Immune-reconstitution and immune-senescence after allogeneic HSCT

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« Hematopoietic stem cell aging »

Hôpitaux Universitaires Genève

Division of Hematology

UNIVERSITÉ DE GENÈVE

Translational Research Centre in Onco-haematology (CRTOH)

Disclosures

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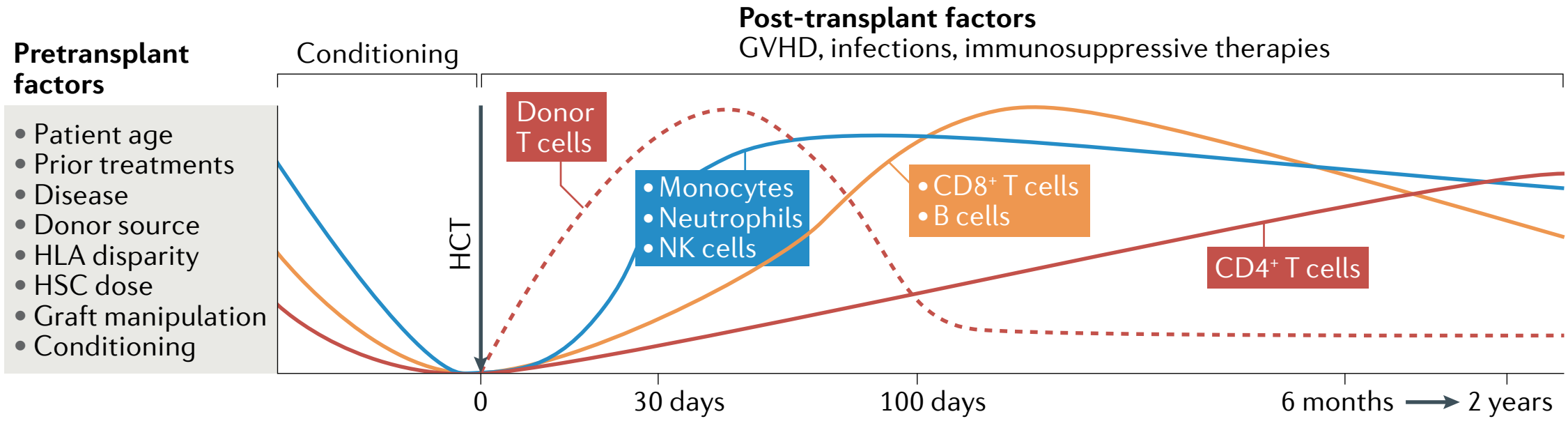
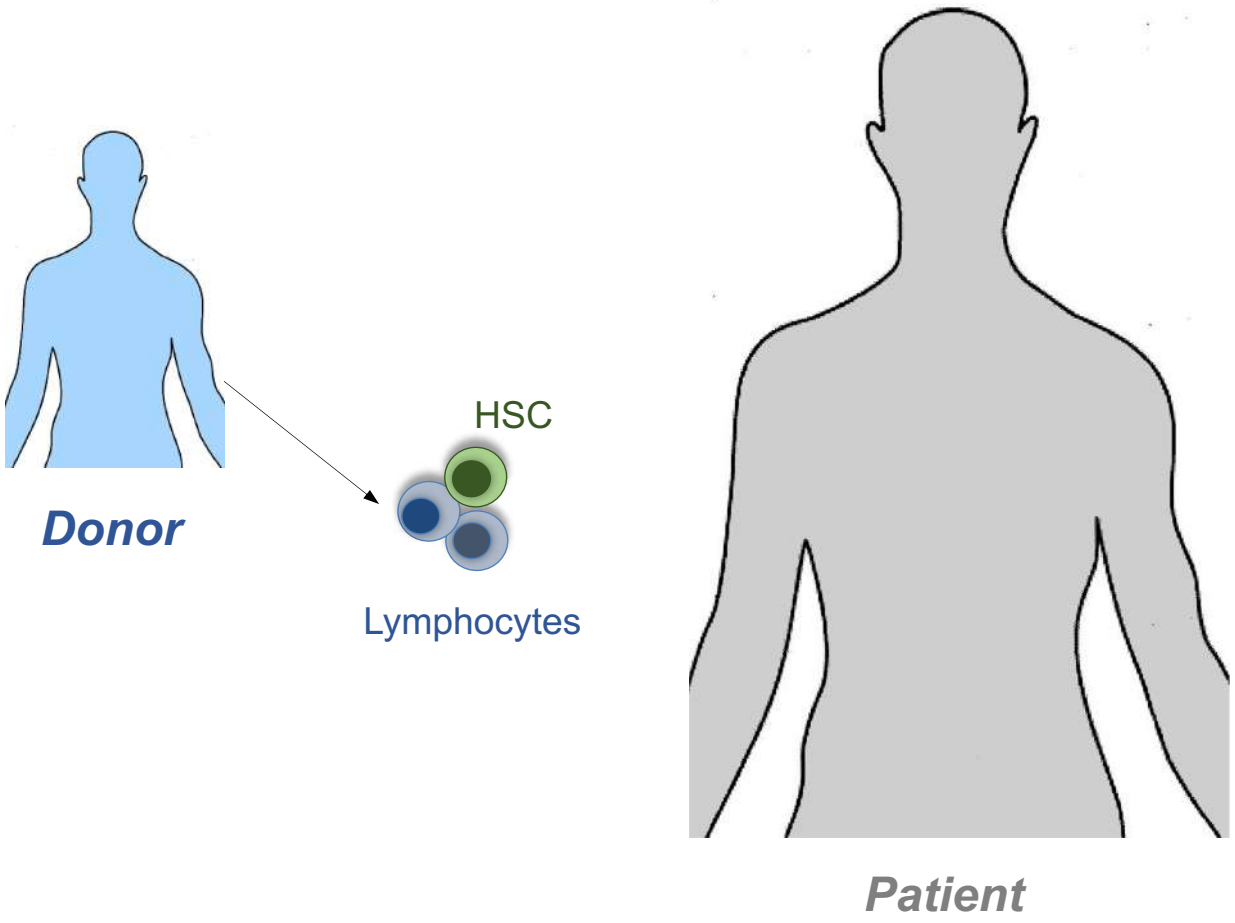
- Research funding: Kite/Gilead, Novartis, BMS/Celgene

Immune-reconstitution after allogeneic HSCT



Velardi et al., Nat Rev Immunol 2021

Immunereconstitution after allogeneic HSCT



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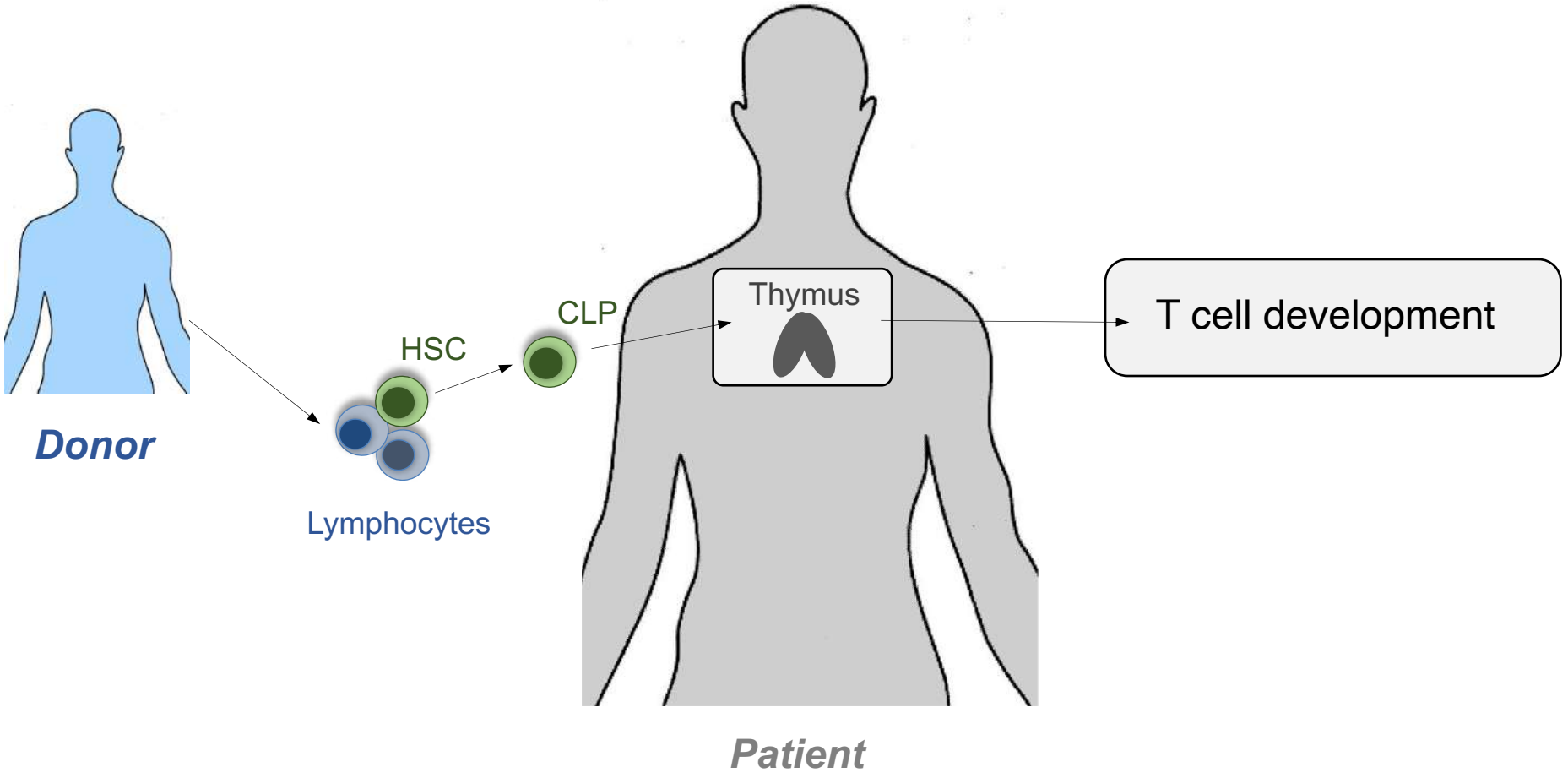

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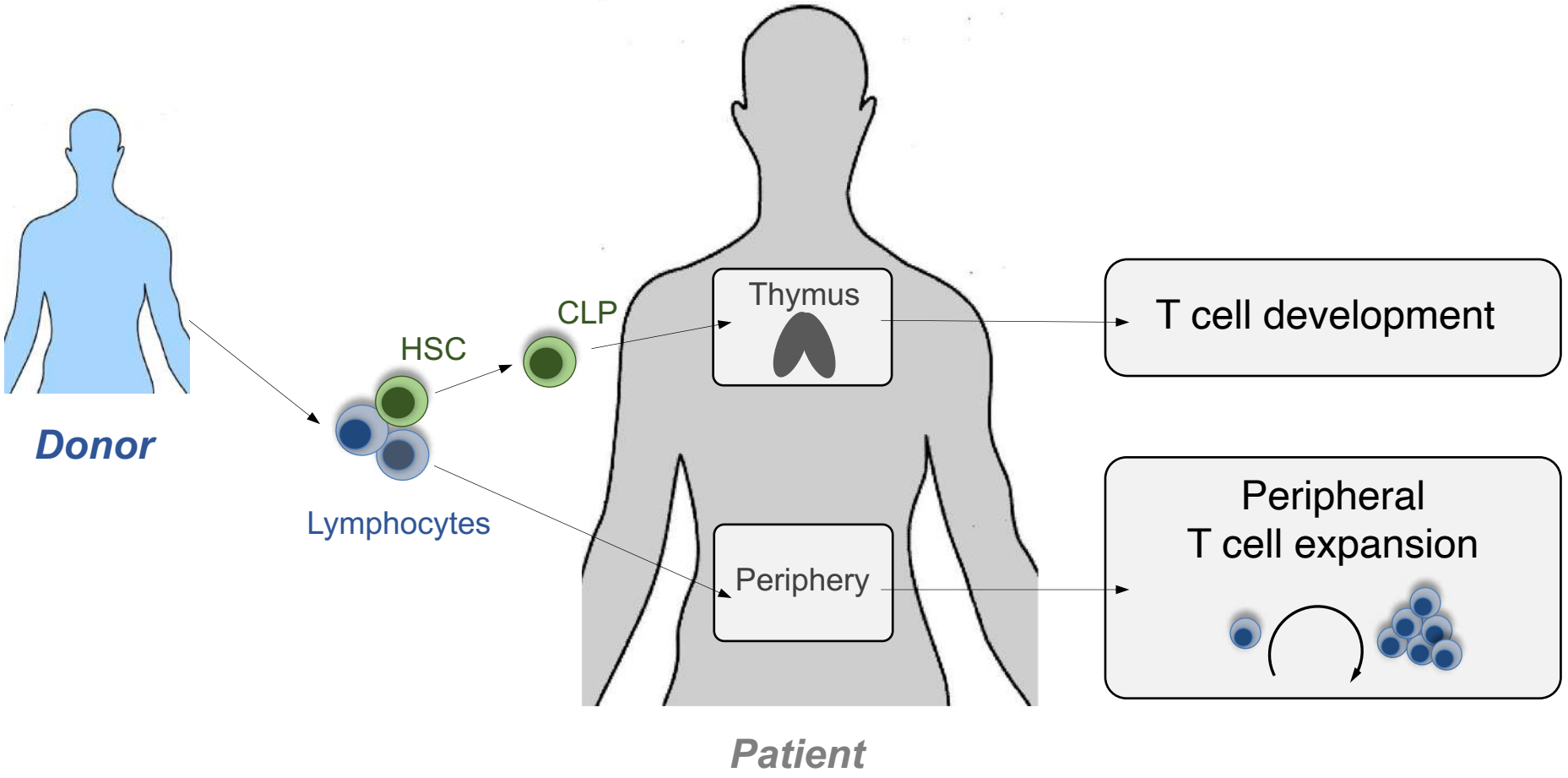

