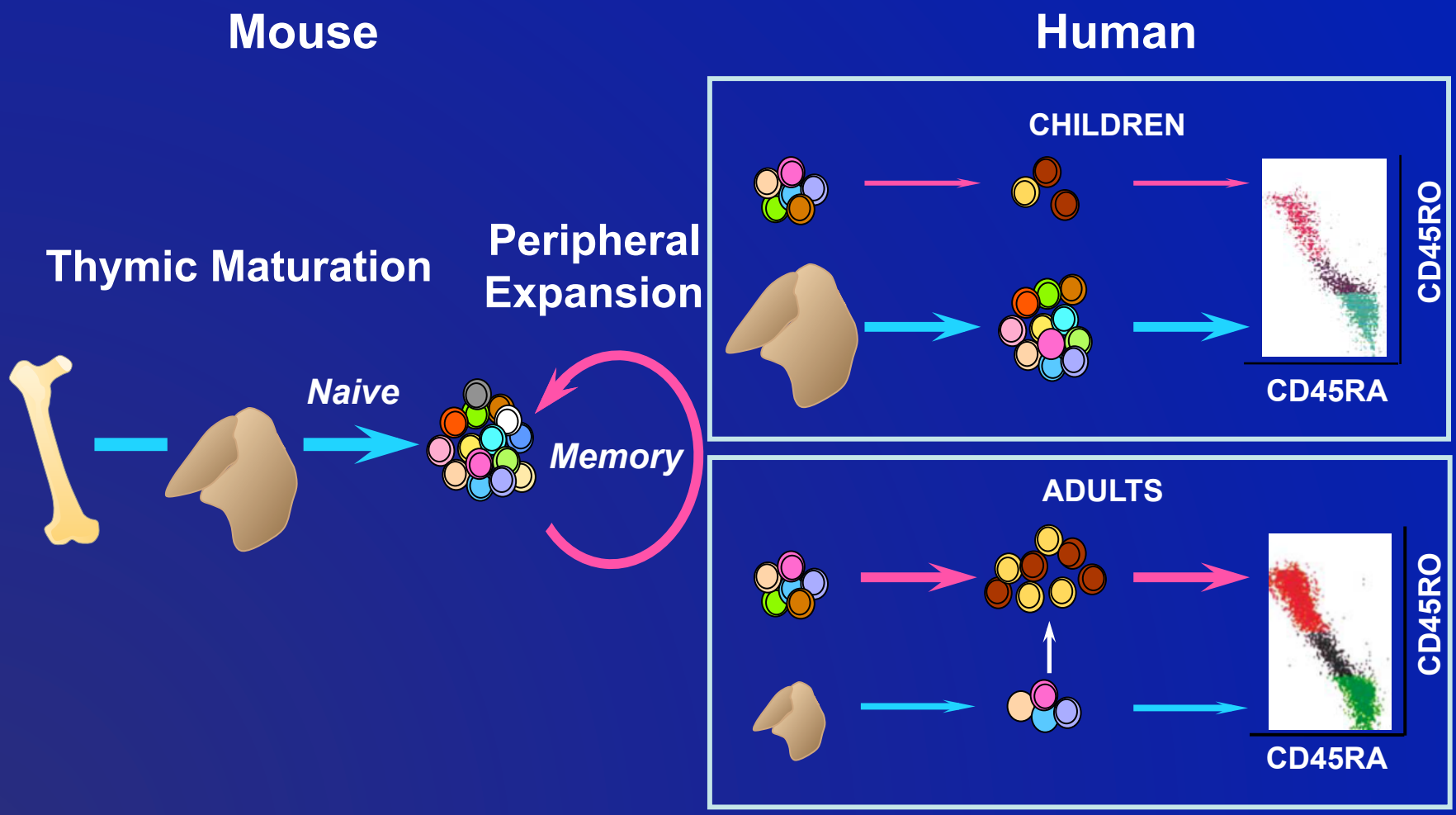
Cord Blood	+++	±	+/ ++	+++

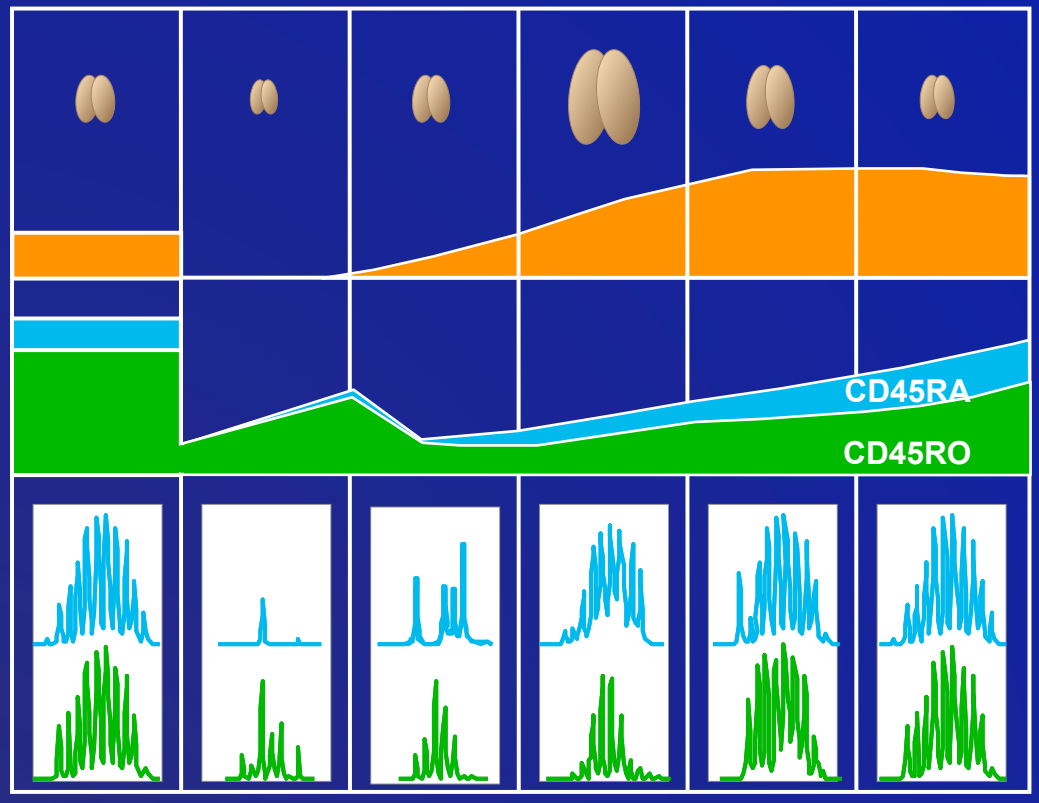
There Are Two Primary Pathways of T Cell Regeneration



