Inherited disorders – management and follow up

AR Gennery

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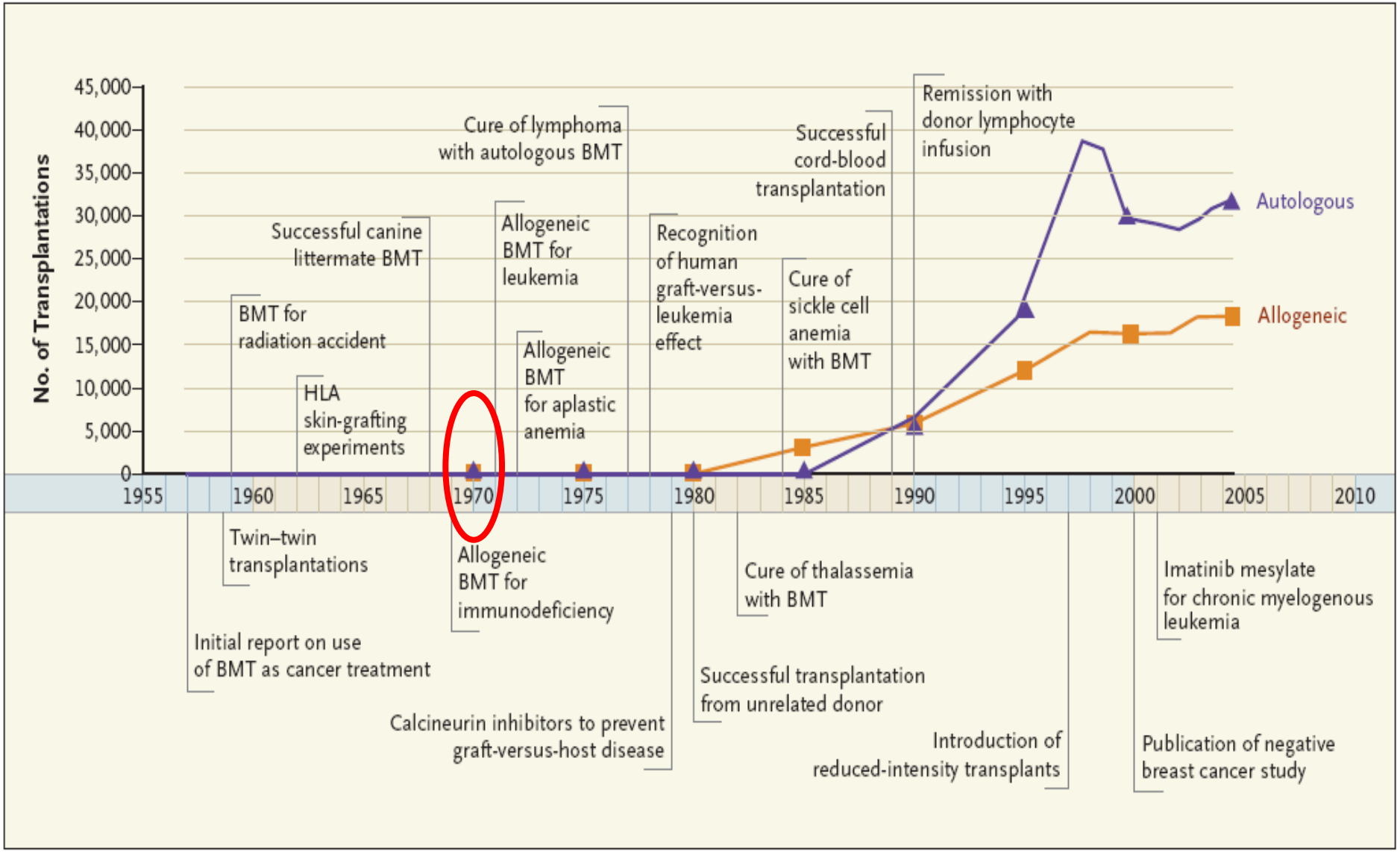
Valencia, Spain 4th April 2016

Introduction

- **Inherited disorders (PID)**
- **What data matters to inform us of outcomes?**



Timeline Showing Numbers of Bone Marrow Transplantations and Advances in the Field, 1957–2006.

BMT denotes bone marrow transplantation, and HLA human leukocyte antigen. Data are from the Center for International Blood and Marrow Transplant Research.

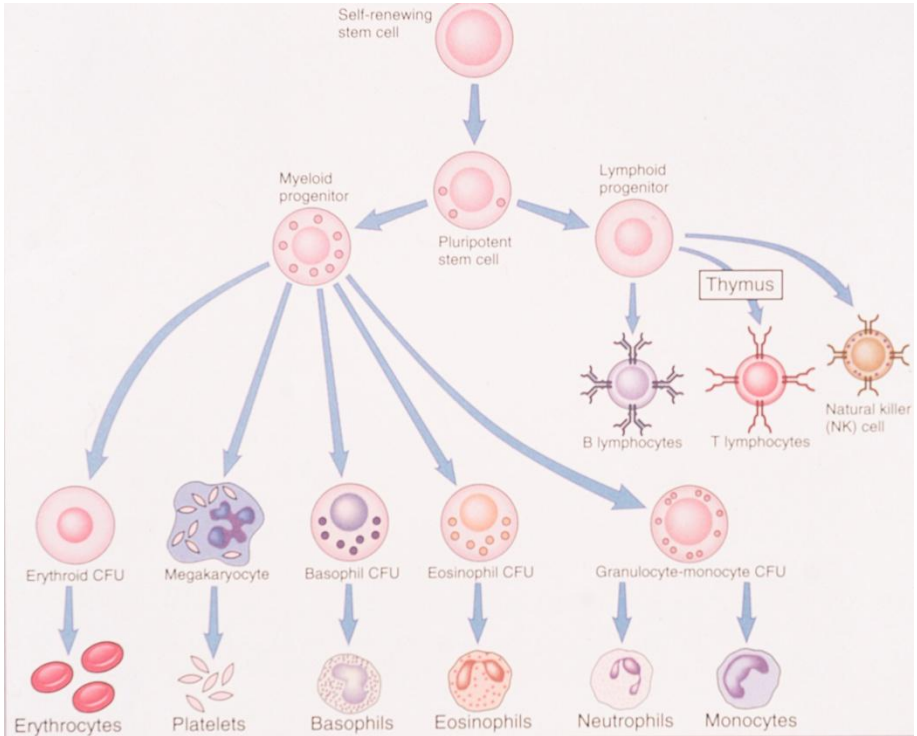
Immunodeficiency

‘a *failure* to achieve immune function to provide efficient, self-limited host defence against the biotic and abiotic environment while preserving tolerance to self.’