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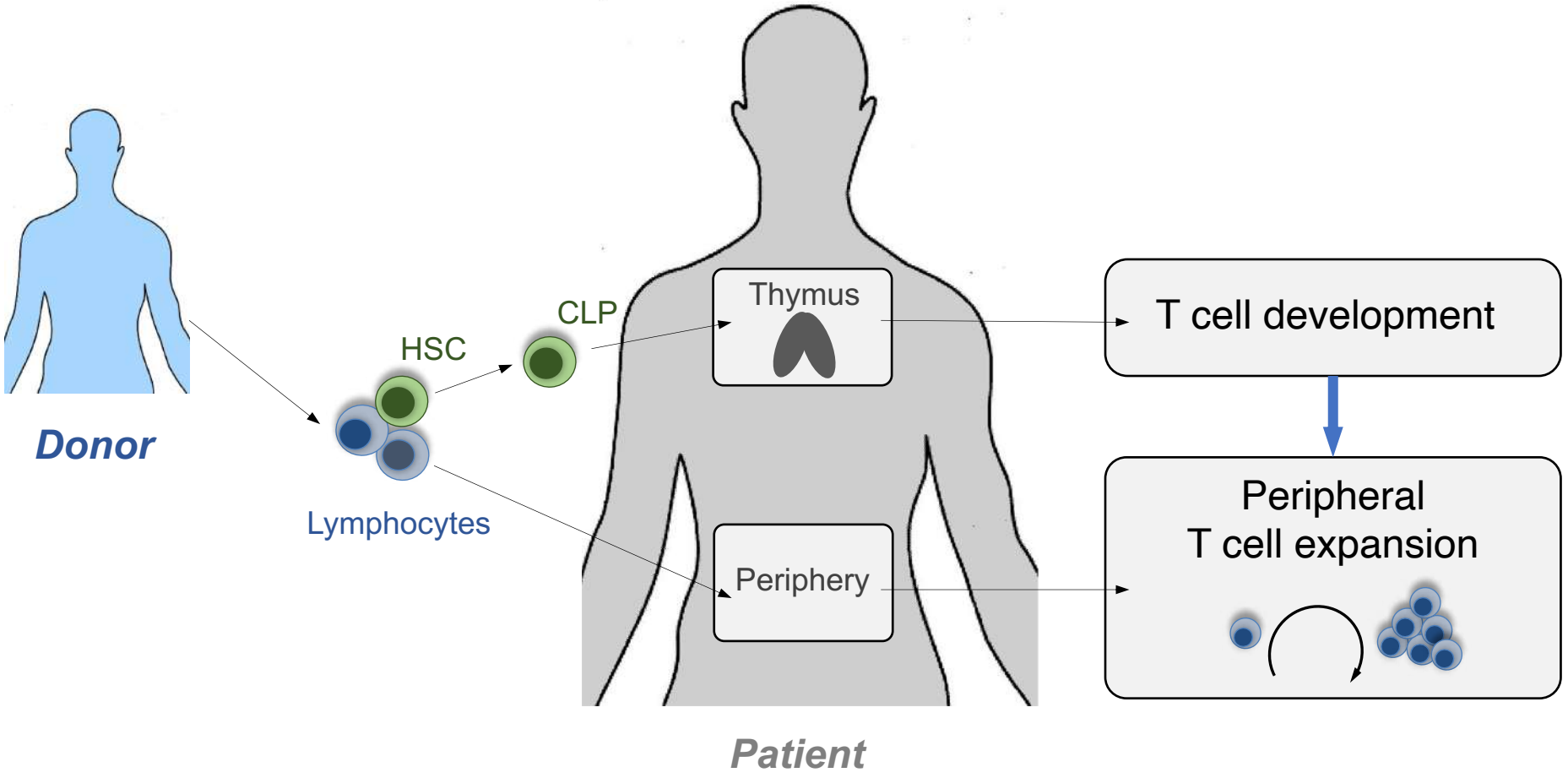

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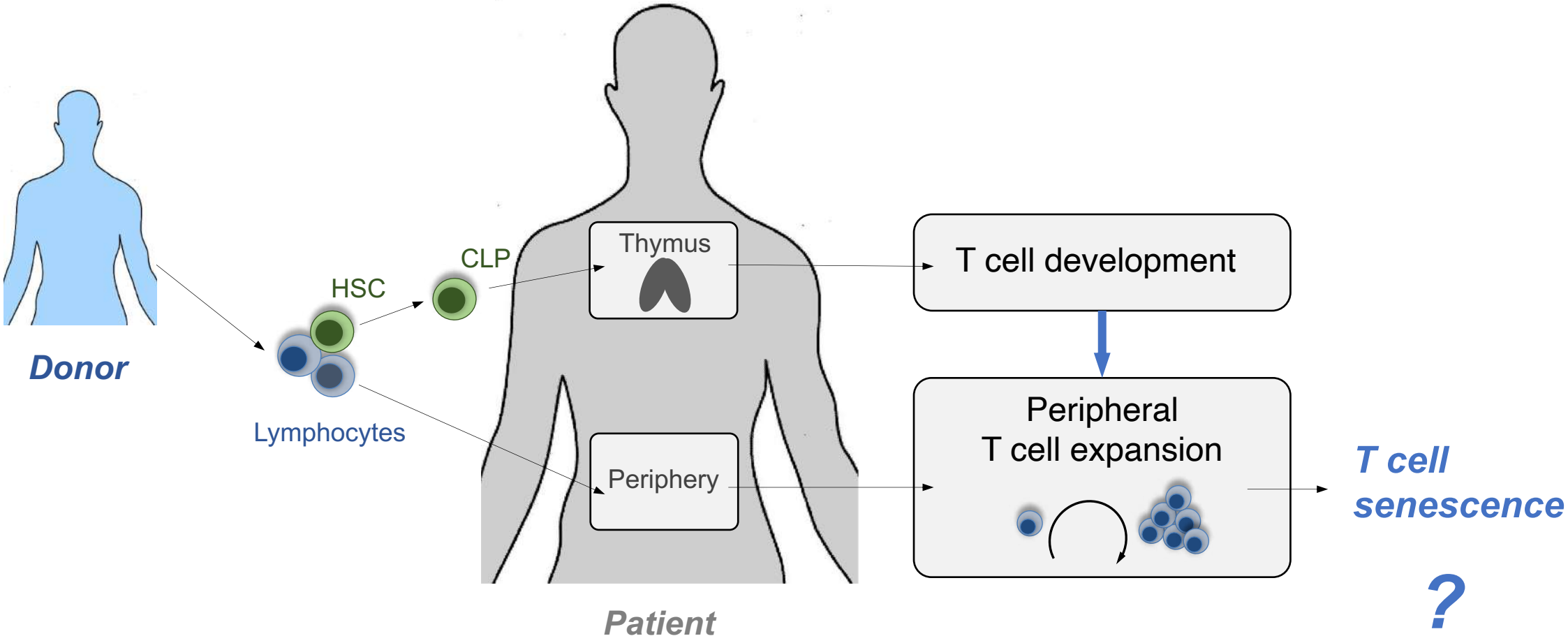
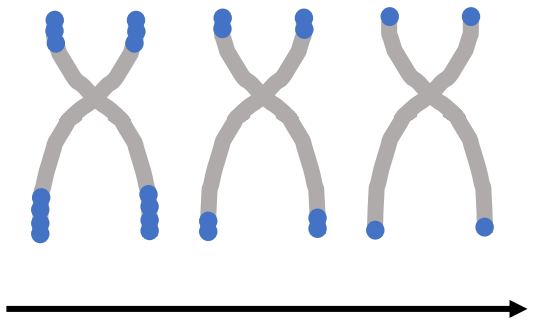


Hallmarks of T cell senescence

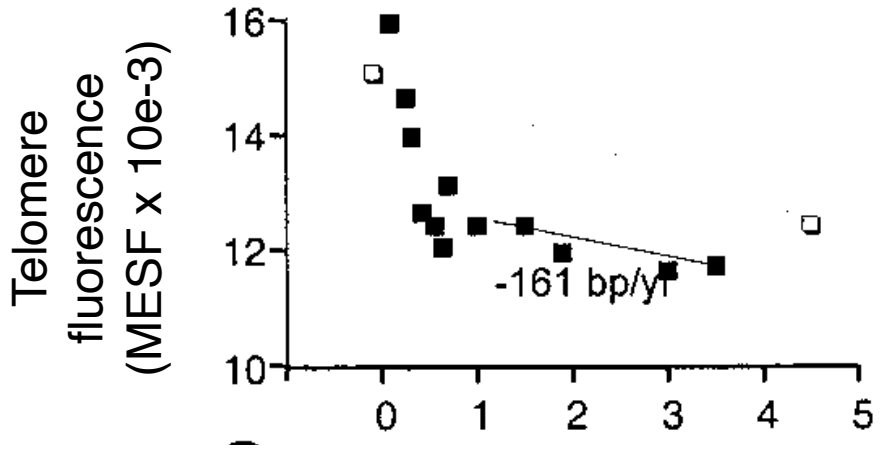
Hallmarks of T cell senescence

Telomere shortening



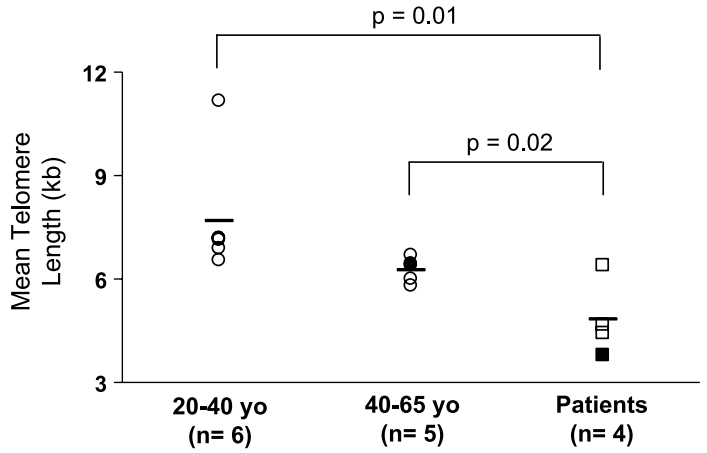
Telomere shortening in T cells after allogeneic HSCT

T Lymphocytes



Rufer et al., Blood 2001

CD8 T cells



Beatty et al., Clin Can Res 2009

Hallmarks of T cell senescence

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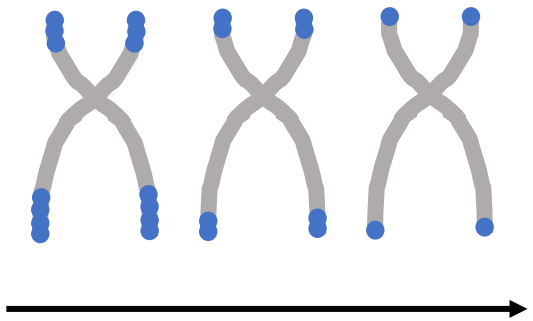

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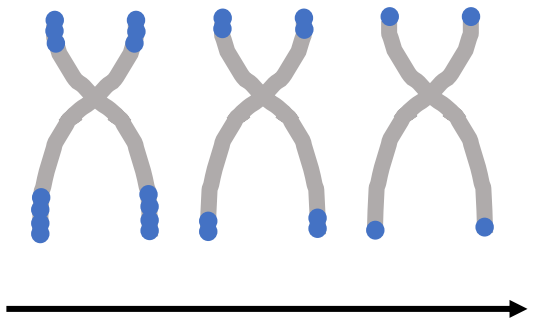
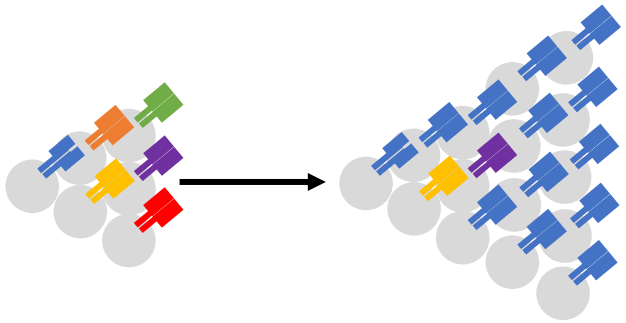
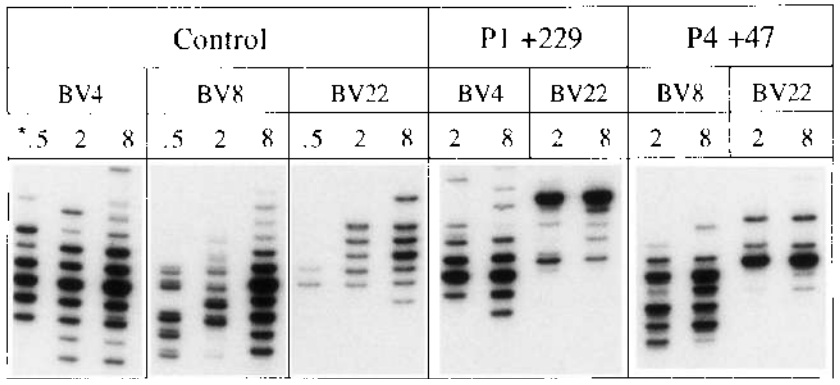


TCR repertoire restriction



TCR repertoire restriction after allogeneic HSCT

TCRβ spectratyping



Dumont-Girard et al., Blood 1998

TCR repertoire restriction after allogeneic HSCT

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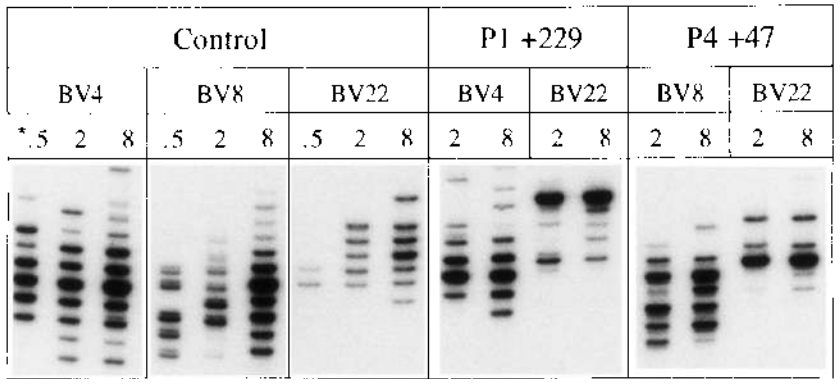
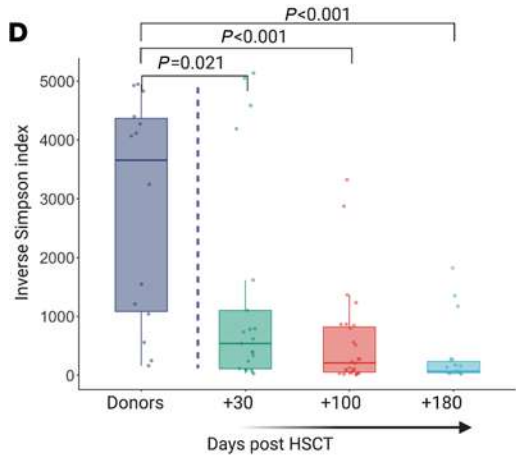
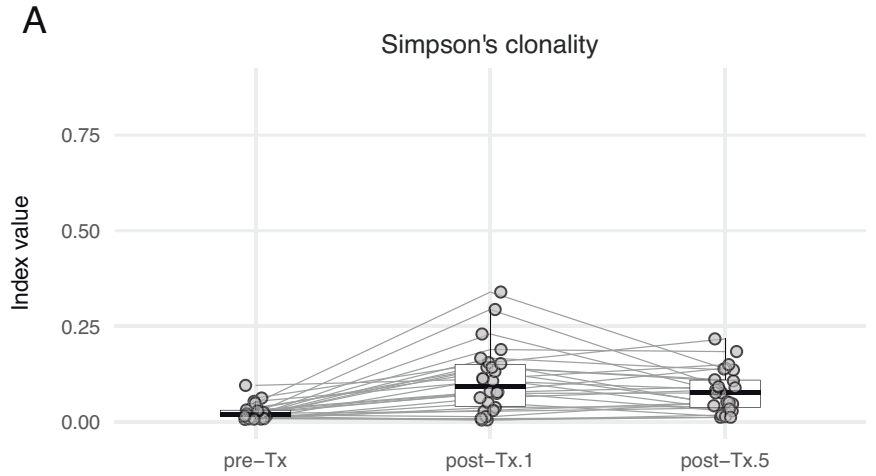