CD4+ T Cell Regeneration in Mice and Humans



CD4+ T Cell Reconstitution: Summary of 3-5 Year Prospective Data In Adults



THYMIC SIZE BY IMAGING

RECENT THYMIC EMIGRANTS BY TREC

CD4 CELLS
- **Memory**
- **Naive**

RA

RO

Vβ TCR DIVERSITY BY CDR3 ANALYSIS

Fran Hakim

Enhancing T Cell Immune Reconstitution: Points to Consider

Two pathways exist

There are constraints in recovery even in the autologous setting:

- CD4+ T cell reconstitution (number and diversity) depends on thymus function
- Recovery of thymus function in terms of frequency and rapidity declines with increasing age
- There is regulation of thymus function

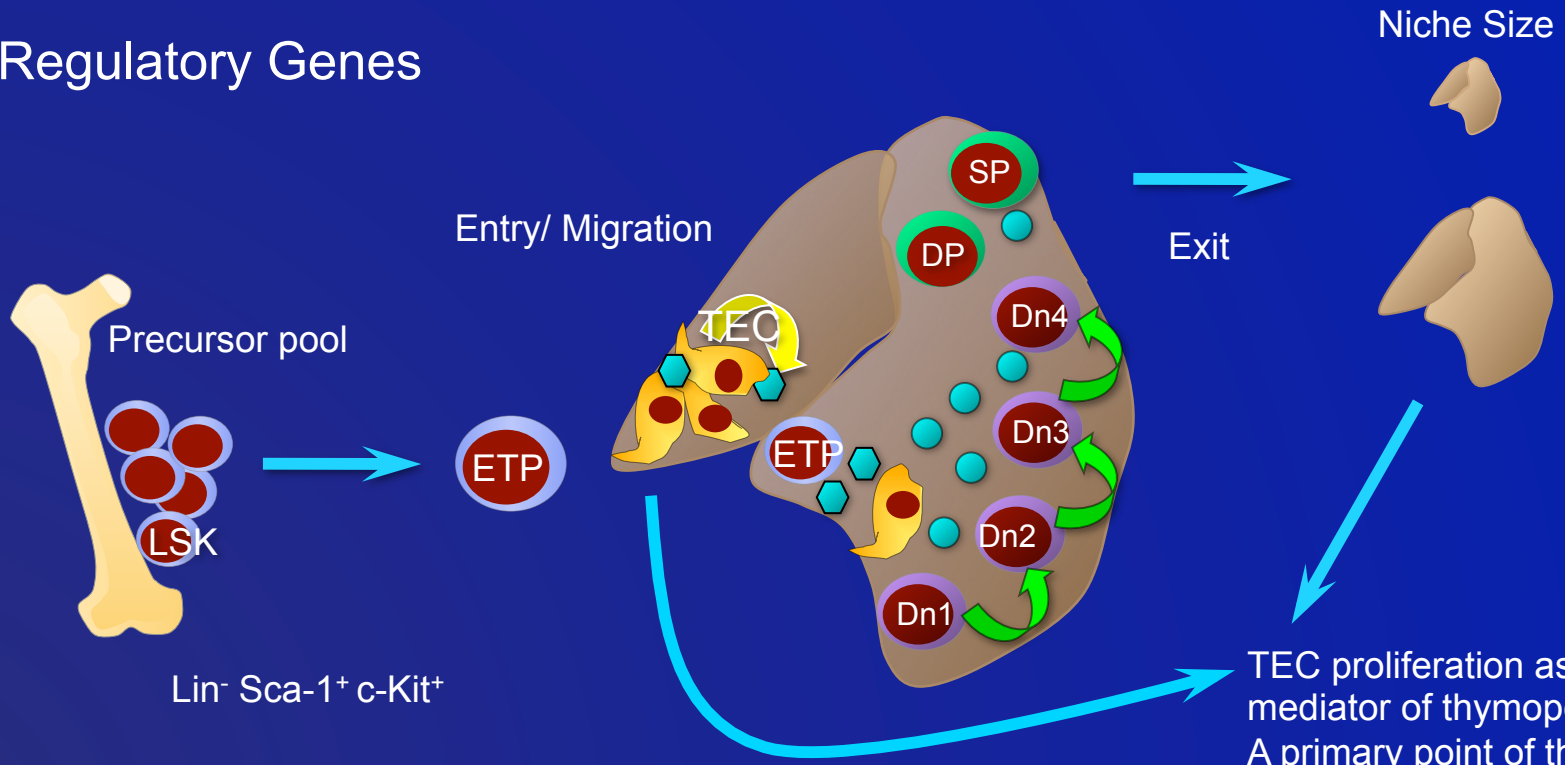
Points of Thymus Regulation

IGF-1

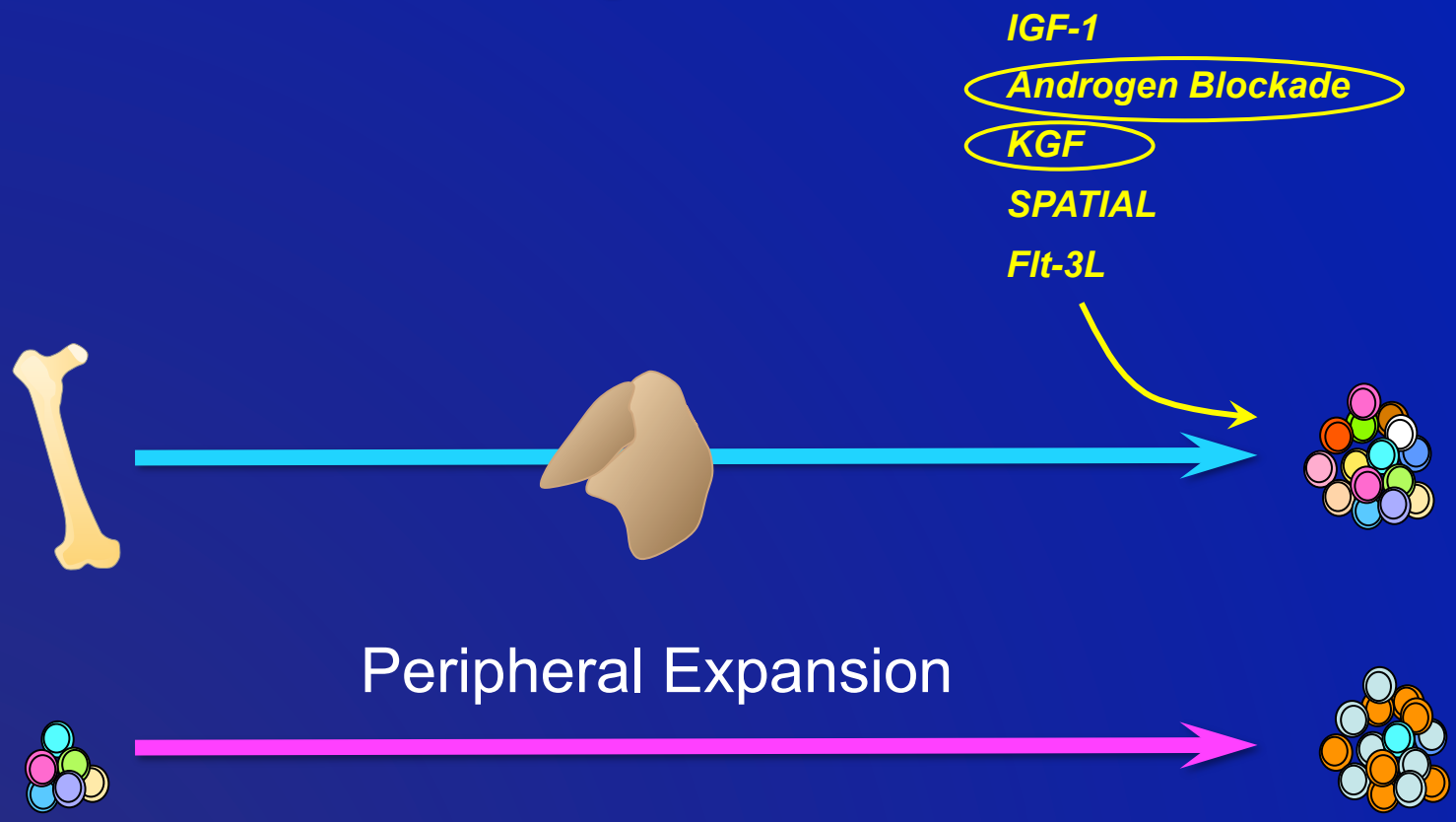
Androgen withdrawal