Casanova et al. *J Allergy Clin Immunol* 2005

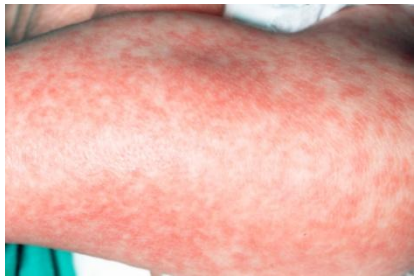
What is Goal of Treatment?

- **Safe**
- **Correction of defect**
- **Long term immune reconstitution**
- **No long term side effects**



Aim of HSCT

- to provide normal hematopoietic stem cells, facilitating correction of the genetic defect
- Stable donor engraftment
  - Partial or full ablation of recipient
  - Chemotherapy, antibody, GvM
- No Graft versus tumour
  - GVHD damages thymus
  - Stable mixed chimerism can lead to cure
- **Good quality immune reconstitution**
- Longterm - quality of life



Severe Combined Immunodeficiency

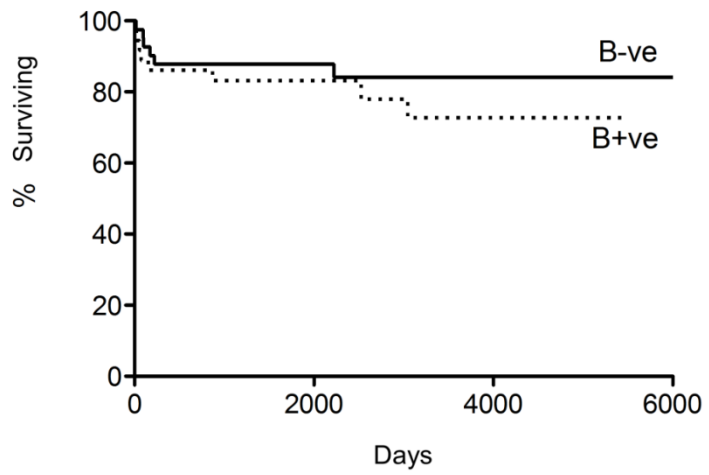
- **Severe** — **Fatal by age 1yr**
- **Combined** — **T + B lymphocyte failure**
- **Incidence** — **1:30 - 50000 live births**

Issues to consider in SCID HSCT

- Genetic type (CgC does better than RAG)
- Infection – better if no infection
- Donor – which is best?
- Chemotherapy conditioning - ?needed
- Is immunity durable?
- What about quality of life?

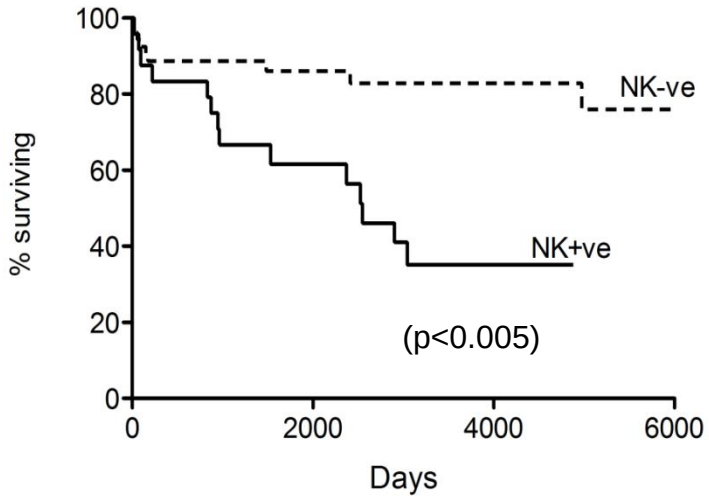
Which Phenotype Does Best?

Figure 1 (b)



Transplant survival outcomes for T^-B^+ and T^-B^- SCID were not statistically different

Figure 2 (c)



Event Free Survival was 81% for NK^-SCID vs 42% in the NK+ve group

Hassan A, et al. J Allergy Clin Immunol 2014;133(6):1660-6

Severe Combined Immunodeficiencies

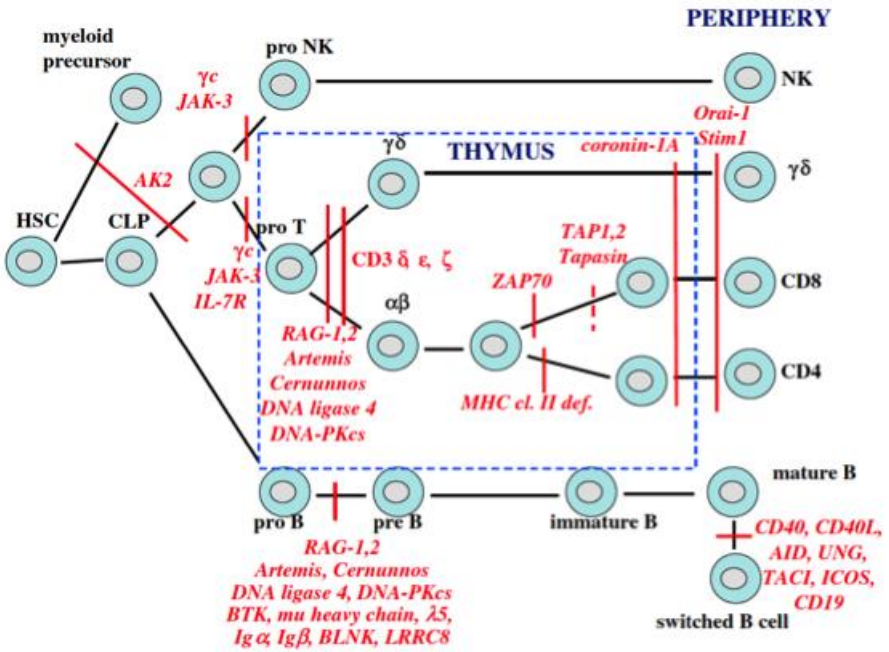


FIG 1. Blocks in T-and B-cell development associated with PIDs.