Dumont-Girard et al., Blood 1998

TCRβ sequencing

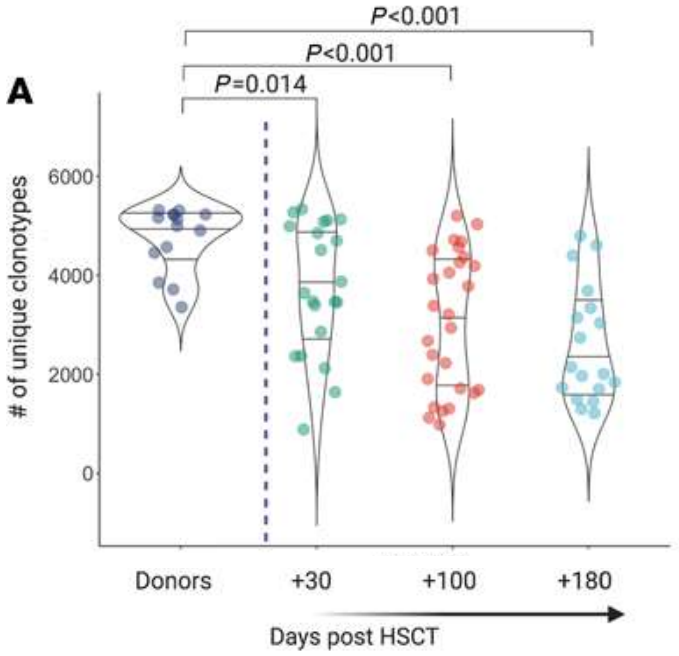


Pagliuca et al., JCI insight 2021



Calderin Sollet et al., Leukemia 2023

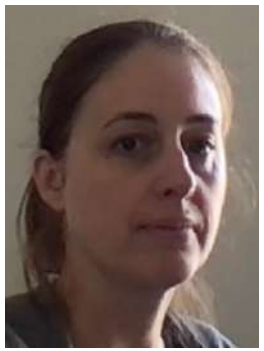
TCR repertoire and clinical outcomes after allogeneic HSCT



	Day +30	*P* value	Day +100	*P* value	Day +180	*P* value
	OS					
	HR (95% CI lower-upper)					
ISI	0.99 (0.99–1)	0.523	0.99 (0.99–1)	0.169	0.99 (0.99–1)	0.453
Overlap coefficient	0.97 (0.81–1.15)	0.729	1.06 (0.88–1.27)	0.525	0.88 (0.56–1.38)	0.605
# of unique clonotypes	0.99 (0.998–0.999)	**0.043**	0.99 (0.99–1)	0.102	0.99 (0.99–1)	0.134
# of pathologically expanded clonotypes	1.01 (1–1.02)	**0.043**	1.01 (0.99–1.03)	0.128	1.04 (1.00–1.09)	**0.047**
Median size of pathological expansion	1.17 (1.03–1.32)	**0.009**	1.00 (0.97–1.03)	0.817	1.02 (0.89–1.11)	0.987
			CIF relapse			
ISI	0.99 (0.99–1)	0.119	0.99 (0.99–1)	0.123	0.98 (0.96–1)	**0.042**
Overlap coefficient	1.07 (0.97–1.18)	0.173	1.01 (0.87–1.13)	0.938	0.91 (0.71–1.13)	0.374
# of unique clonotypes	0.98 (0.97–0.99)	**0.035**	0.98 (0.97–0.99)	**0.022**	0.98 (0.96–0.99)	**0.005**
# of pathologically expanded clonotypes	1.02 (1–1.04)	**0.023**	1.01 (0.99–1.02)	0.442	1.01 (0.99–1.03)	0.231
Median size of pathological expansion	1.02 (0.94–1.11)	0.541	1.04 (1.01–1.06)	**0.001**	1.1 (0.90–1.21)	**0.043**

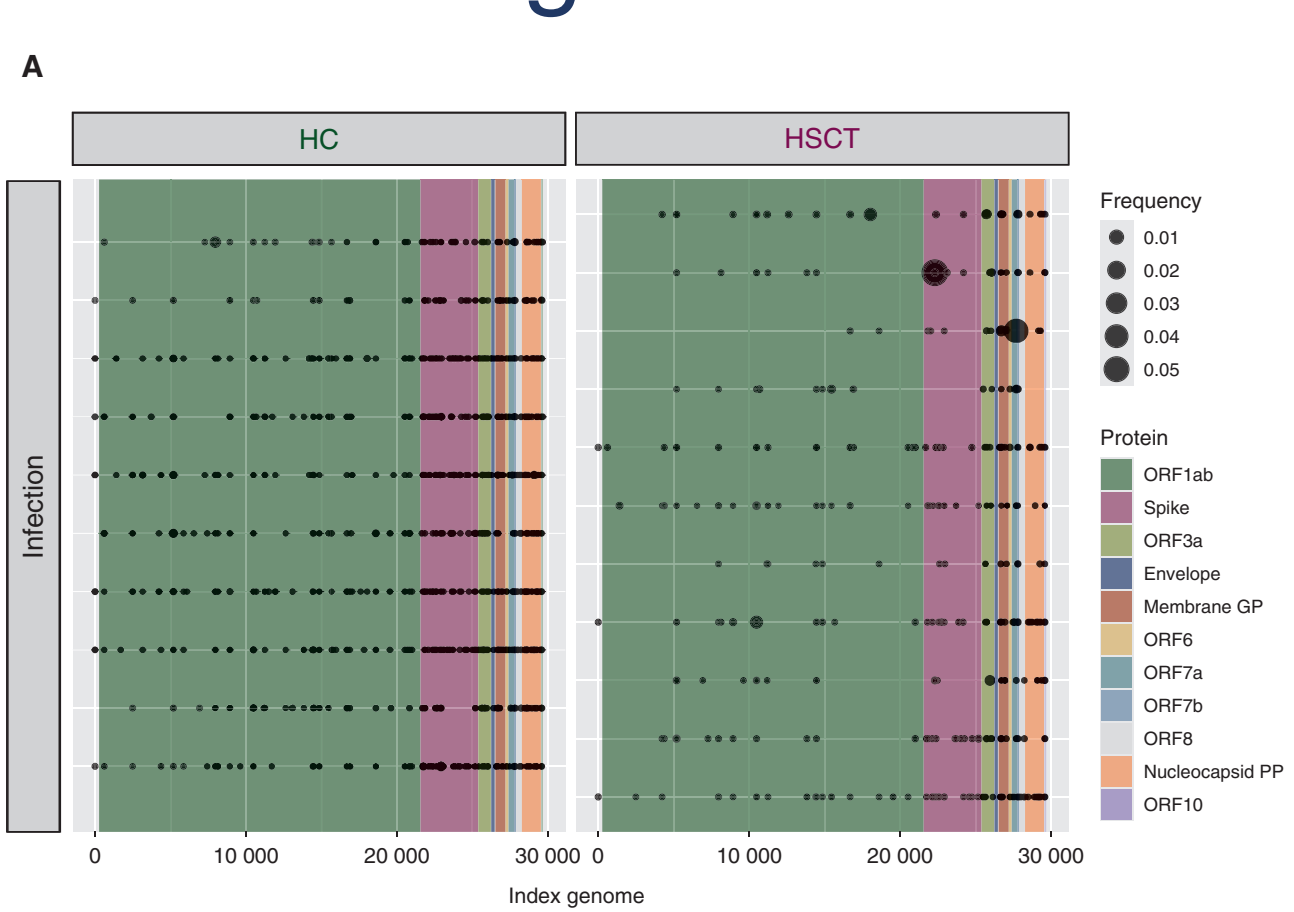
Pagliuca et al., JCI insight 2021

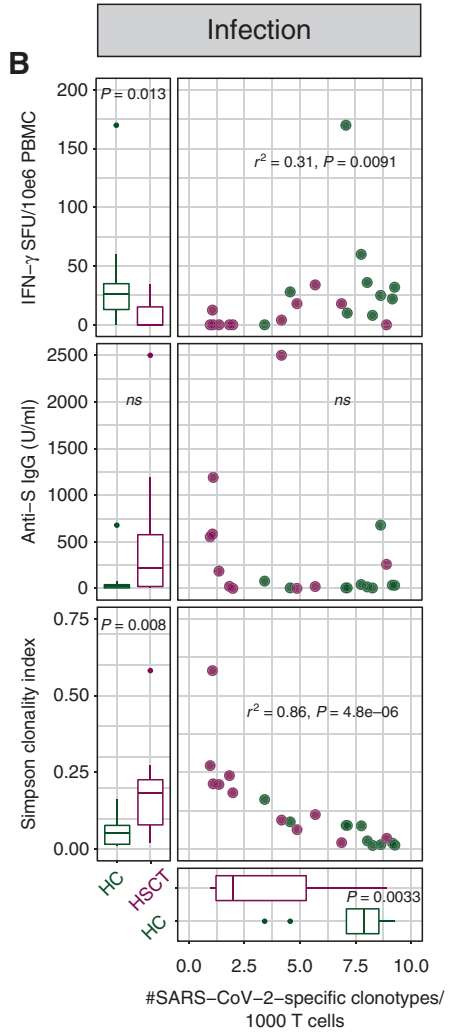
TCR repertoire and response to COVID19 infection after allogeneic HSCT



A. Pradier

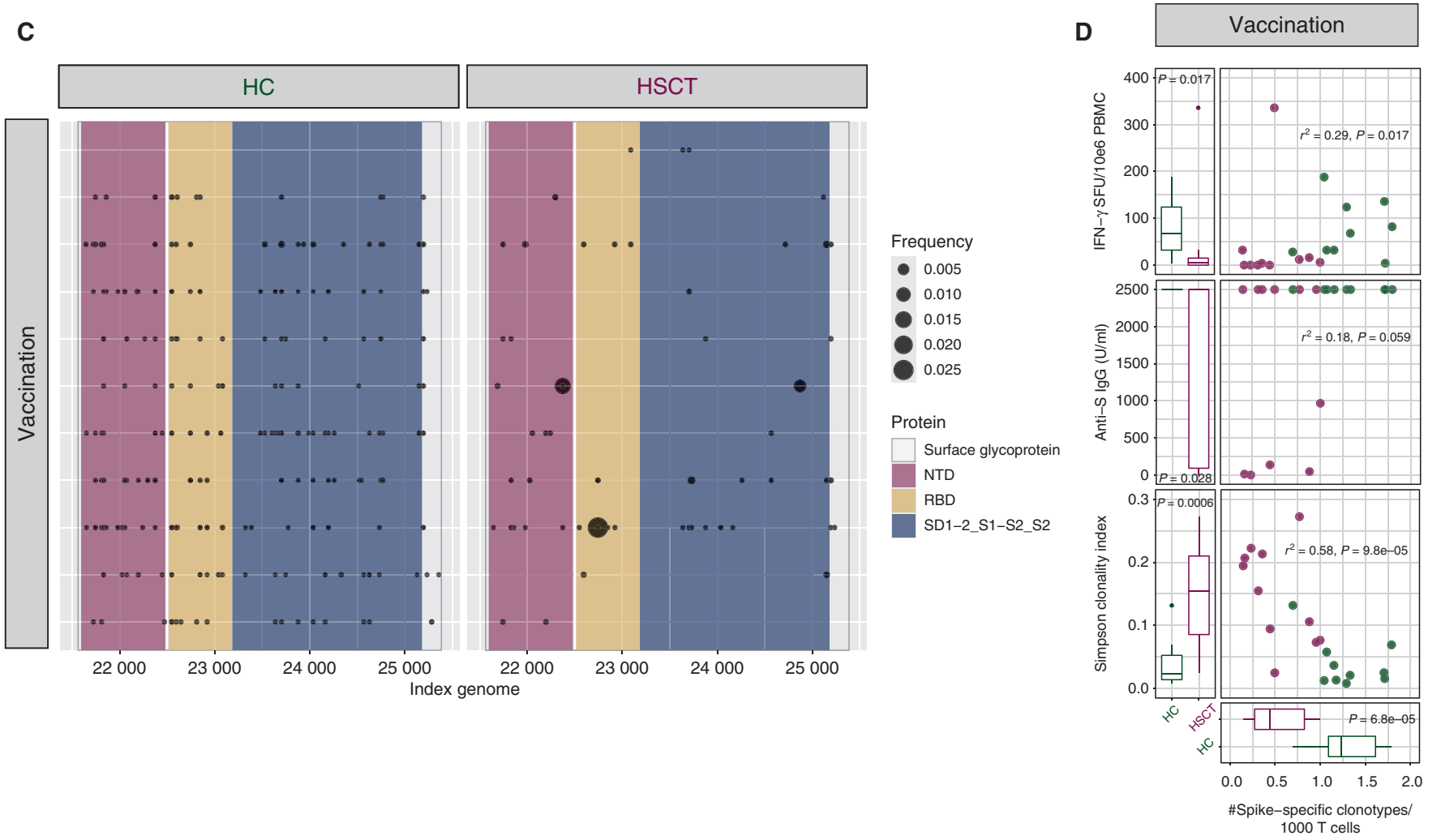
AC. Mamez





Pradier, Mamez* et al., Ann Oncol 2022*

TCR repertoire and response to COVID19 vaccination after allogeneic HSCT



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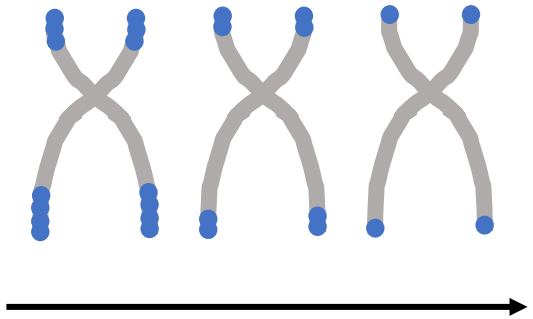
Hallmarks of T cell senescence