KGF

Regulatory Genes



There Are Two Primary Pathways of T Cell Regeneration

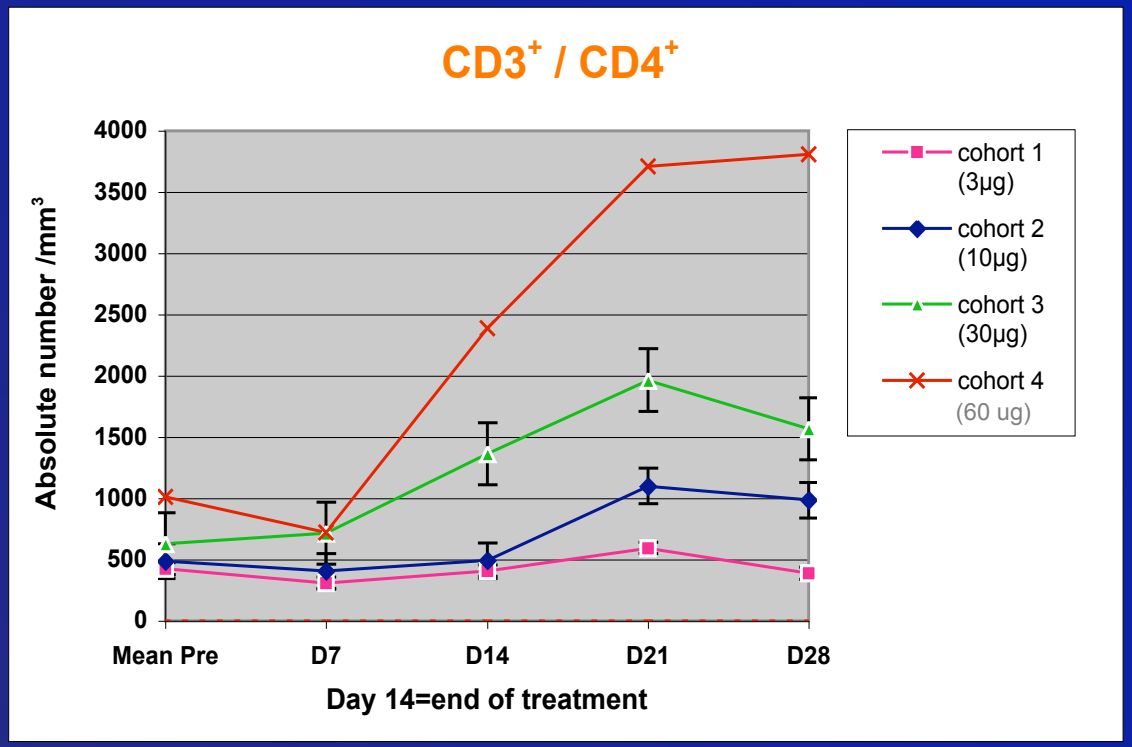


T Cell Maintenance: Role of Cytokines

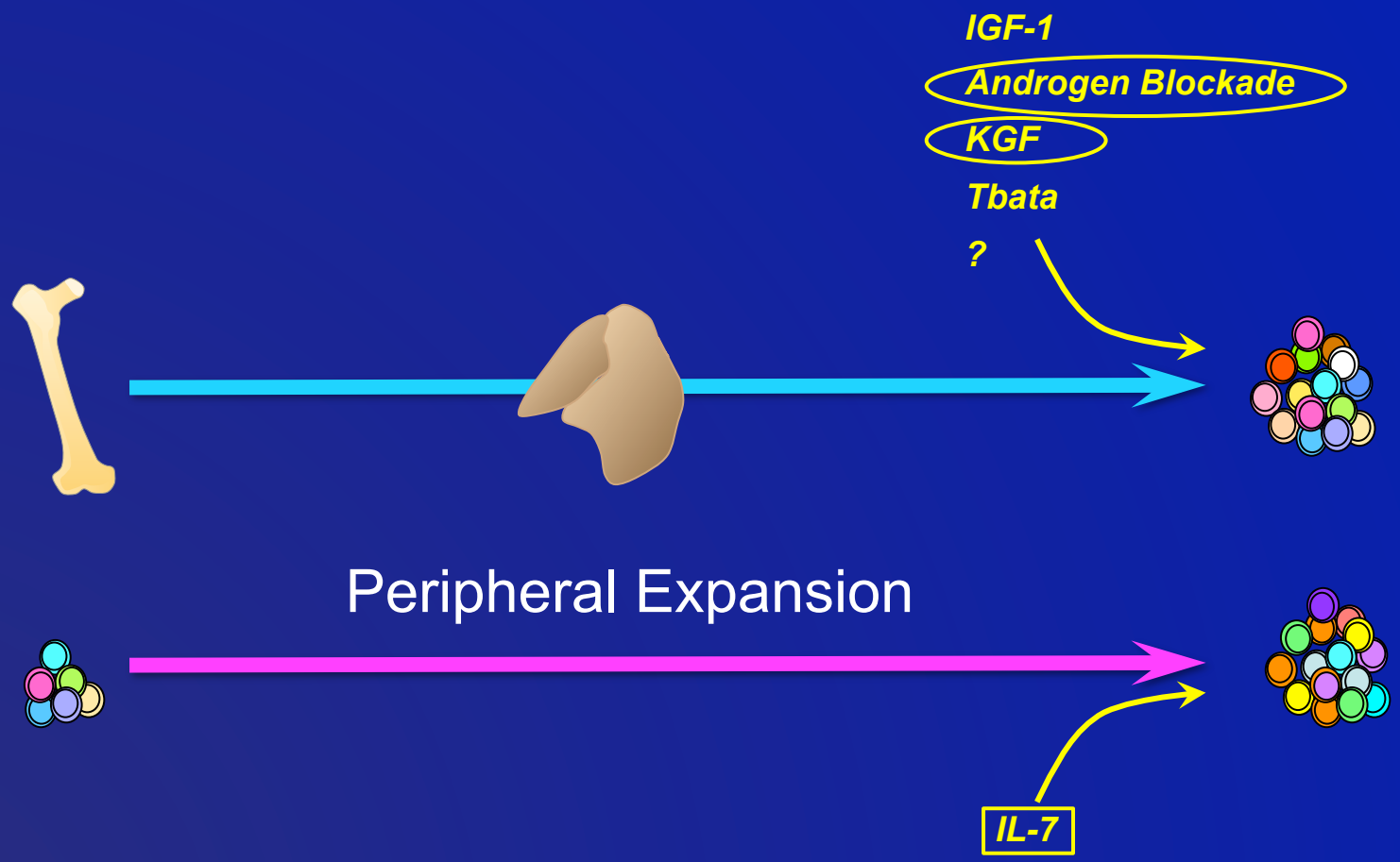
Niche 1	Naïve $CD4^+$ T cells	**IL-7**
	Naïve $CD8^+$ T cells	
Niche 2	Central memory $CD8^+$ T cells	**IL-15**
	Activated $CD8^+$ T cells	
	Memory CD4+ T cells	**Unknown**