Notarangelo LD. J Allergy Clin Immunol 2010;125:S182-S194

Defect	Gene Defect	Inheritance	T,B, NK Cells
Cytokine signalling	CgC	XL	- + -
	JAK 3	AR	- + -
	IL7 Ra	AR	- + +
Nucleotide biosynthesis salvage pathway defects	ADA	AR	T_{low} B_{low} NK_{low}
	PNP	AR	$T_{low}B_{low}NK_{low}$
Defects affecting signalling through the T cell antigen receptor	CD45	AR	- + -
	CD3d	AR	- + -
	CD3e	AR	- + -
	CD3z	AR	- + +
	ZAP70 kinase	AR	+ + + (absent CD8)
VDJ recombination defects	RAG 1 & 2	AR	- - +
	Artemis	AR	- - +
	Cernunnos	AR	T_{low} B_{low} NK+
	DNA ligase 4	AR	T_{low} B_{low} NK+
Thymic defects	22q11	Sporadic/AD	T-B+NK+
	CHD7	Sporadic/AD	T-B+NK+
	FOXN1	AR	T-B+NK+
Other	AK2 (RD)	AR	- - - (+ myeloid dysfunction)
	MHC class II deficiency	AR	+++ (absent CD4)
	ORAI1	AR	Ca-dependent T cell activation
	STIM1	AR	

Function of Thymus

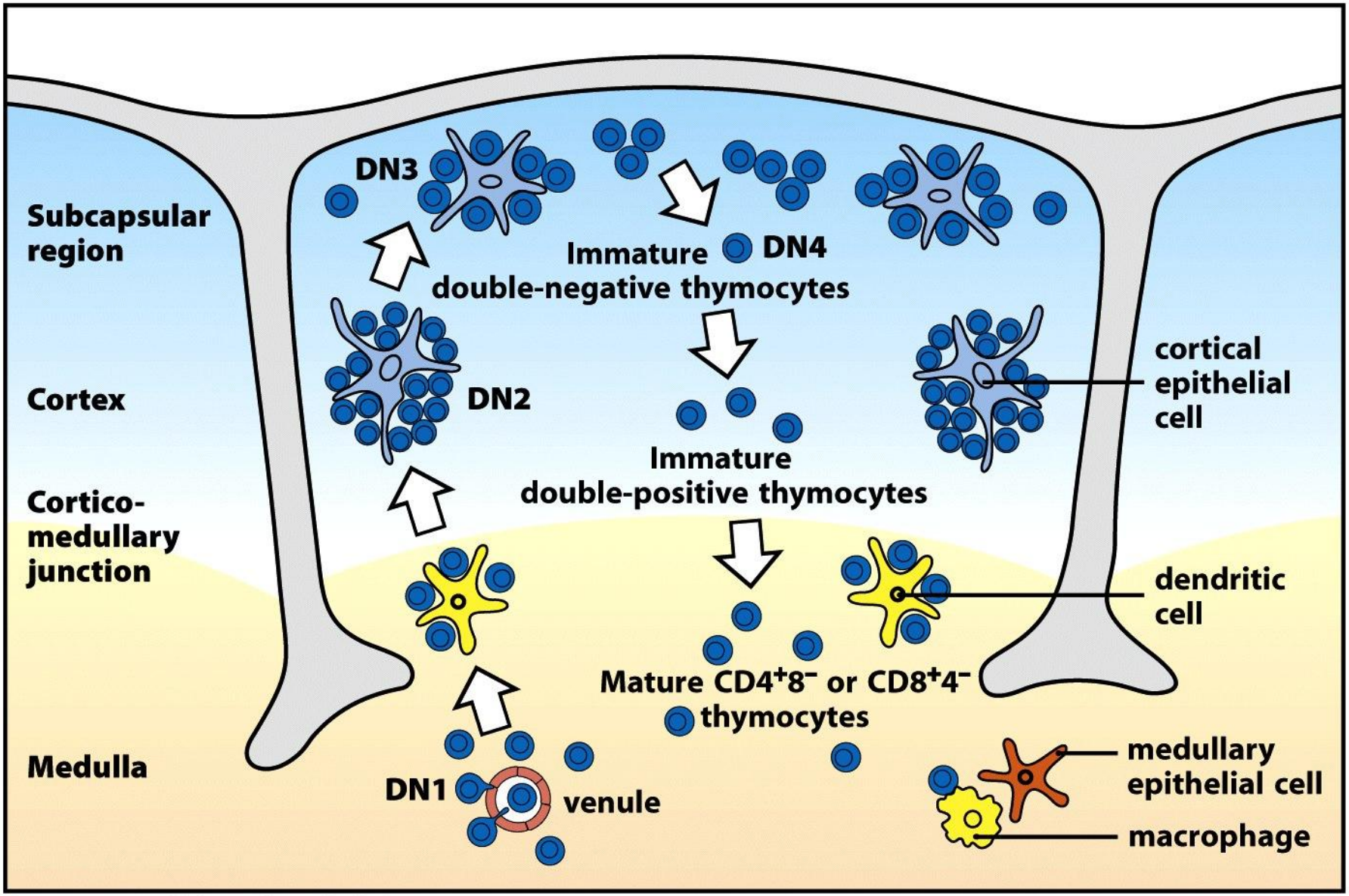
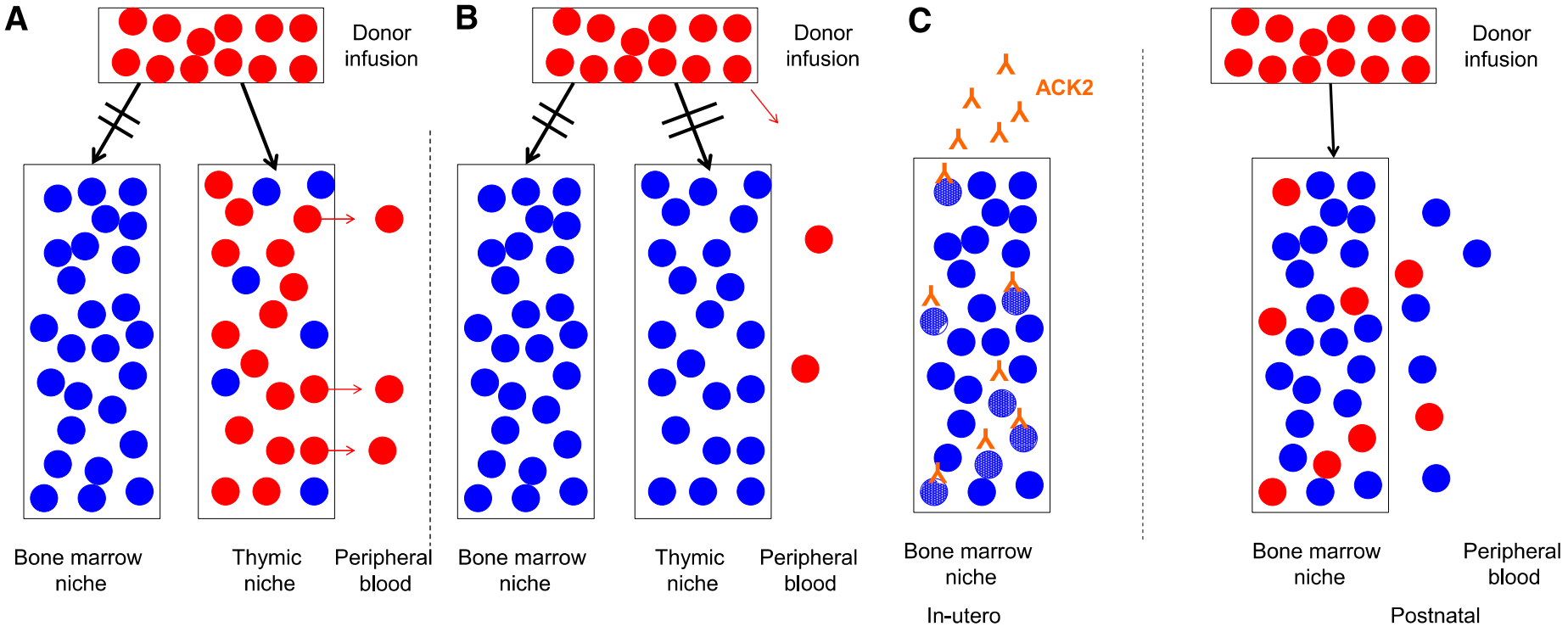