Telomere shortening



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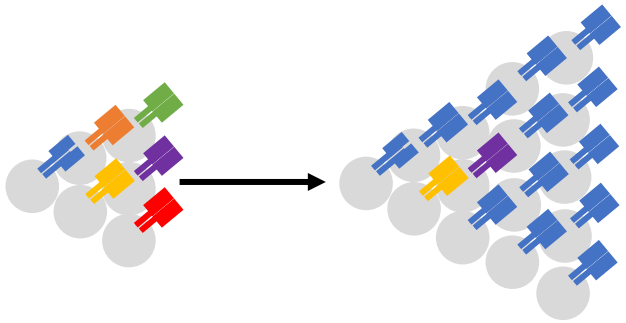

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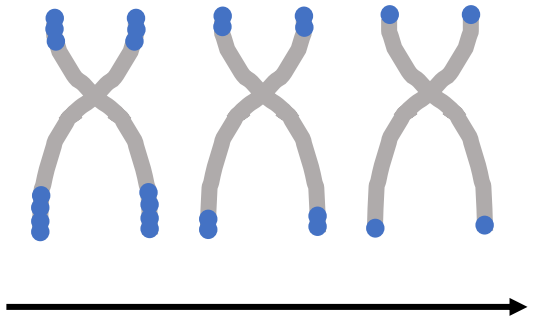

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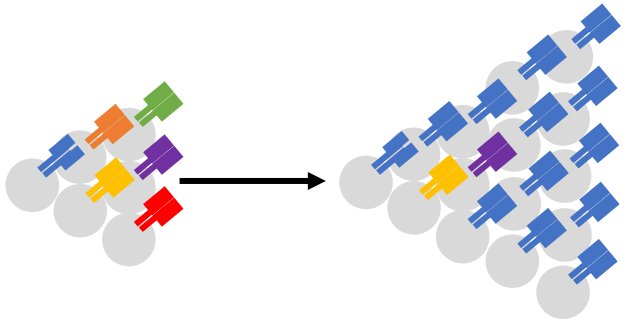
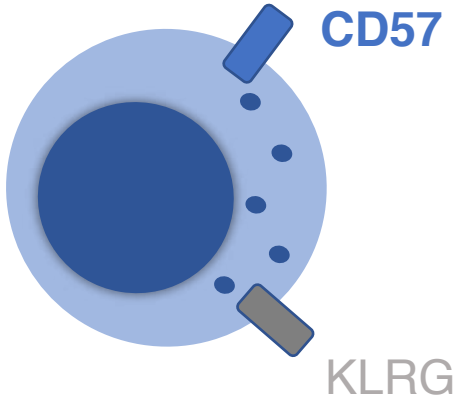
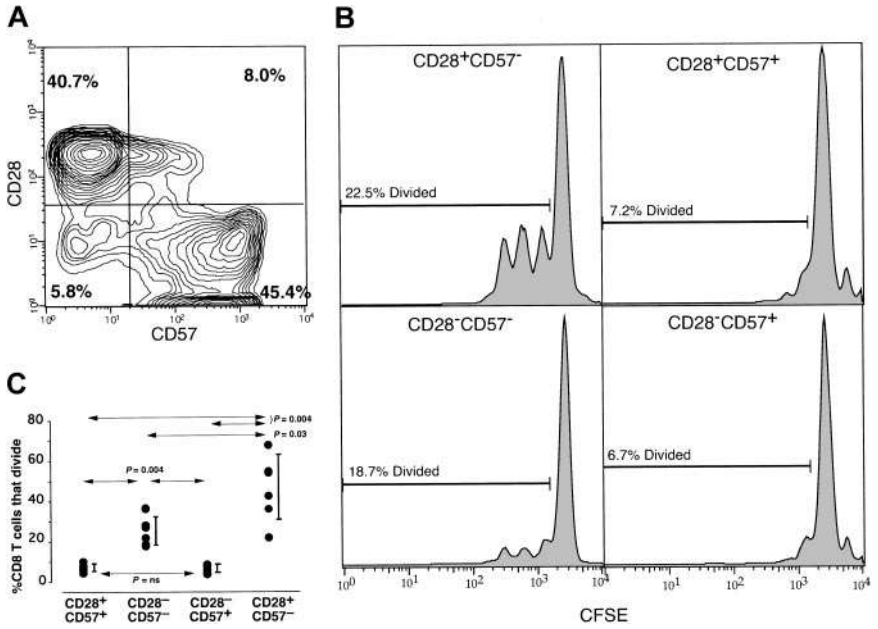


Phenotype

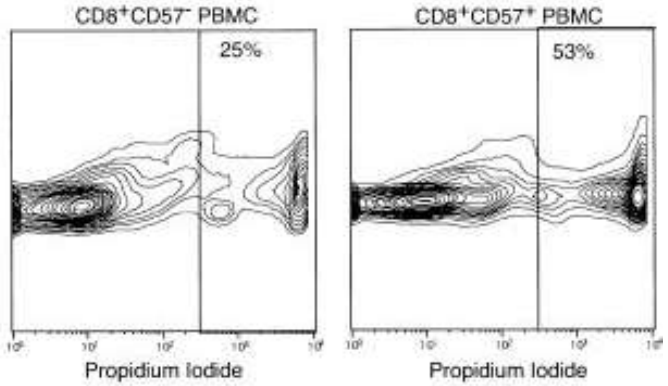


CD57 expression identifies replicative senescent T cells in HIV infection

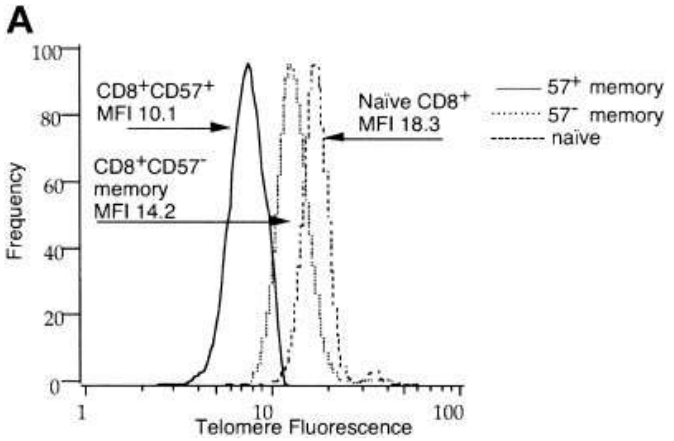
Decresased proliferation



Increased apoptosis

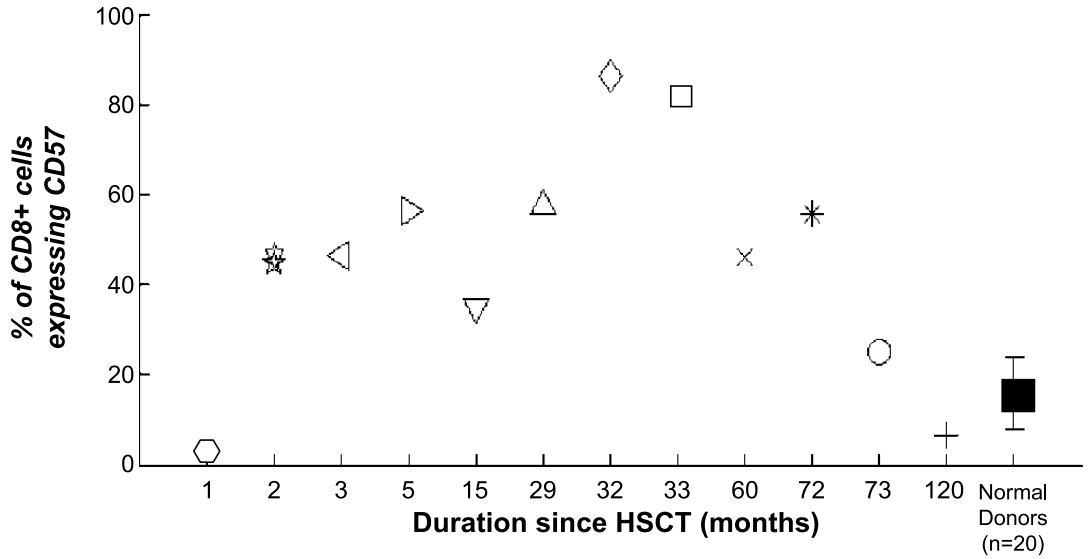


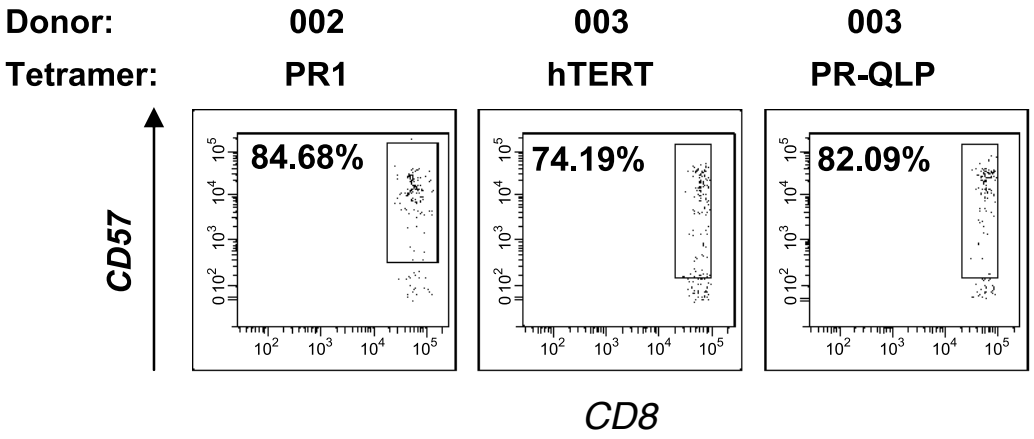
Reduced telomere lenght



Brenchley et al., Blood 2003

CD57 expression is increased after allogeneic HSCT





Beatty et al., Clin Can Res 2009

Leroy et al., J Immunol 1986
Autran, Blood 1991

Fukuda et al, BMT 1994
Gorochov et al., Blood 1994
Dolstra et al., BJH 1995

CD57+ CD8 cells after allogeneic HSCT display a restricted TCR repertoire

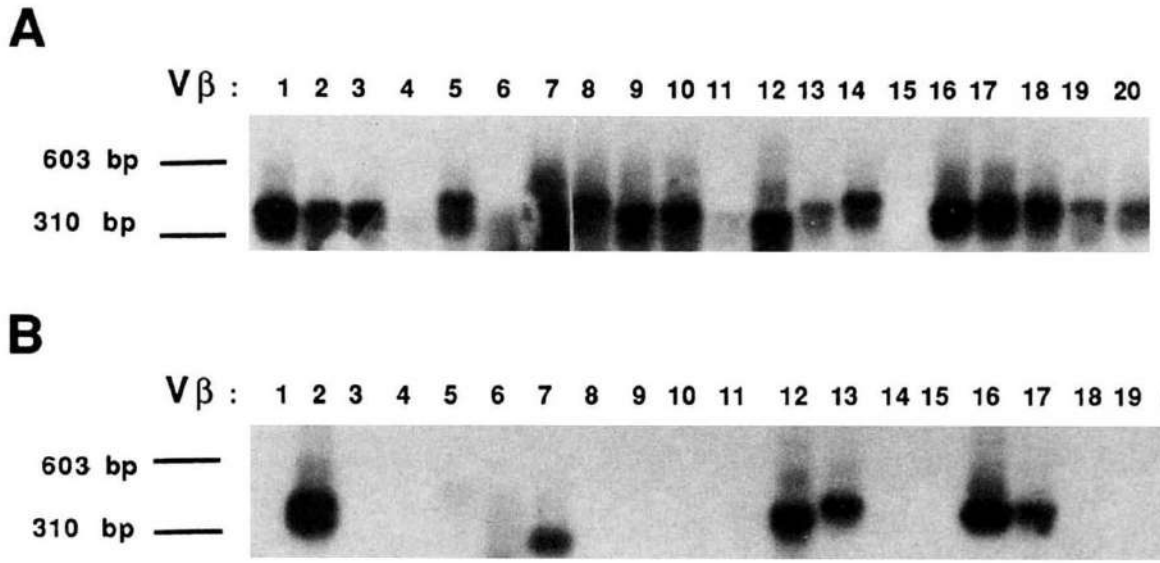


Fig 2. Southern blot analysis of the PCR products obtained from patient no. 6. $CD57^-$ cells (A) and $CD8^+57^+$ cells (B), using a $[P^{32}]$-labeled $C\beta$ internal probe. Specific $V\beta$ products are ranging in size from 250 to 350 bp. Predominance of the $V\beta16$ and $V\beta2$ specific products in the $CD57^+$ fraction.