Phase I study of IL-7

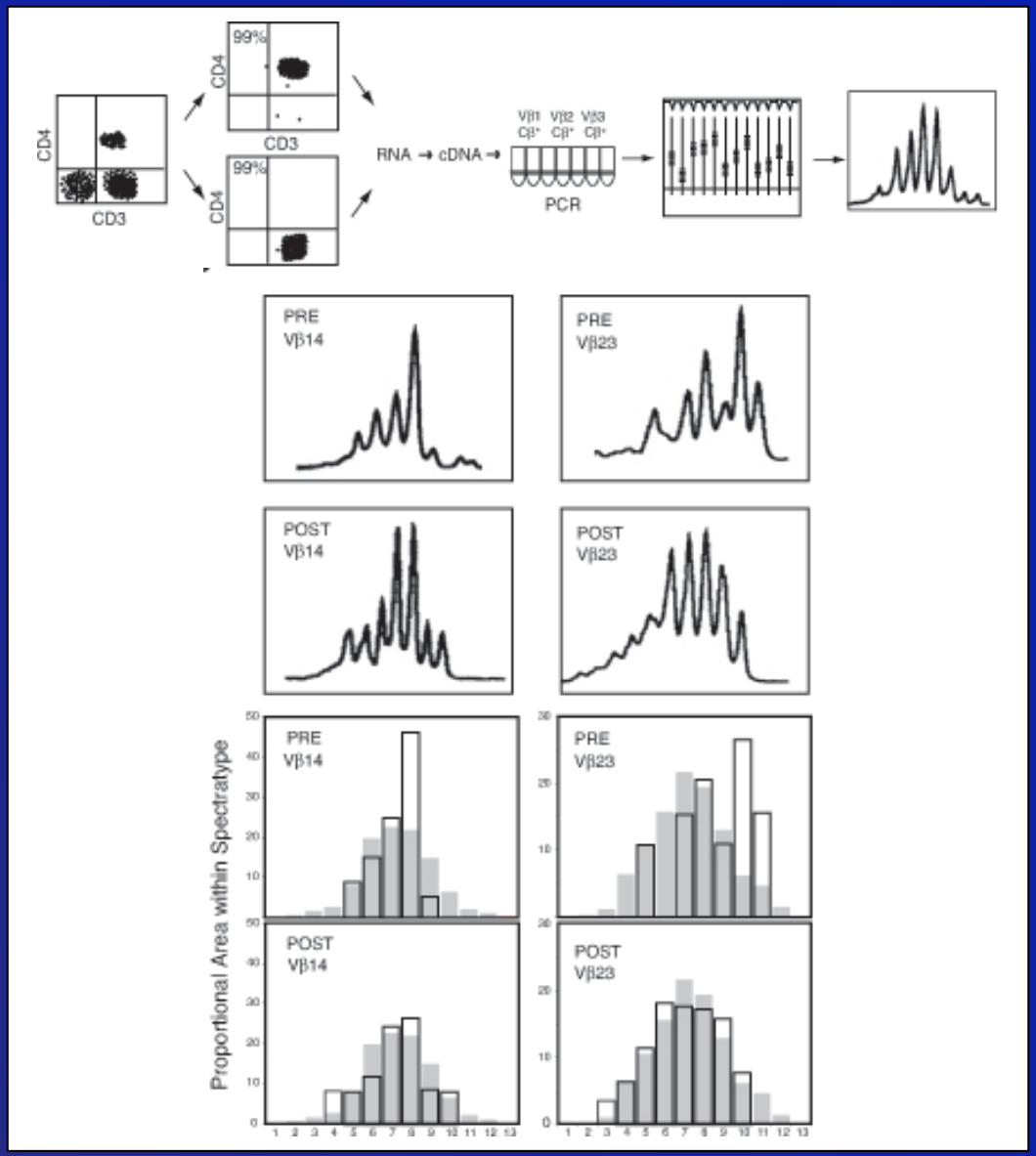
Preliminary results: biologic activity



There Are Two Primary Pathways of T Cell Regeneration



IL-7 Rejuvenates T Cells