Figure 7-21 Immunobiology, 7ed. (© Garland Science 2008)



Gennery AR, et al Blood. 2014;12:838-40

A hierarchy of conditioning intensity

Nil

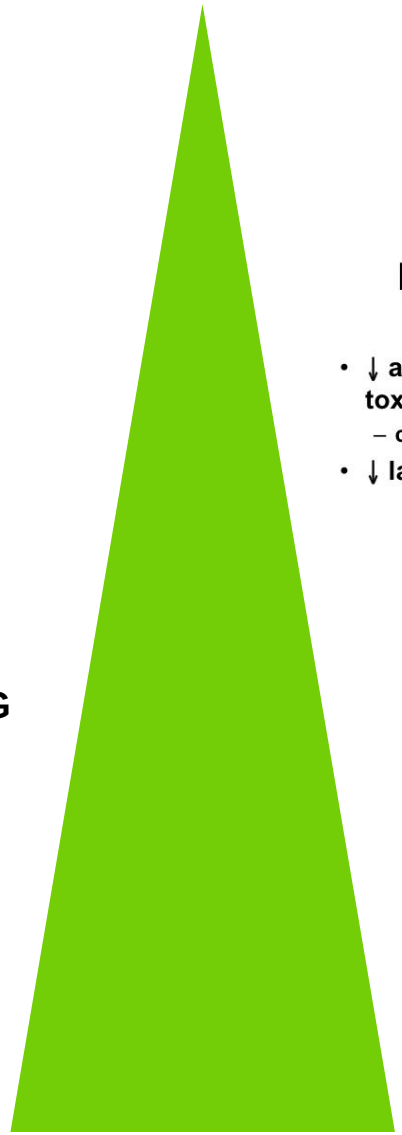
MIC
MMF/CYA
2Gy TBI +/-Flu
Cyclo +/- 3Gy TBI
+Thymic DXT
Flu/Cyclo