CD8+ CD57-

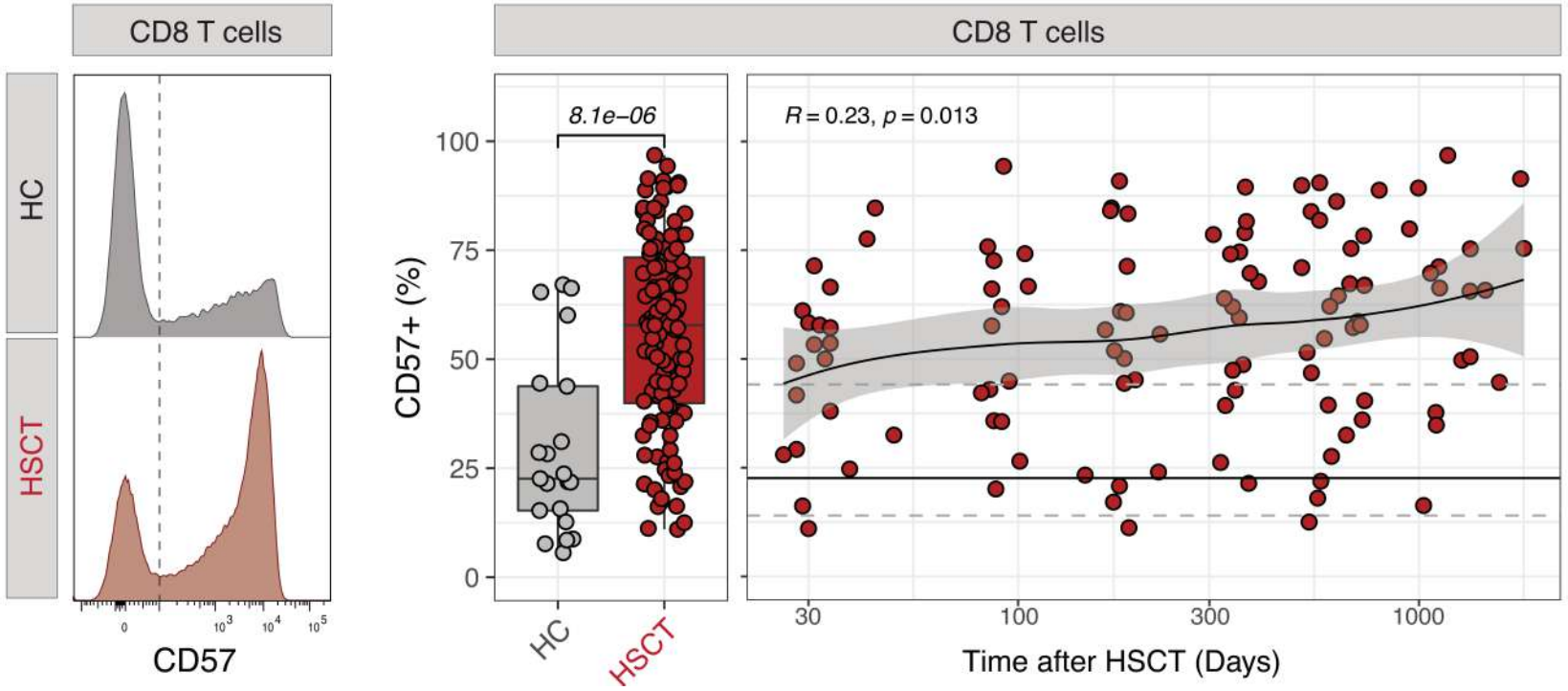
CD8+ CD57+

Gorochov et al., Blood 1994

Expression of CD57 on CD8 T cells after allogeneic HSCT

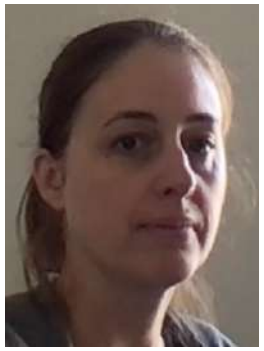
HC, n=21

HSCT, n=115



CD57+ CD8 T cells are expanded after allogeneic HSCT

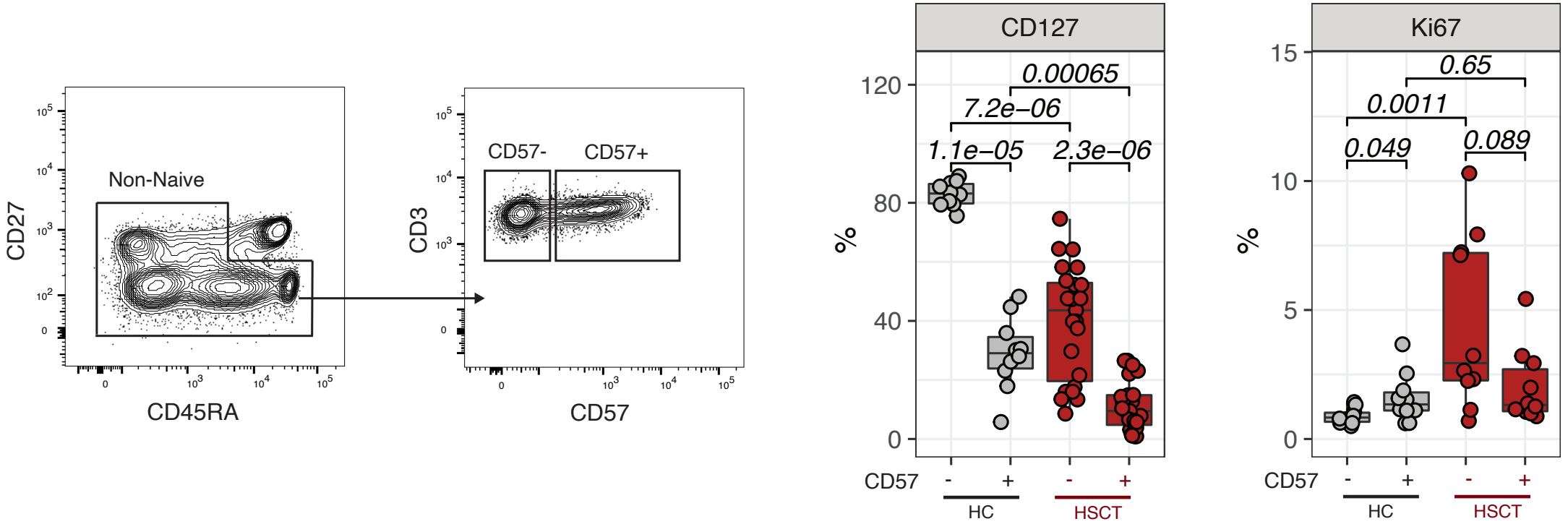
S. Morin



A. Pradier

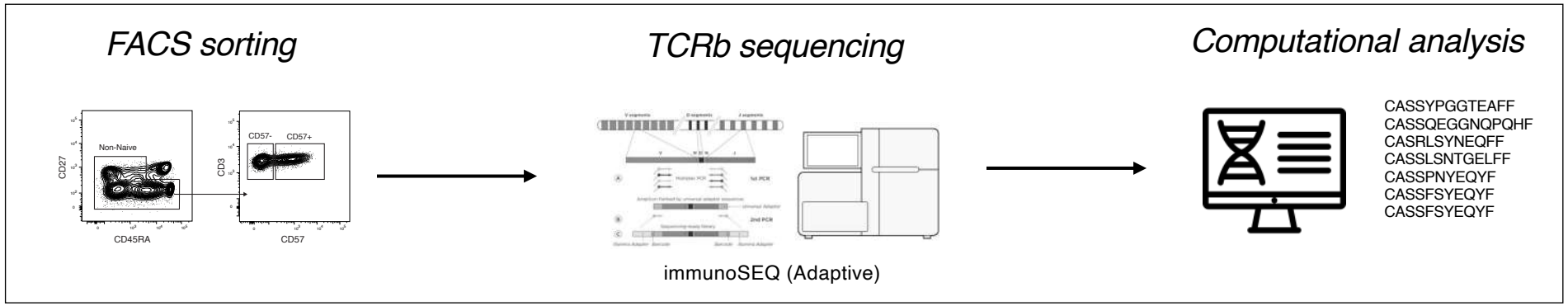
Morin, Pradier*, et al., EBMT Meeting 2022*

Phenotypic characterization of CD57+ CD8 T cells after allogeneic HSCT



CD57+ CD8 T cells from allogeneic HSCT recipients display a senescent phenotype

TCRβ-sequencing analysis of CD57+ CD8 T cells



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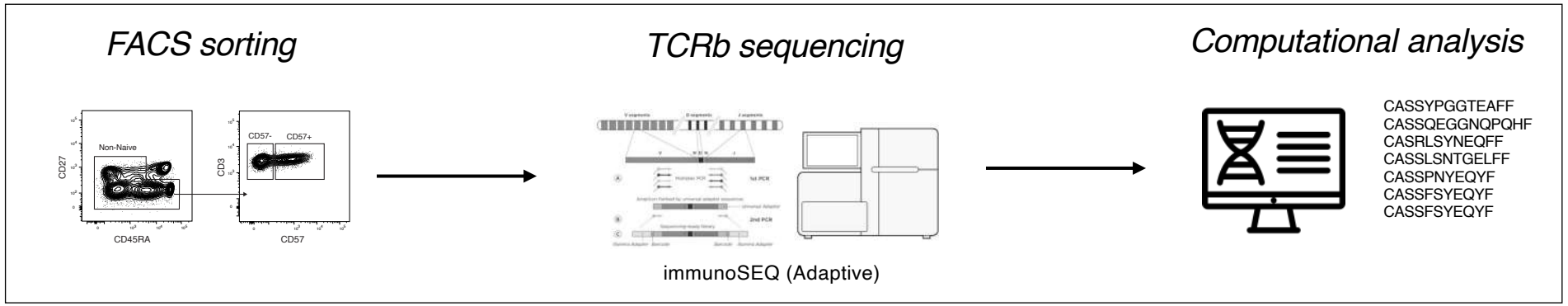