Sportès C et al. J Exp Med 2008;205:1701-1714

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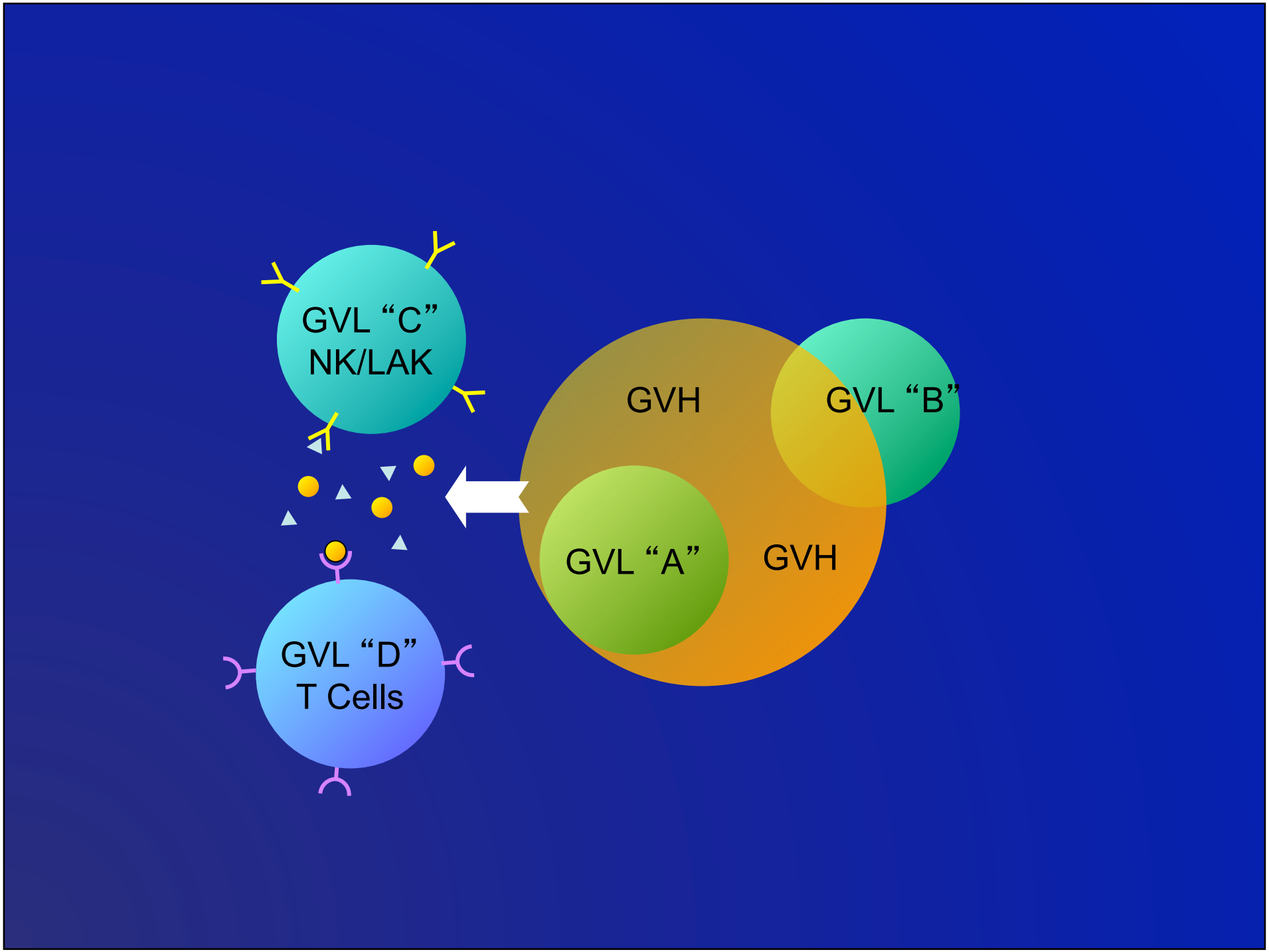
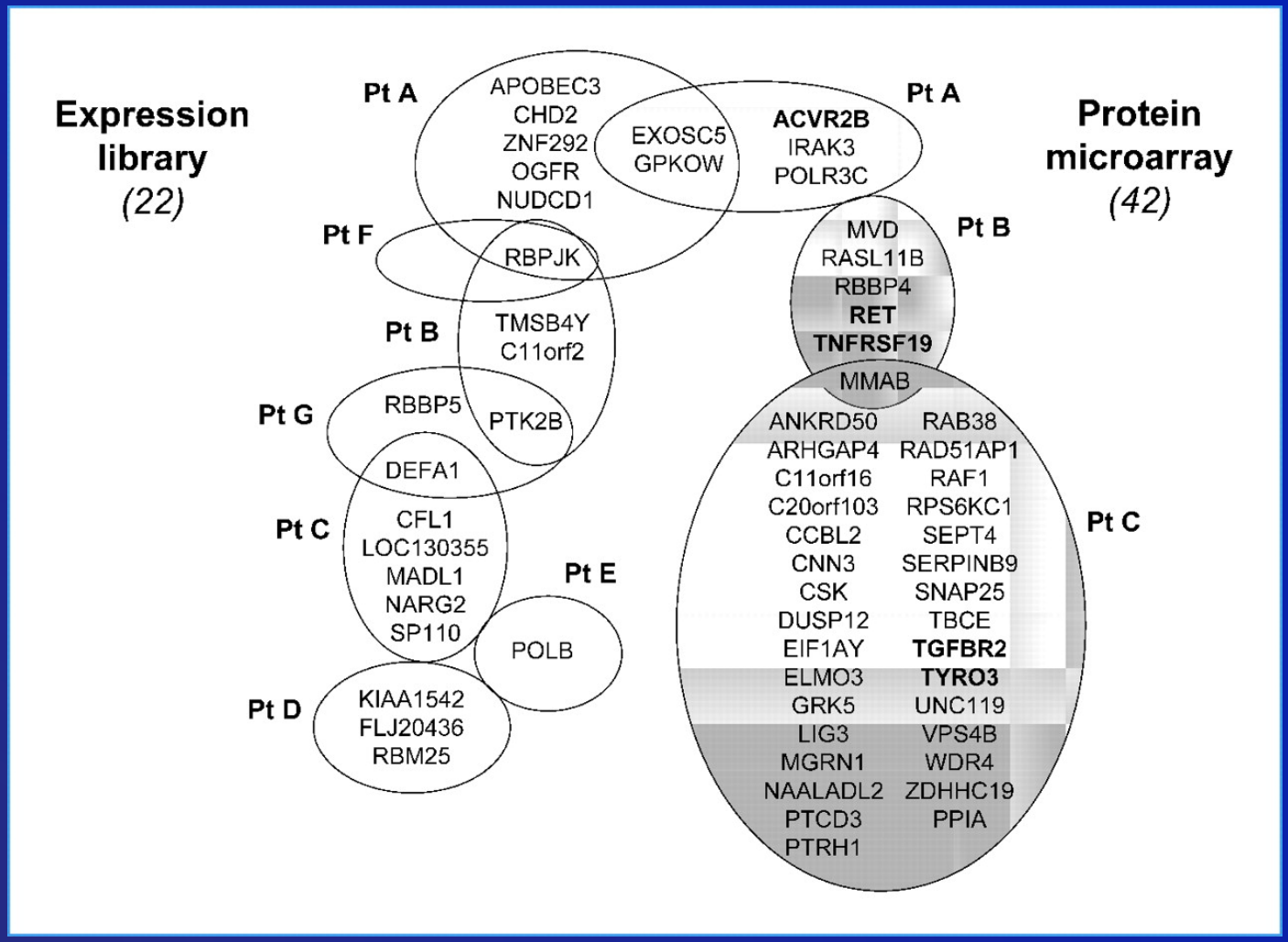