+DLI

RIC
Bu(8)/Flu or Cyclo
Melphalan/Flu
Melphalan/Cyclo
Treosulphan/Flu

+/- Campath/ATG

MAC
Treosulphan/Cyclo
Bu(14-16)/Cy(120-200)
TBI/Cy(120) or VP16
Flu/TBI/Cy



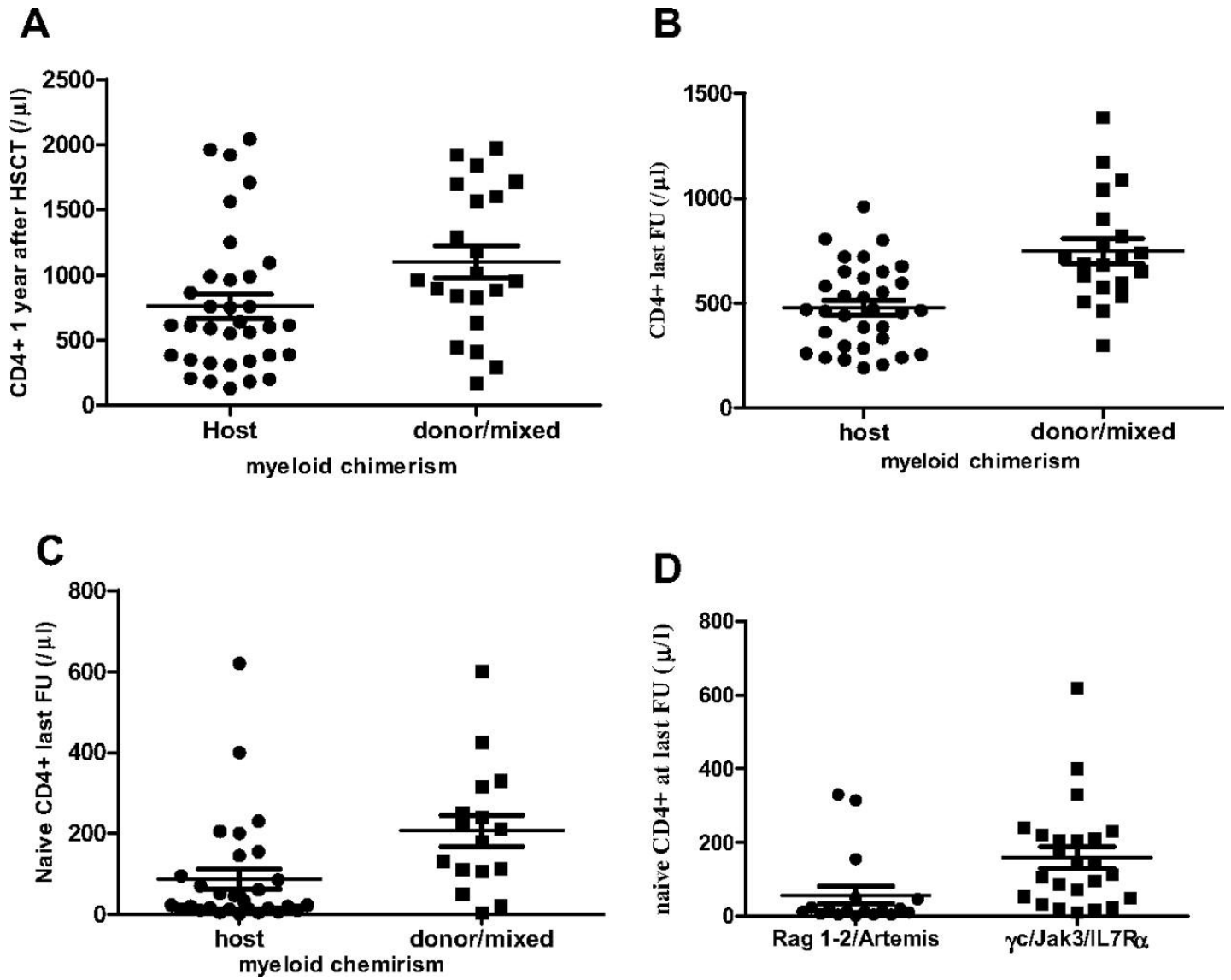
Pros

- **↓ acute toxicity**
  - **co-morbidity**
- **↓ late effects**

Cons

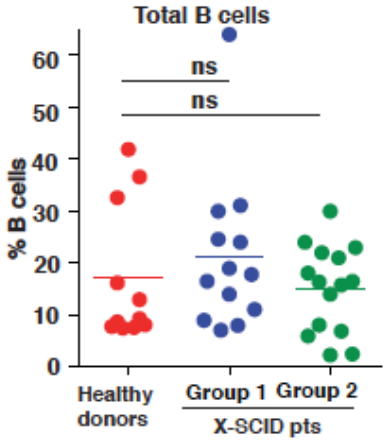
- **↑ rejection**
- **↑ mixed chimerism**

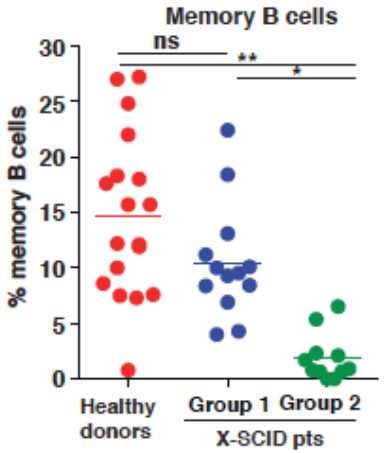
Engraftment of donor-derived myeloid cells correlates with a higher CD4+ T-cell count (1 year after HSCT and at last follow-up) and higher naive CD4 T-cell counts.



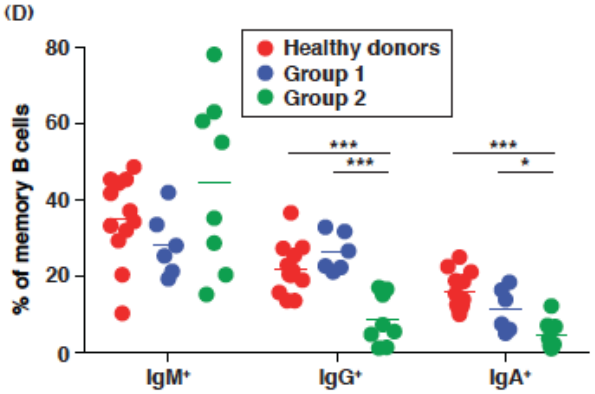
Neven B et al. Blood 2009;113:4114-4124

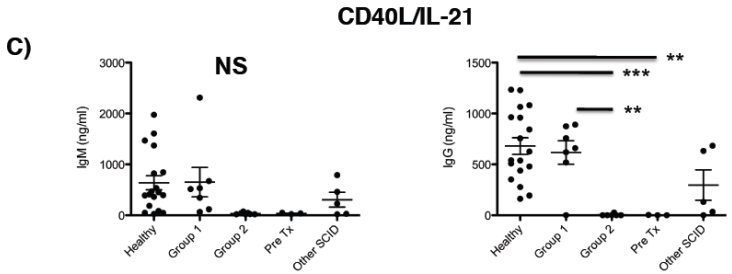
Immune Reconstitution

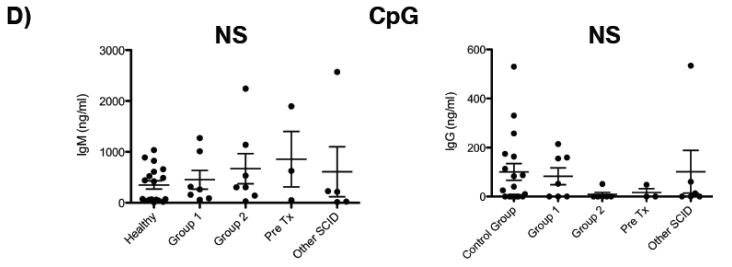




- 28 transplanted patients with *IL2RG/JAK3*-deficiency
- Lack of donor B cell engraftment associated with persistent humoral dysfunction and reduced memory B cells
- *in vitro* stimulation with CD40L/IL-21 induced B cell proliferation, plasmablast differentiation and antibody secretion in patients with donor B cells, but not those with autologous B cells