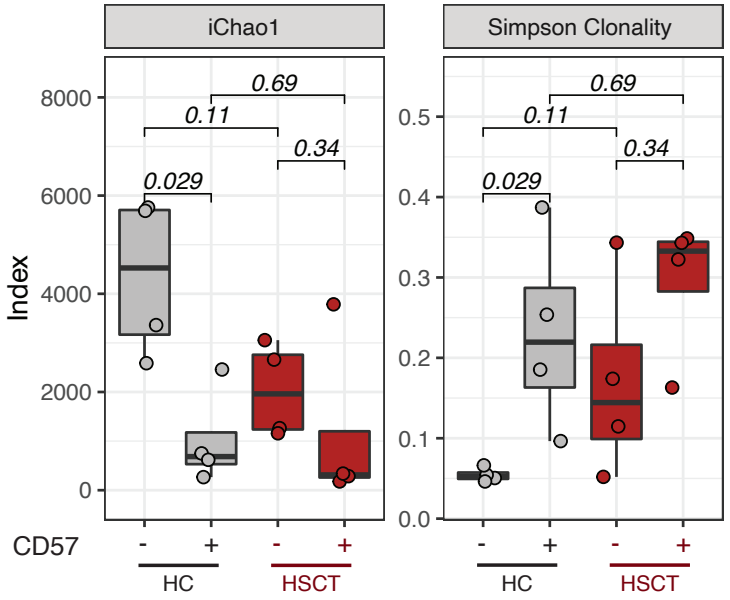

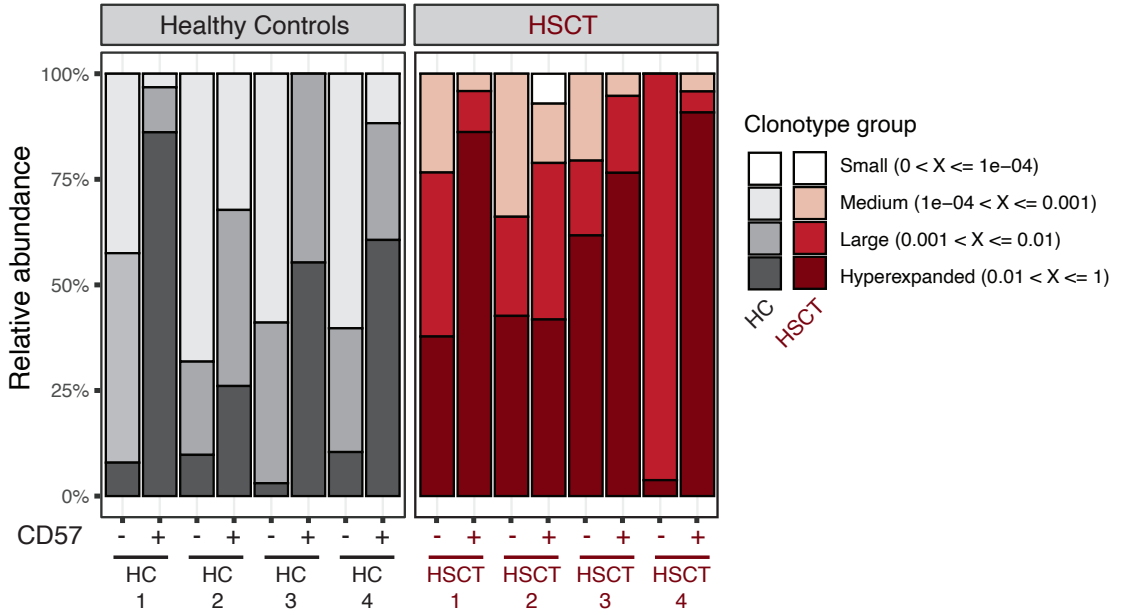

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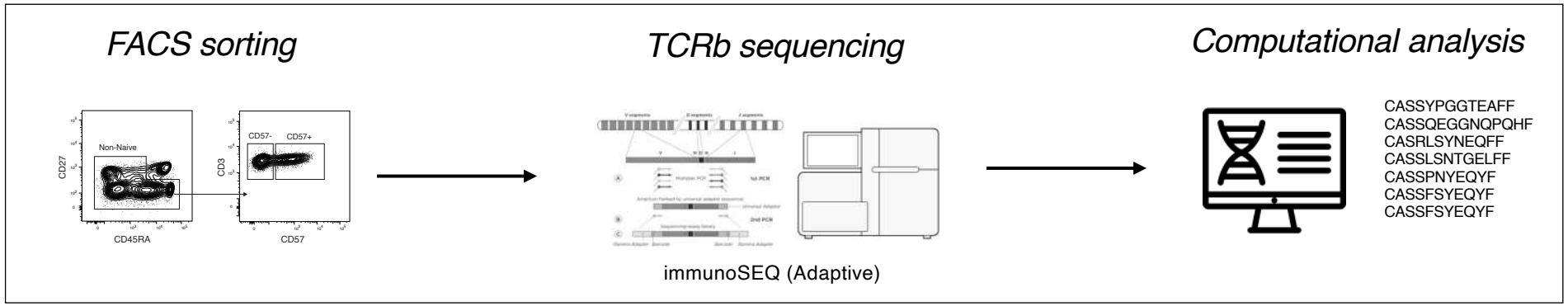
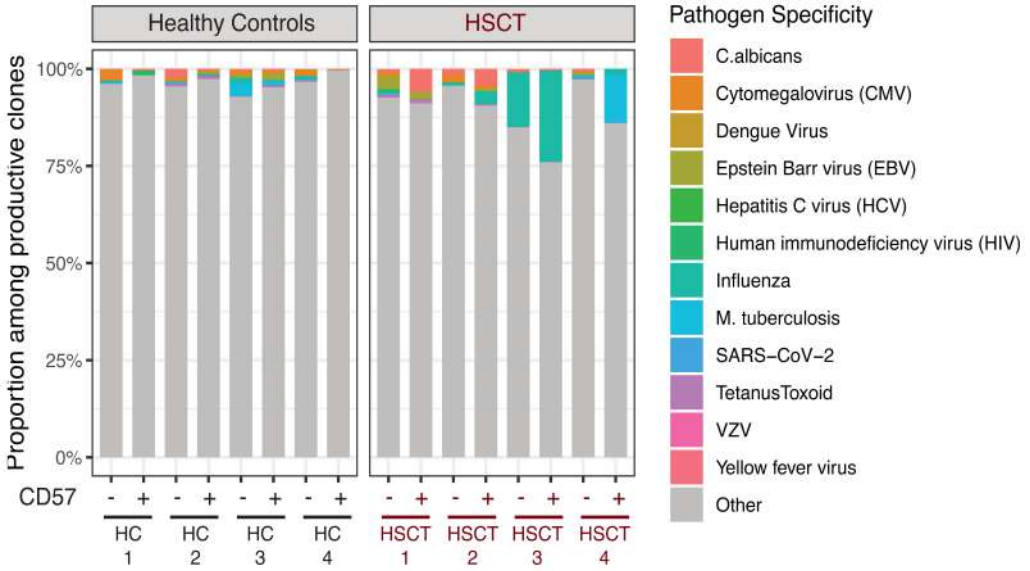
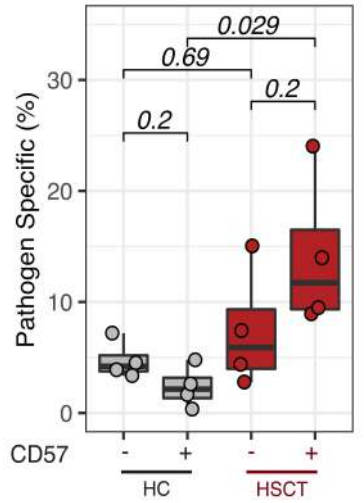
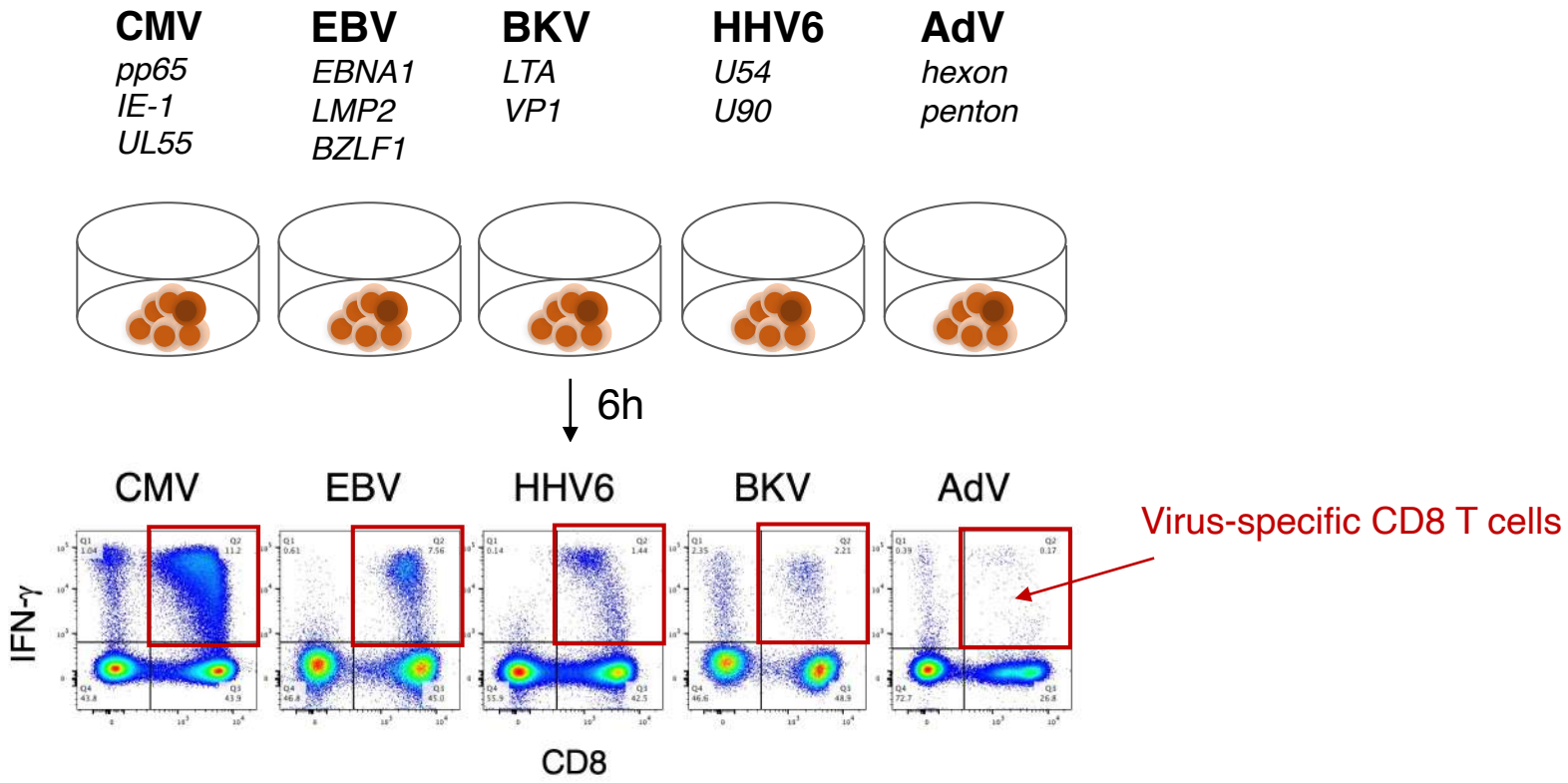






TCRb-sequencing reveals high pathogen-specific clonotypes enrichment in CD57+ CD8 T cells from allo-HSCT recipients

CD57 expression on virus-specific CD8 T cells after allogeneic HSCT



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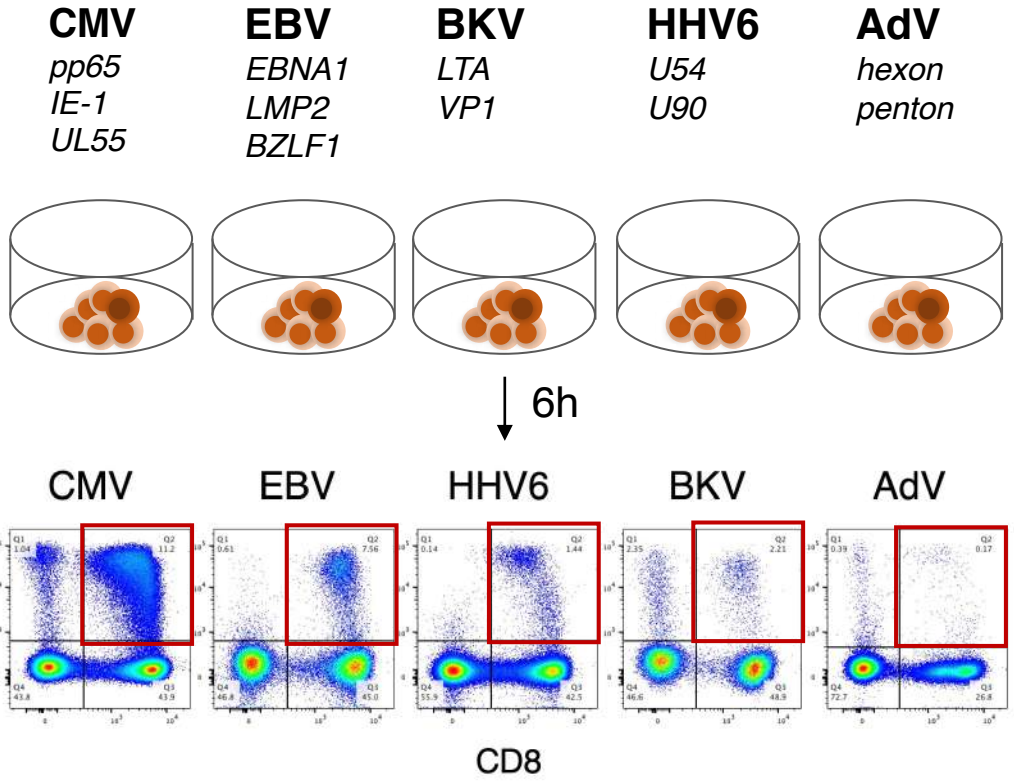
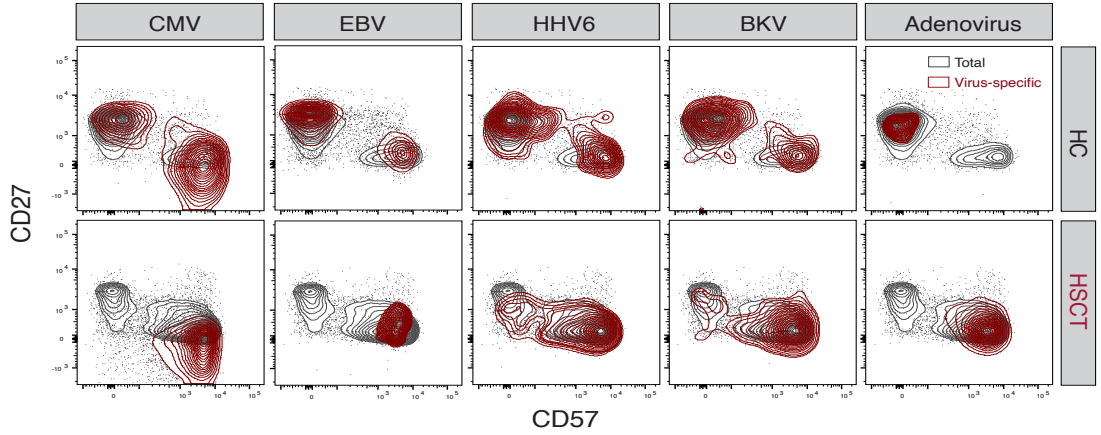
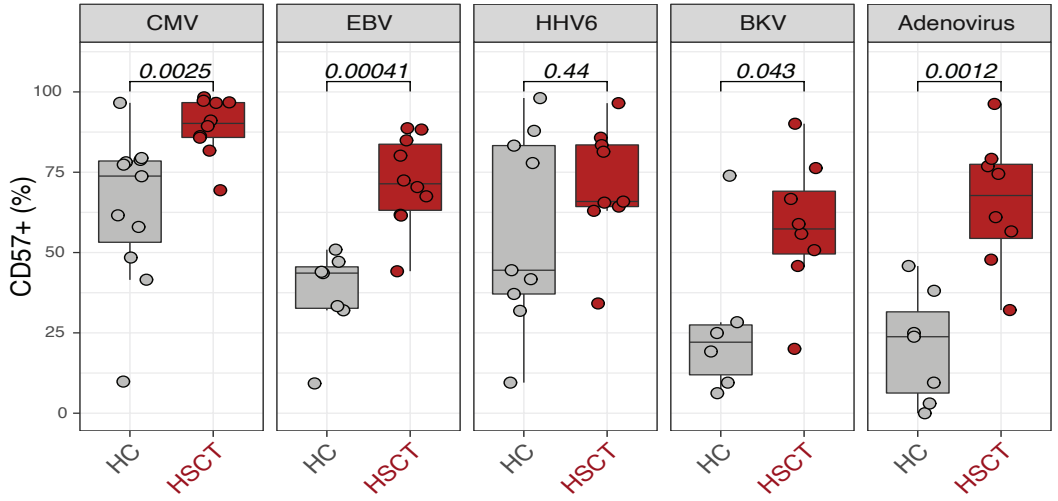
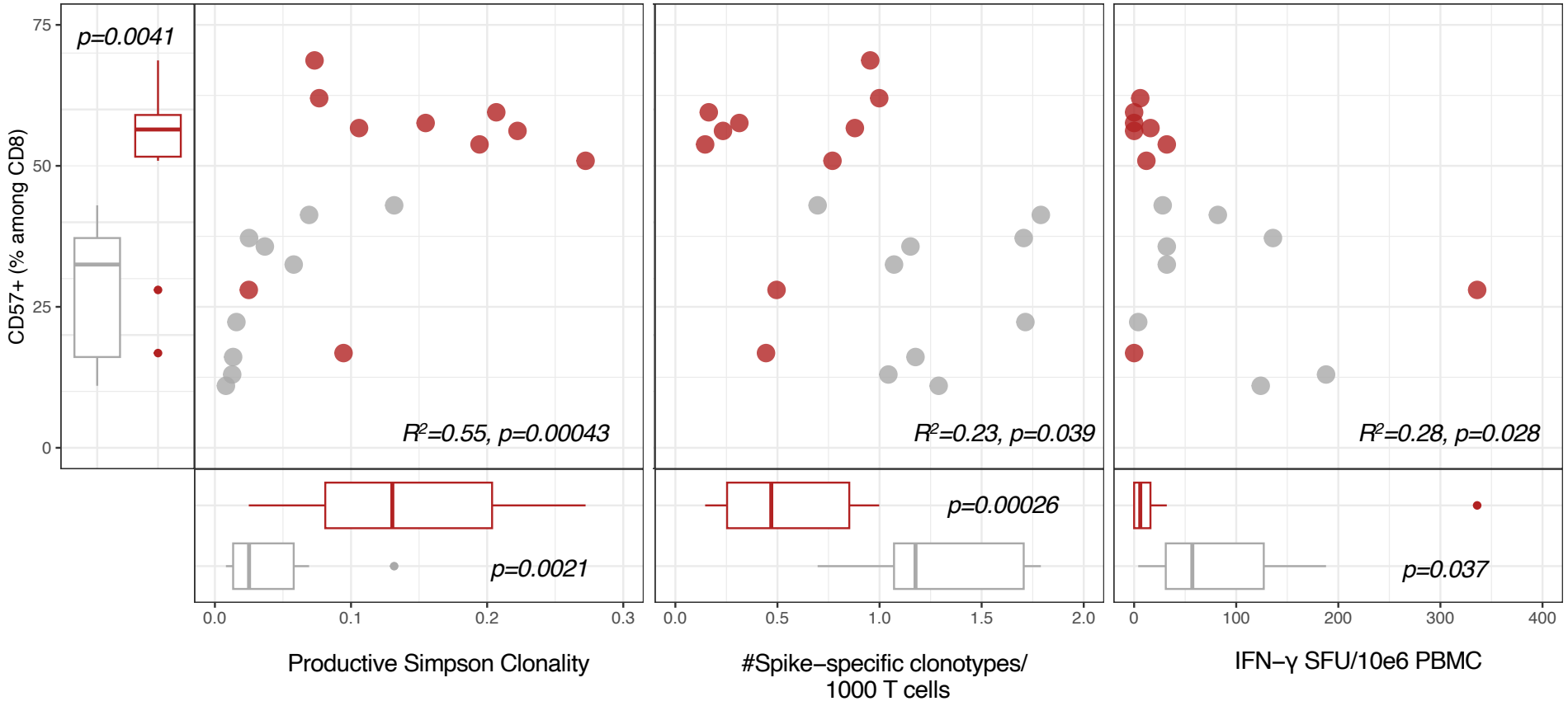