GVL “C”
NK/LAK
GVH
GVL “B”
GVL “A”
GVH
GVL “D”
T Cells

Candidate Antigens in CML

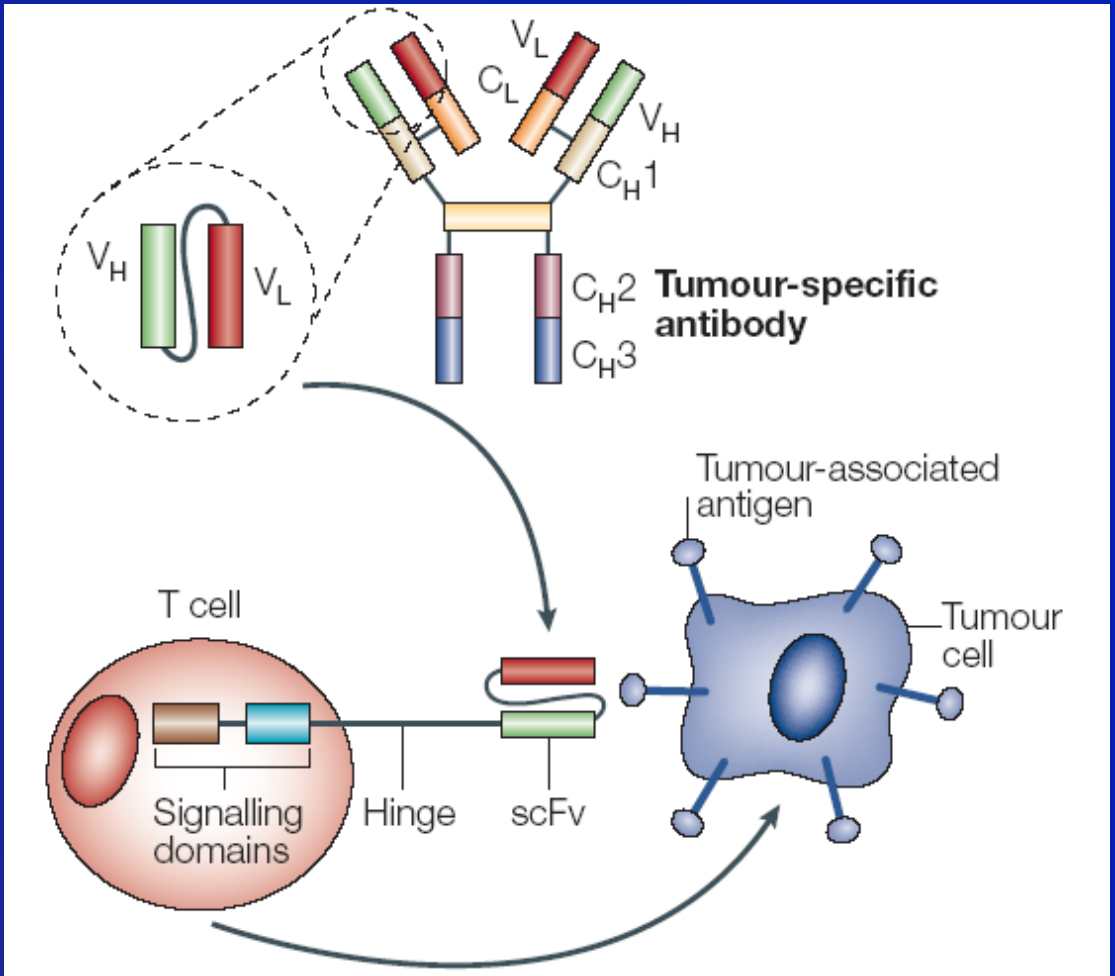


Biernacki M A et al. Cancer Res 2010;70:906-915

Chimeric Antigen Receptors (CARs)

•CARs contain antigen receptors such as the heavy and light chain variable regions of antibodies connected by a linker (scFv).

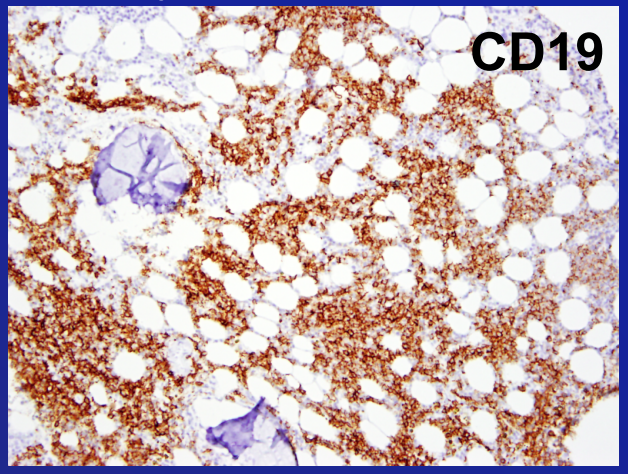
•CARs include signaling molecules such as CD3-zeta and may contain costimulatory molecules such as CD28.

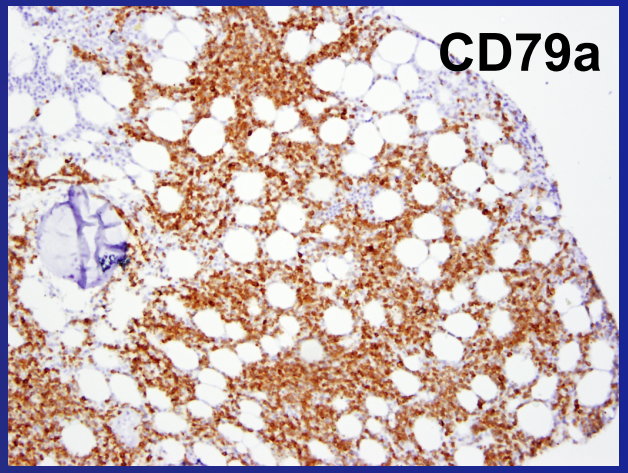


M.H. Kershaw et al. Nature Reviews Immunology (2005) 5:928.

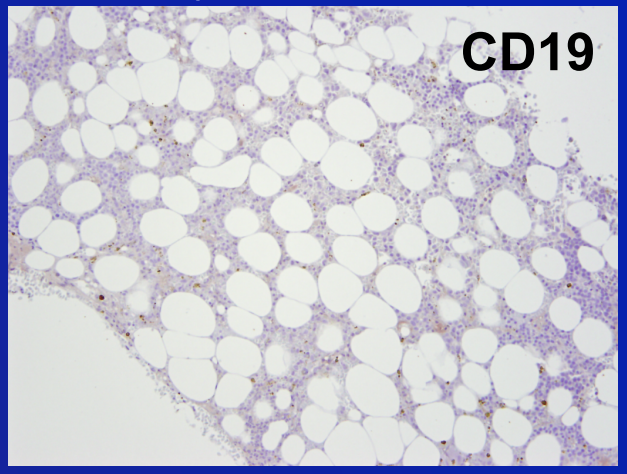
Bone Marrow B-lineage Cells Were Nearly Eliminated After Infusion of Anti-CD19-CAR Transduced T Cells