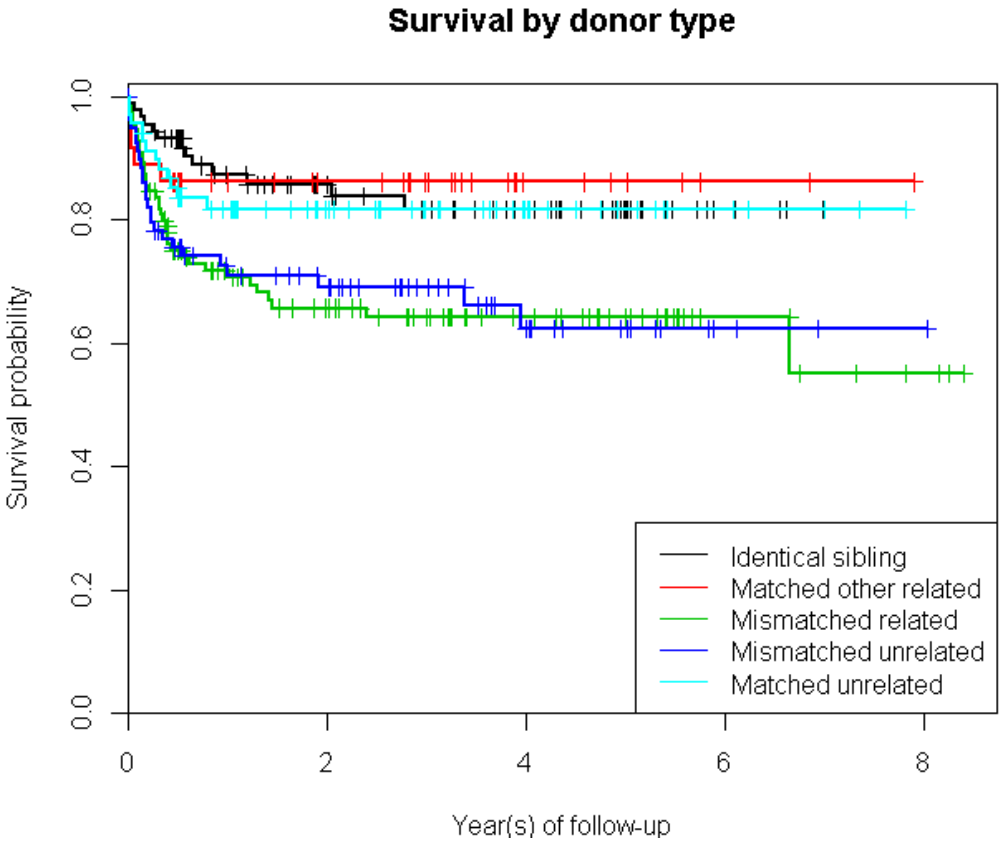


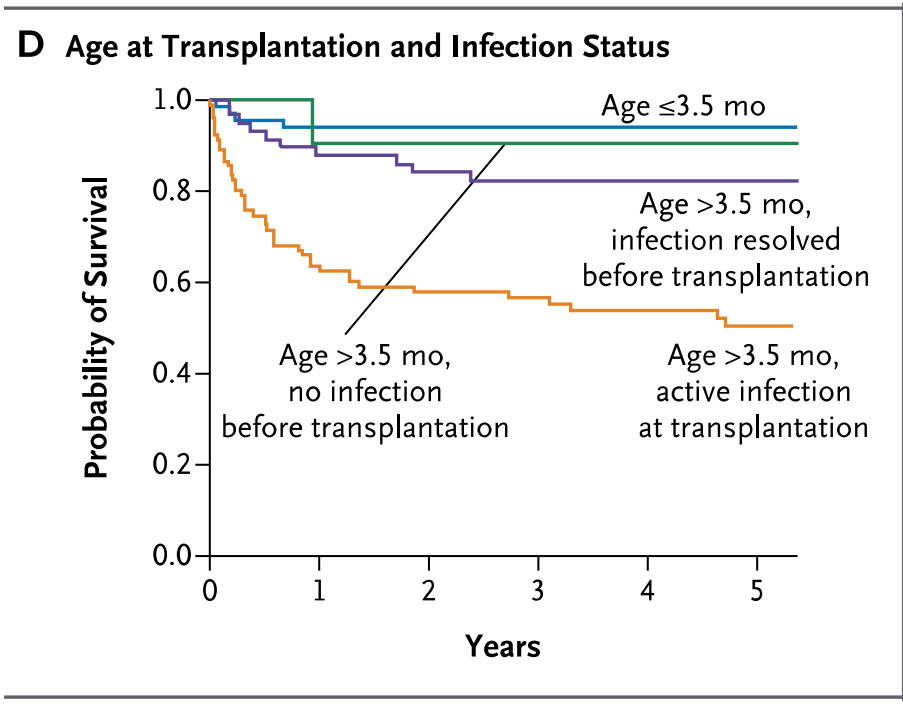


Recipient B cells from X-SCID/JAK3-deficient patients failed to produce IgM or IgG following CD40L/IL-21 stimulation, compared to donor B cells. IgM, but not IgG was produced from recipient B cells following stimulation with CpG

Recher M, et al Blood 2011;118:6824

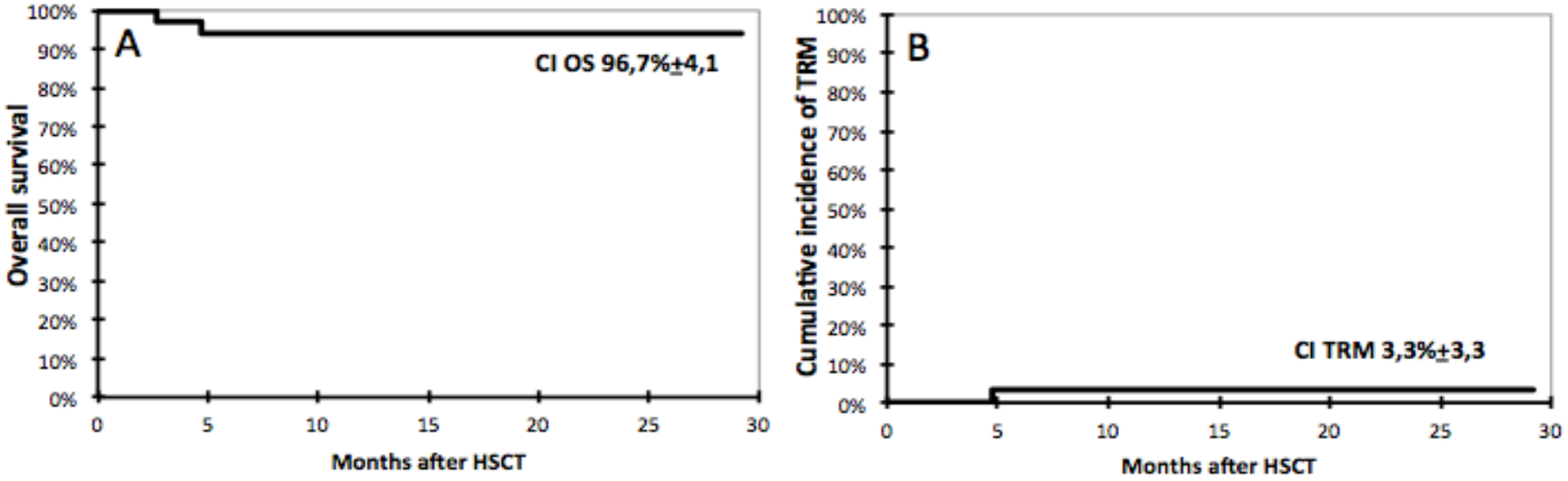
Outcome of HSCT for SCID





Pai S-Y, et al. N Engl J Med 2014;371:434-46.