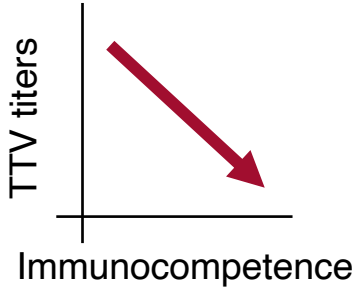
Virus-specific CD8 T cells from allo-HSCT recipients are enriched in CD57+ cells

CD57 expression and COVID19-specific T cell responses after vaccination in allogeneic HSCT recipients



Correlation between proportions of CD57+ CD8 T cells and TTV titers in allo-HSCT recipients

Torque Teno Virus (TTV)
Non pathogenic annellovirus



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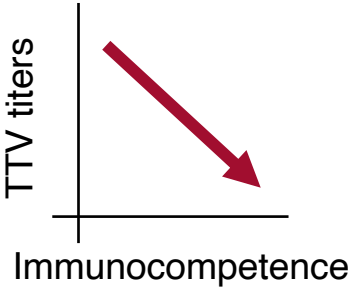
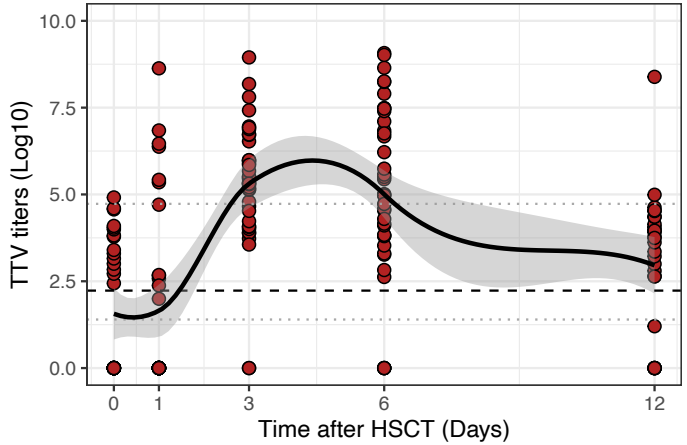
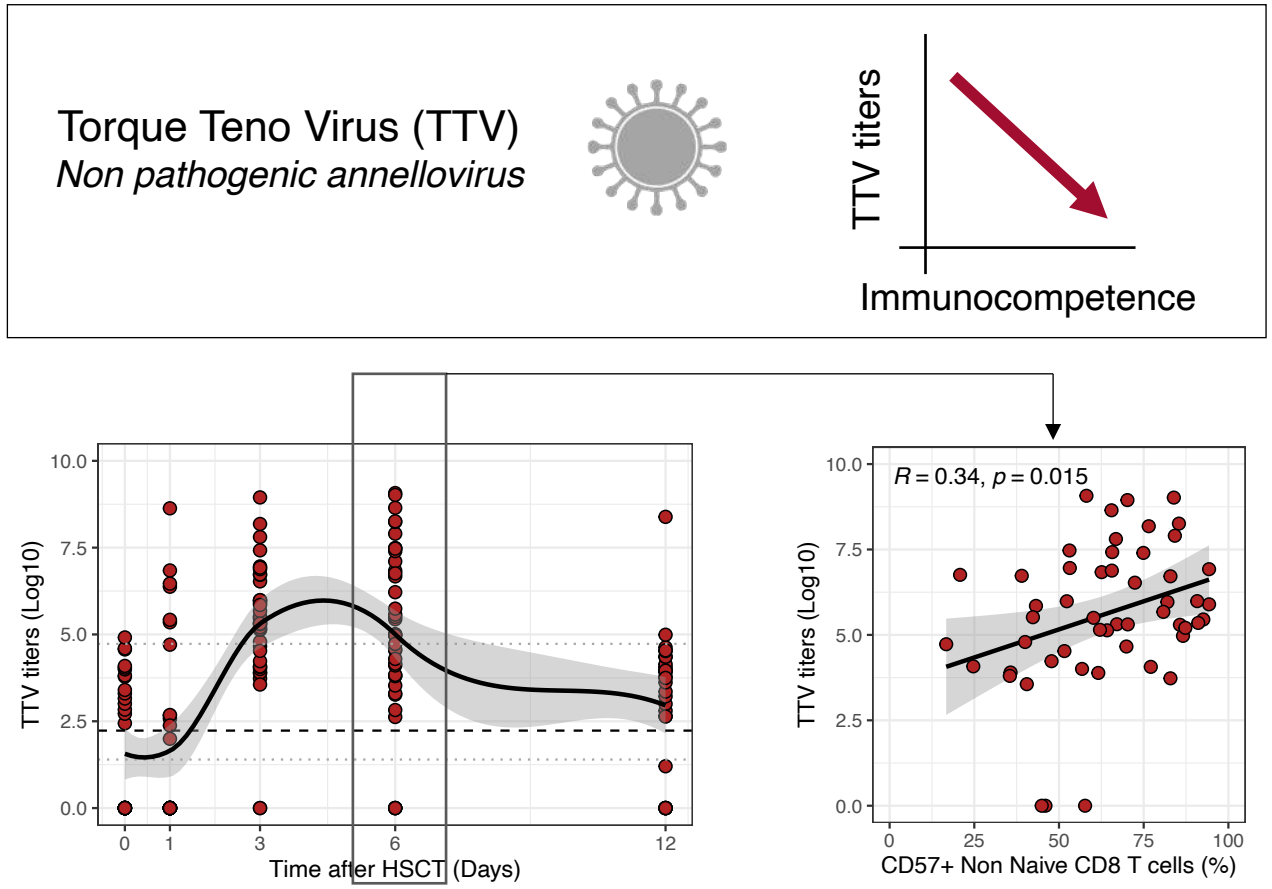
Torque Teno Virus (TTV)
Non pathogenic annellovirus



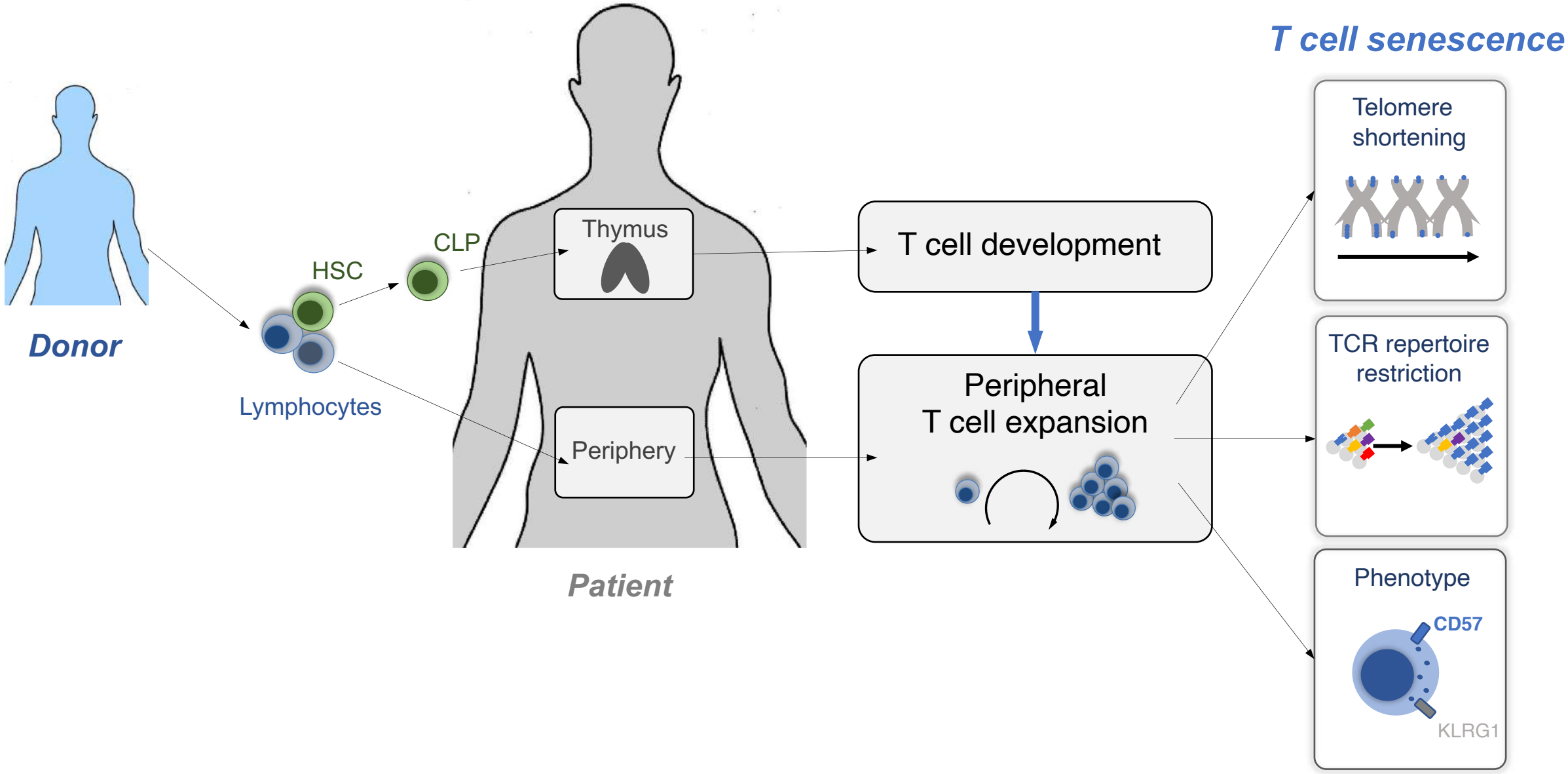


Correlation between proportions of CD57+ CD8 T cells and TTV titers in allo-HSCT recipients

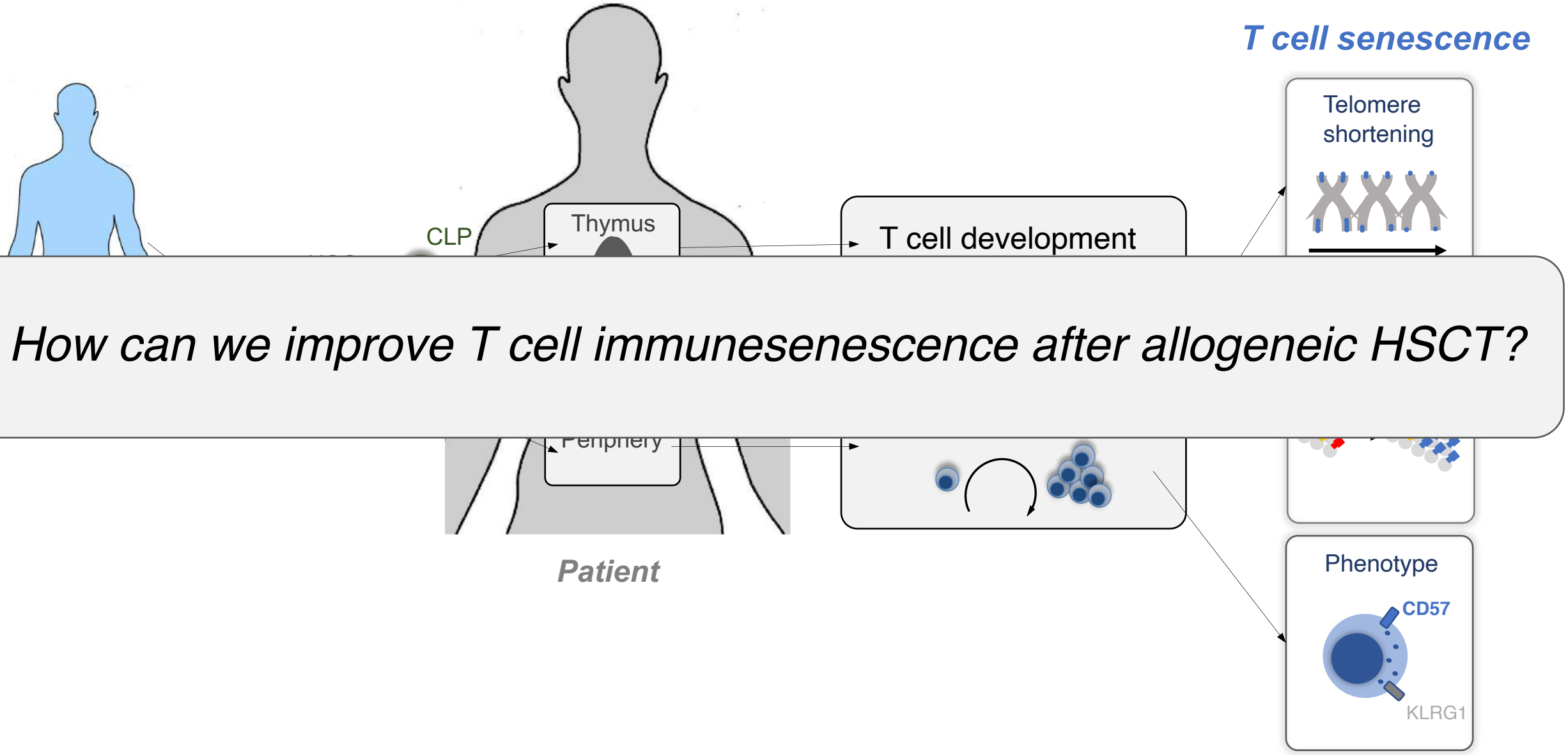


Proportion of CD57-expressing cells among non-naive CD8 T cells positively correlates with TTV titers in allo-HSCT recipients