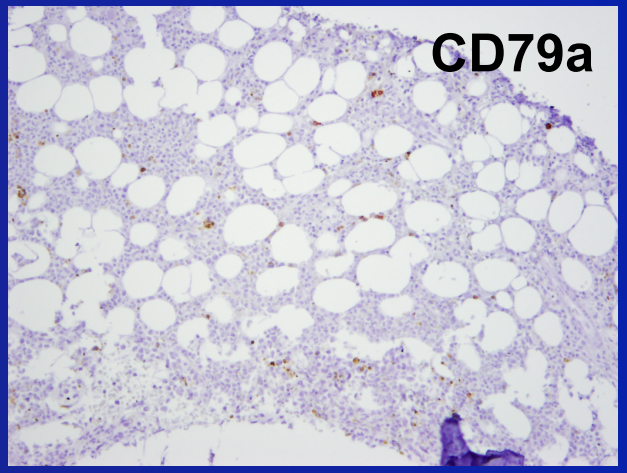
2 days before infusion



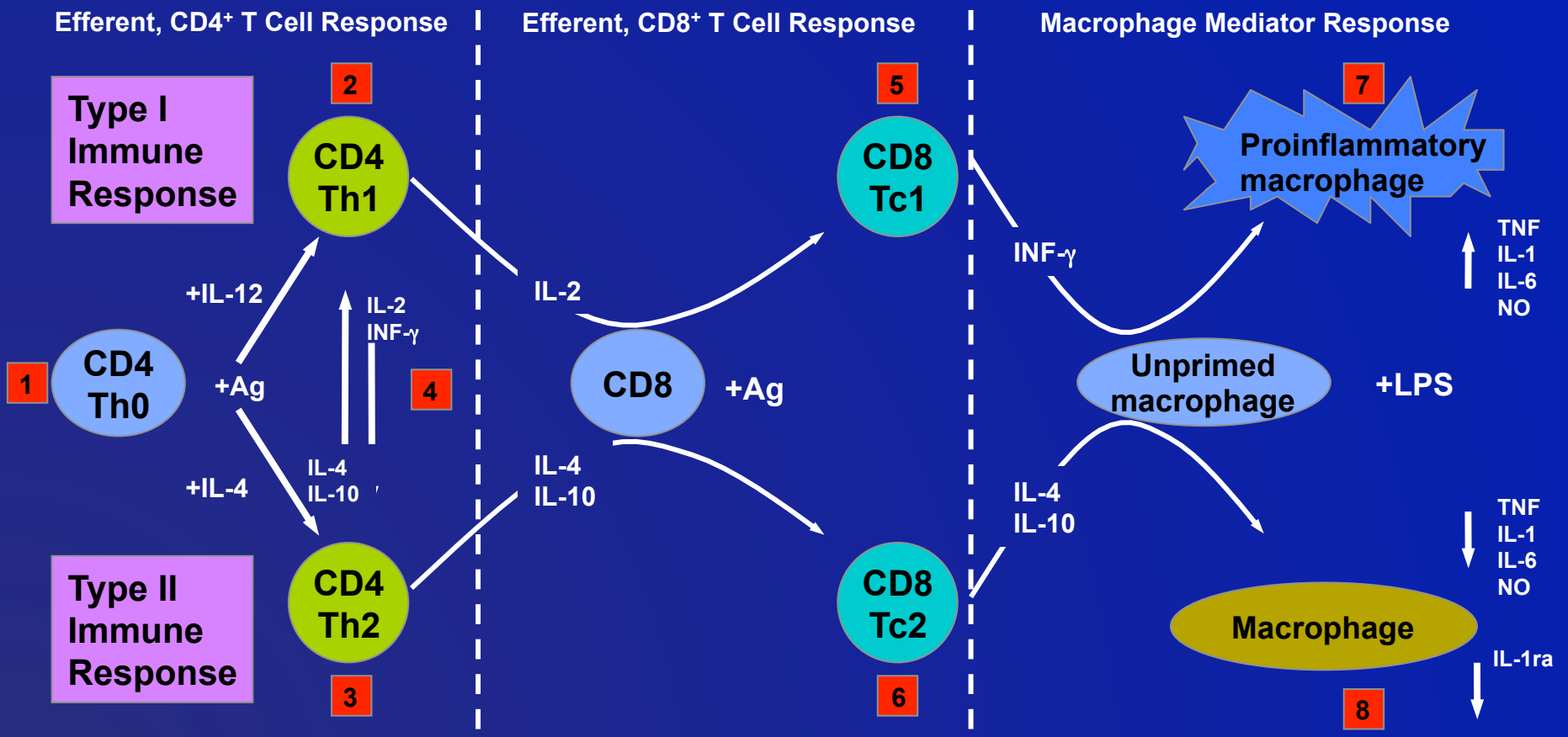


26 days after infusion





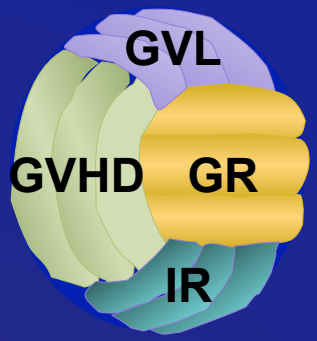
Graft Engineering: T Cells



HSCT: Evolution in Concepts, Revolution in Practice – A Field in Motion

- Marrow stem cells → Bone marrow transplantation therapy
- Transplant in remission → Transplant as standard therapy
- Modulating hematopoiesis by growth factors → G-CSF to enhance marrow function and mobilize cells
- Allogeneic transplant as immunotherapy → Reduced intensity therapy
- Enhancing immune reconstitution
- Optimizing GVL while controlling GVHD
- Cord blood as a viable alternative to treat adults

After 50 Years



GR

GVHD

GVL

IR

Three Things That Have Moved HSCT Forward

- Knowledge
- Knowledge
- Knowledge

Acknowledgements

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