Federal Research Center for Pediatric Hematology, Oncology and Immunology – Moscow, Russia

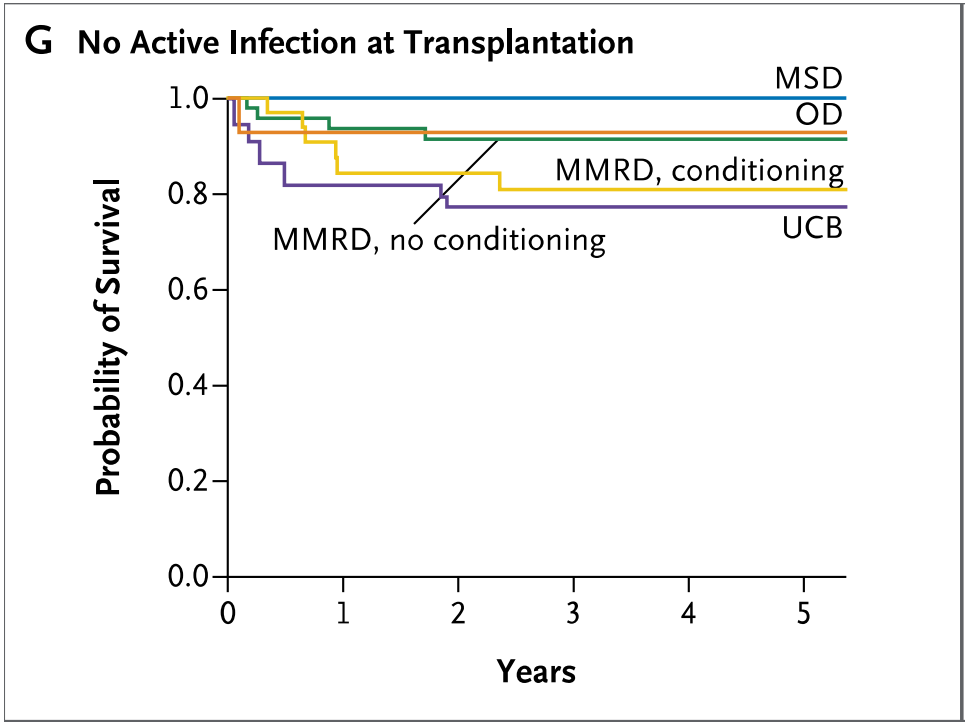


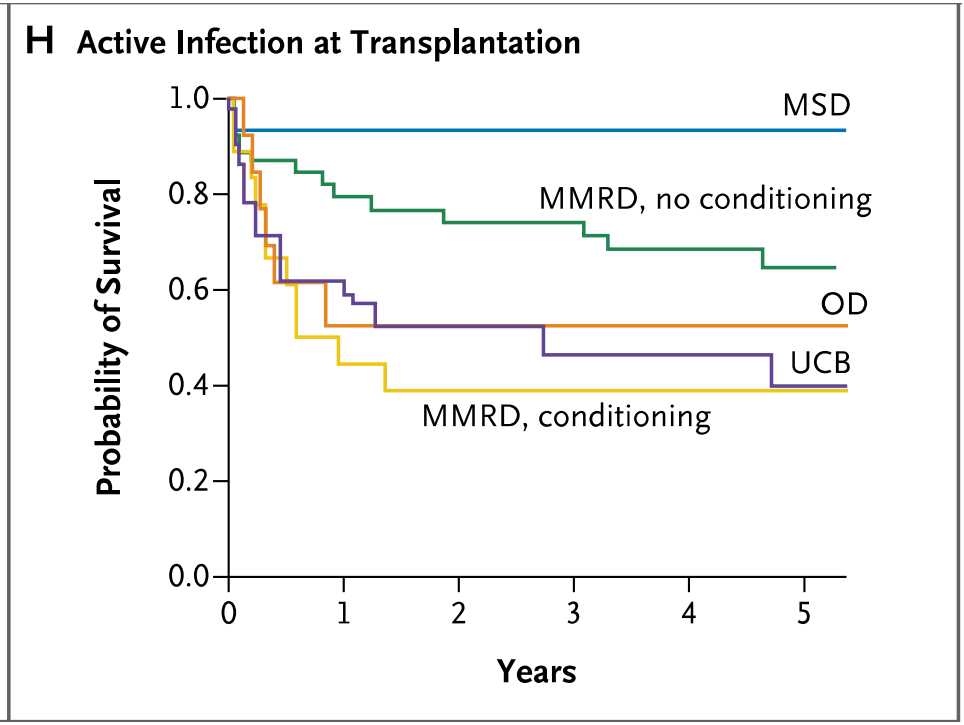
TCRαβ depletion in PID – 37 patients

A – probability of overall survival
B - cumulative incidence of transplant-related mortality

Balashov D et al, Biol Blood Marrow Transplant 2015

Effect of infection and conditioning on outcome - SCID





Pai S-Y et al. N Eng J Med 2014;371:434

Late Effects - SCID

	Artemis (n=47)	RAG (n=45)	
overall	33 (**70%**)	11 (24%)	**p<0.001**
Severe or recurrent infections	16 (34%)	6 (14%)	**p<0.05**
cGvHD or autoimmunity, -inflammation	14 (30%)	8 (18%)	ns
⟹ miscellaneous events	7 (**15%**)	0	**p<0.01**
growth < 3rd percentile	23 (**49%**)	4	**p<0.001**
nutritional support	10	2	**p<0.01**
dental abnormalities	10 (**21%**)	0	**p<0.01**
sequelae of pre HCT morbidity	4 (10%)	2	ns