Immunereconstitution after allogeneic HSCT

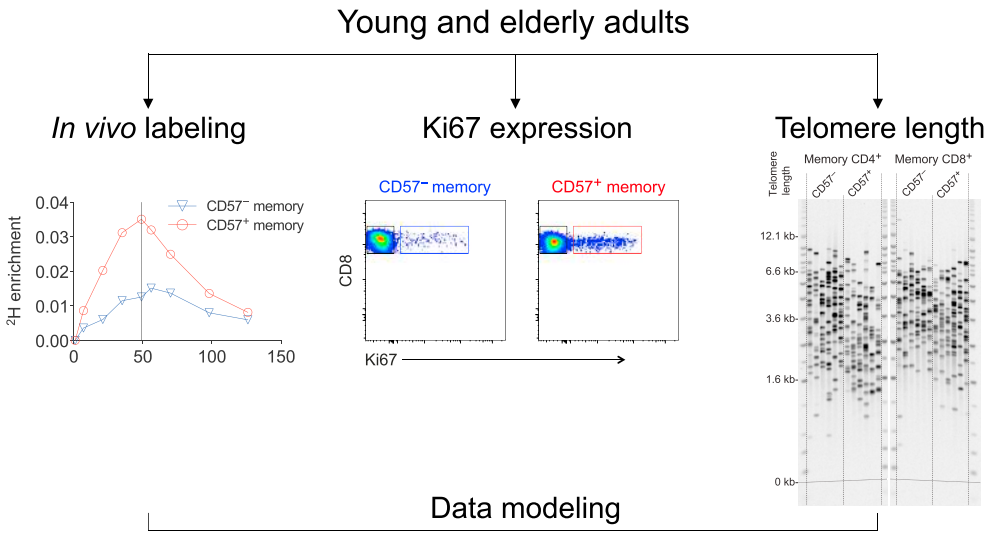


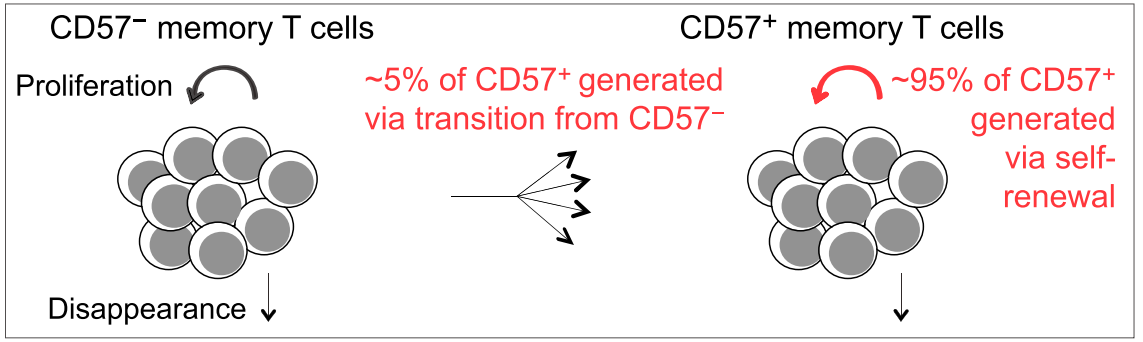
Immunereconstitution after allogeneic HSCT



How can we improve T cell immunesenescence after allogeneic HSCT?

Where do CD57+ senescent cells come from?

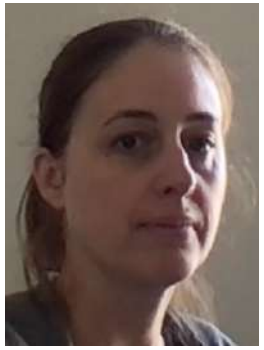




Ahmed et al., Cell Reports 2020

Improving immunesenescence after allogeneic HSCT

CD45RA-depleted DLI



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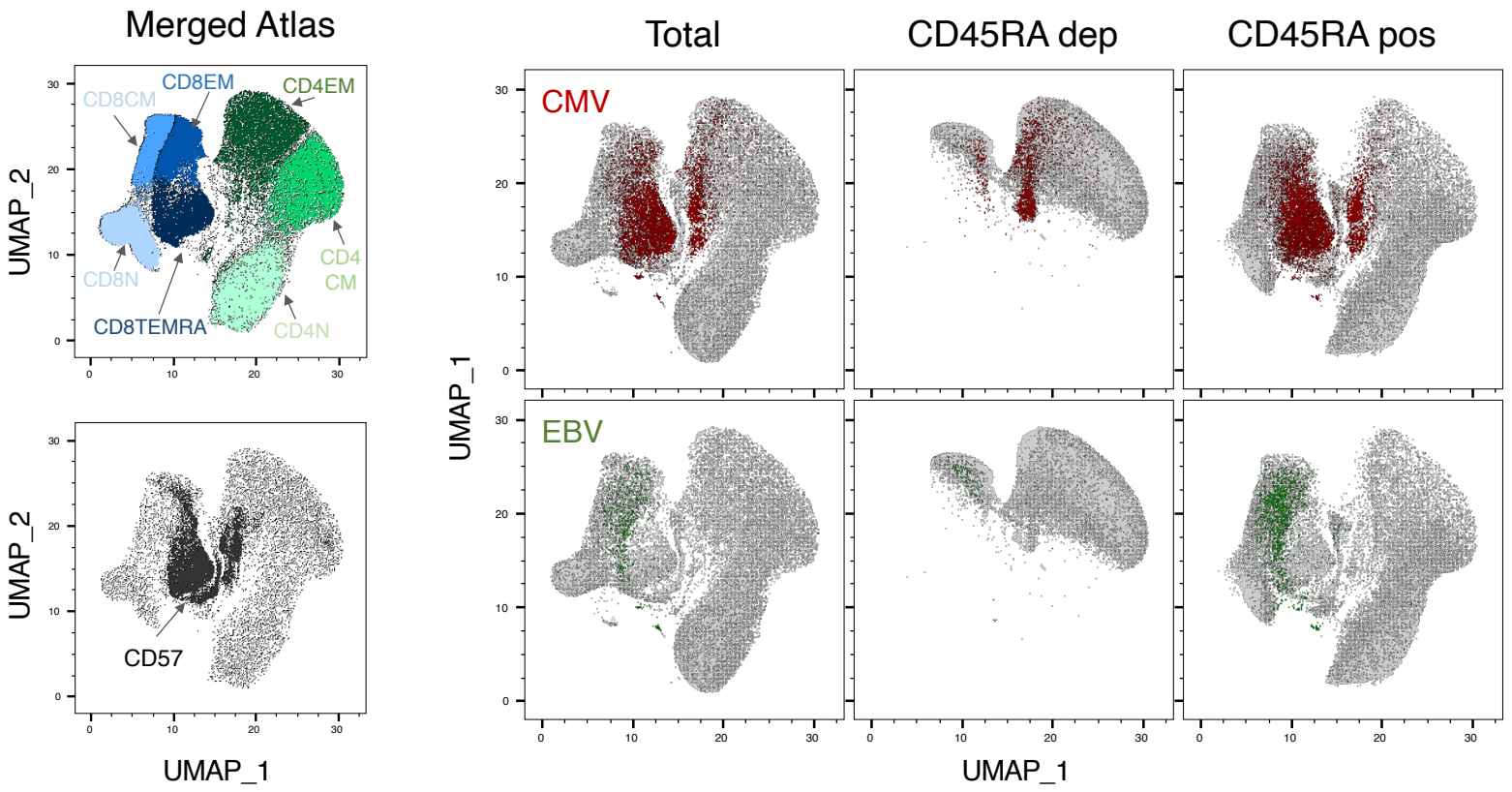

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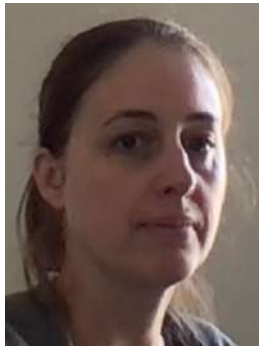
Improving immunesenescence after allogeneic HSCT

CD45RA-depleted DLI



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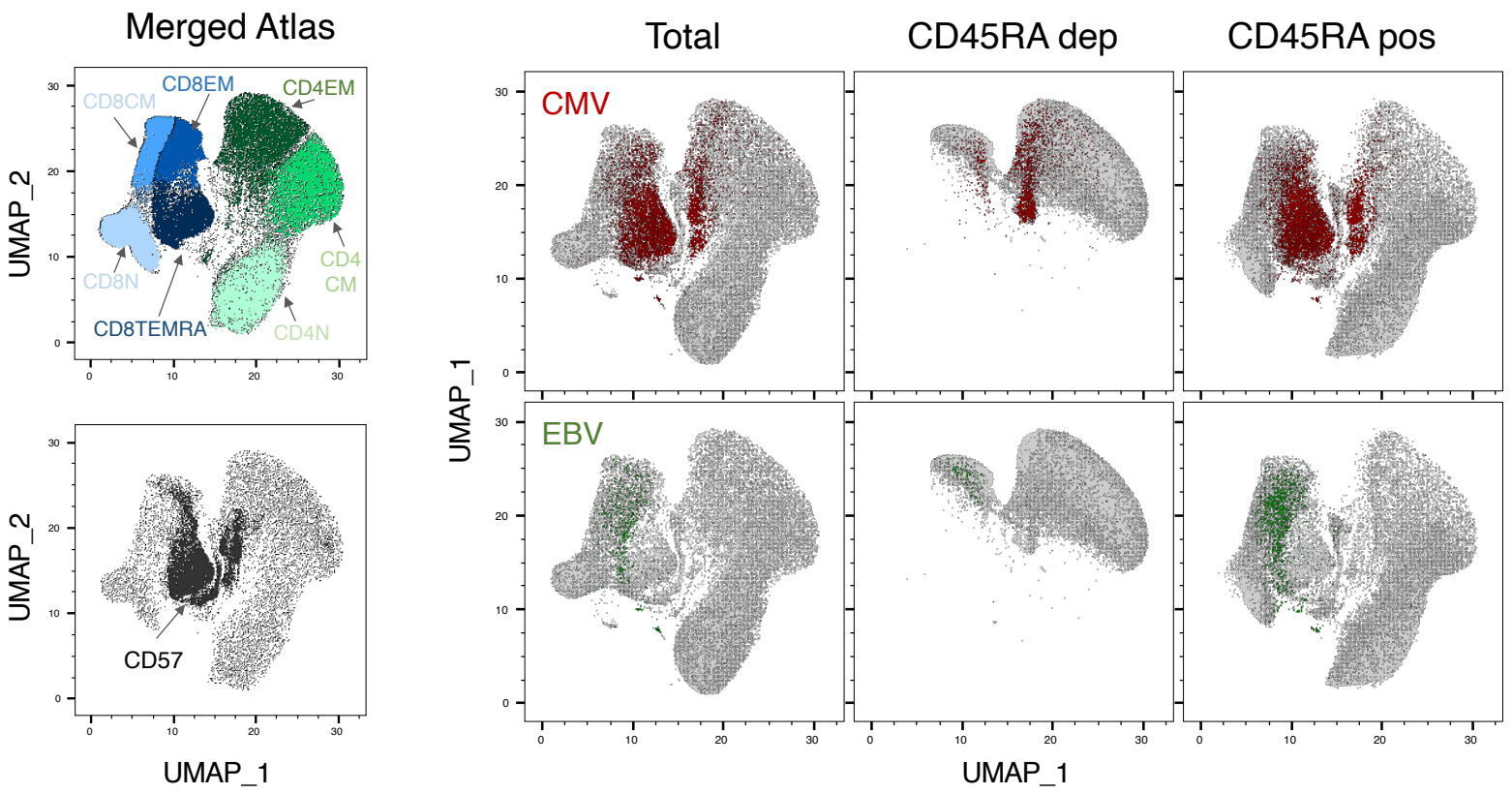

Prophylactic CD45RA-depleted DLI After Haploidentical Transplantation/RIC

ClinicalTrials.gov ID: NCT05066412

Sponsor: University Hospital, Geneva

PI: Anne-Claire Mamez

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Table 1. Comparison of exhausted and senescent T-cell characteristics.

Category	Exhaustion	Senescence	References
Cause	Continuous antigenic stimulation	Repetitive stimulation; DNA damage agents; stress signals	13, 14, 38, 61
Typical feature	Proliferative activity ↓ Cell cycle arrest: p27, p15 ↑; cyclin E-Cdk2, Cdc25A ↓	Proliferative activity ↓ Cell cycle arrest: p16, p21, p53 ↑ DNA damage-associated molecules ↑ Telomere length, telomerase activity ↓ SA-β-gal activity ↑	13, 37, 95
Surface marker	PD-1, CTLA-4, Tim-3, LAG-3, BTLA, TIGIT, CD244, CD160, CD39, 4-1BB ↑	CD27, CD28 ↓ CD57, KLRG1, Tim-3, TIGIT, CD45RA ↑	14, 20, 30, 38–45, 65, 67, 135, 136
TCR signaling machinery	Lck, ZAP70 ↓	Lck, ZAP70, DLG1, Lat, SLP-76 ↓	47, 72
Cytokine profile	Early stage: IL-2 ↓ Intermediate stage: TNF ↓ Terminal stage: IFN-γ, β-chemokines ↓	SASP, Proinflammatory cytokines: IL-6, IL-8, IFN-γ, TNF ↑ Inhibitory factors: IL-10, TGF-β ↑	14, 15, 21, 32, 70
Transcriptional profile	NFAT, Nr4a, Blimp-1, BATF, FoxP3 ↑ Progenitor subset: T-bet^{high} Eomes^{low} PD-1^{int} Terminal subset: T-bet^{low} Eomes^{high} PD-1^{high}	FoxP3 ↑	26, 48, 54, 55, 58, 59
Epigenetic change	Exhaustion-associated DNA methylation programs	SAHF ↑	56, 57, 137
Metabolic alternation	Glycolysis ↓ Mitochondrial biogenesis ↓ Reactive oxygen species ↑	Glycolysis ↑ Mitochondrial biogenesis ↓ Reactive oxygen species ↑	112, 126
Functional alteration	Cytotoxic activity ↓ Effector molecule: GzmB ↓	Cytotoxic activity ↓ Suppressive functions ↑ Effector molecules: perforin, GzmB ↓	8, 33, 37, 71

SA-β-gal senescence-associated β-galactosidase, *SAHF* senescence-associated heterochromatin foci, *SASP* senescence-associated secretory phenotype, *PD-1* programmed cell death protein 1, *CTLA-4* cytotoxic T-lymphocyte antigen-4, *Tim-3* T-cell immunoglobulin and mucin domain containing-3, *LAG-3* lymphocyte activation gene 3, *BTLA* B- and T-lymphocyte attenuator, *TIGIT* T-cell immunoreceptor with Ig and ITIM domains, *KLRG1* killer cell lectin-like receptor G1, *Lck* lymphocyte-specific protein tyrosine kinase, *ZAP70* zeta-chain-associated protein kinase 70, *DLG1* disks large homolog 1, *Lat* linker for activation of T cells, *SLP-76* SH2 domain-containing leukocyte protein of 76 kD, *GzmB* granzyme B, *NFAT* nuclear factor of activated T cell, *BATF* basic leucine transcription factor, *Blimp-1* B lymphocyte-induced maturation protein-1, *T-bet* T-box transcription factor, *Eomes* eomesodermin, *FoxP3* forkhead box P3, *Cdk2* cyclin-dependent kinase 2
Symbols: ↑, increased; ↓, decreased; ^{int}, intermediate