Schuetz C et al, Blood 2014;123:281-9

Factors associated with late complications

	IRR (95% CI)	P	aIRR (95% CI)	P
Molecular diagnosis (Artemis)	4.4 (2.5-7.7)	<0.0001	3.2 (2.1-4.9)	**<0.0001**
Viral infection prior transplantation	2.2 (1.1-4.3)	0.02	1.7 (1.2-2.6)	**0.008**
Myeloablative conditioning	2.0 (1.0-3.8)	0.05		
Use of alkylators	3.0 (1.6-5.6)	0.001	3.1 (2.0-4.9)	**<0.0001**
Type of donor		0.007		
MSD	1			
MFD	1.0 (0.3-3.)	1.0		
MMFD	1.8 (0.5-6.2)	0.4		
Haplo	3.5 (1.5-9.8)	0.001		
MUD	1.2 (0.3-4.6)	0.8		
Retransplantation	2.3 (1.1-4.8)	0.03		
Boost	2.6 (1.3-5.3)	0.009		
Additional procedure	3.2 (1.7-5.9)	<0.0001	2.0 (1.3-3.0)	**0.001**
IVIG requirement	3.0 (1.7-5.5)	<0.0001	1.9 (1.2-3.0)	**<0.0001**

Schuetz C et al, Blood 2014;123:281-9

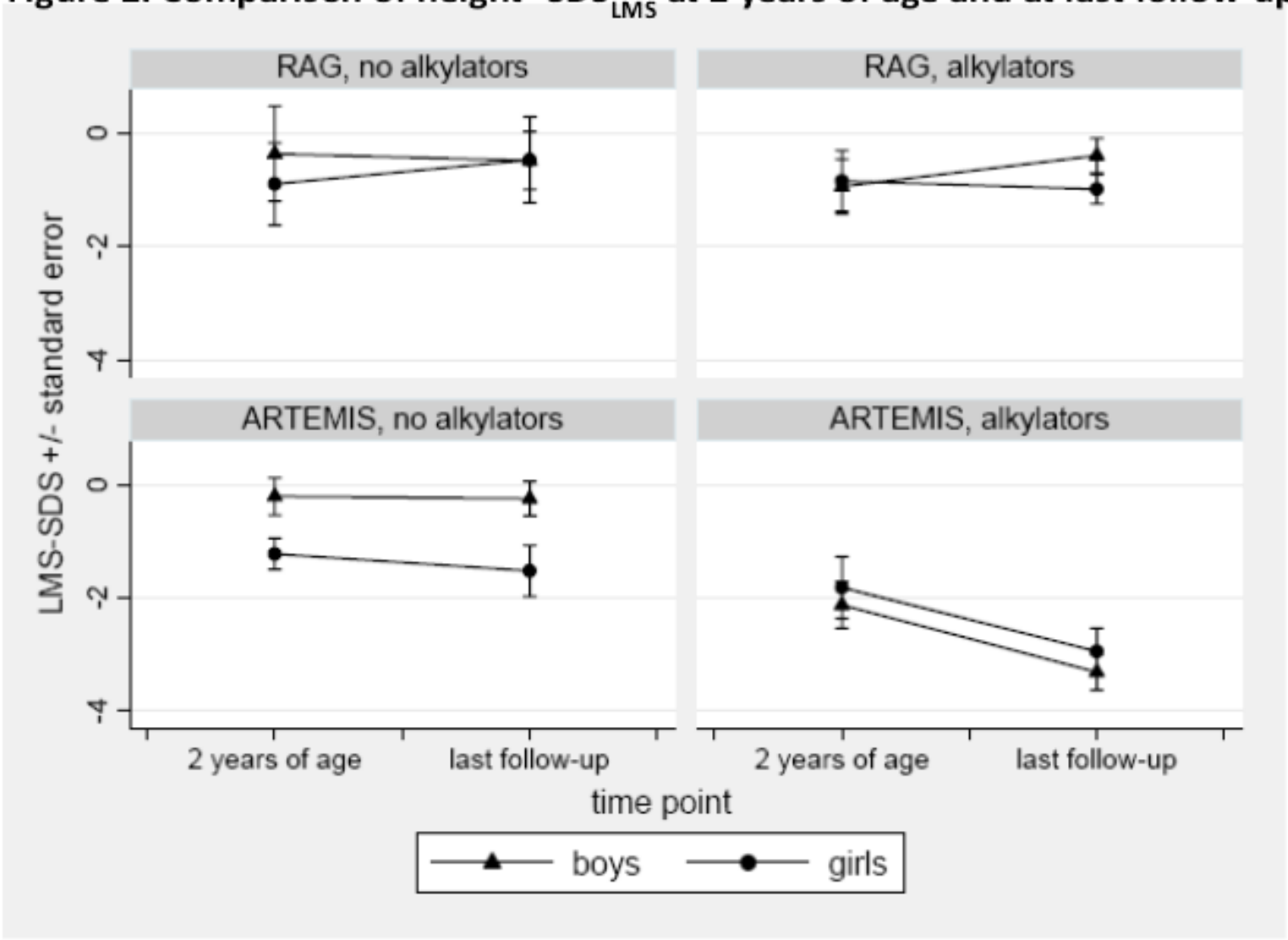
Factors associated with growth retardation & nutritional support

	IRR (95% CI)	P	aIRR (95% CI)	P
Molecular diagnosis (Artemis)	4.5 (2.5-8.1)	<0.0001	4.2 (2.6-6.7)	**<0.0001**
Viral infection prior HCT	2.2 (1.1-4.4)	0.03	1.9 (1.3-2.9)	**0.003**
Ulcers	2.2 (0.9-5.4)	0.07		
Type of conditioning		**0.003**		
No or IS only	1			
Low Busulfan dose	0.9 (0.3-2.8)	0.8		
High Busulfan dose	*3.1 (1.5-6.5)*	*0.002*		
Myeloablative conditioning	3.2 (1.7-6.3)	0.001	2.9 (1.7-5.1)	**<0.0001**
Use of alkylators	3.6 (1.8-7.0)	<0.0001	2.4 (1.4-4.3)	**0.003**
Haploidentity	3.6 (2.0-6.7)	**<0.0001**		
Additional procedure	2.5 (1.3-4.8)	**0.005**		
IVIG requirement	2.2 (1.2-4.3)	**0.02**		

Schuetz C et al, Blood 2014;123:281-9

Late Effects

Figure 2. Comparison of height- SDS_{LMS} at 2 years of age and at last follow-up



Schuetz C et al, Blood 2014;123:281-9

Conclusion

- Inherited diseases have different challenges to malignant disorders
- Successful HSCT is curative
- GvHD is to be avoided
- Different diseases have different requirements for successful outcome
- Measuring ‘success’ requires an understanding of the disease

Conclusion

- Different parameters required depending on disease, to measure success
- Long-term outcomes important – detailed specific data collection required
- Communication between clinicians and data managers/registries critical if useful information is to be gathered