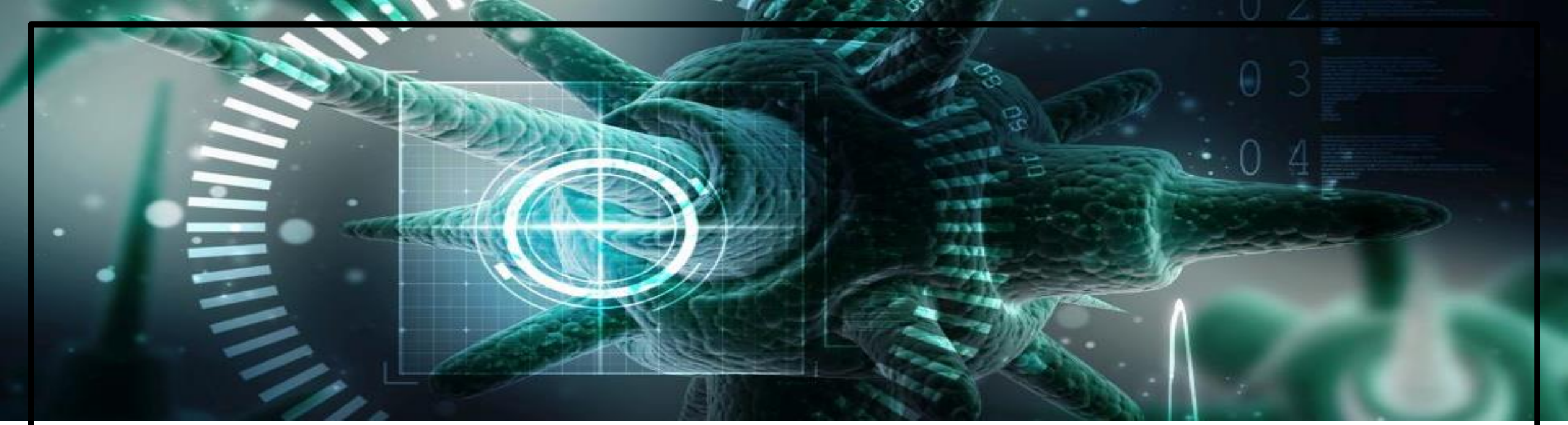

Aging of the immune system

Leen SLAETS

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Healthy Aging
Research Consortium

Immune Aging or Immunosenescence

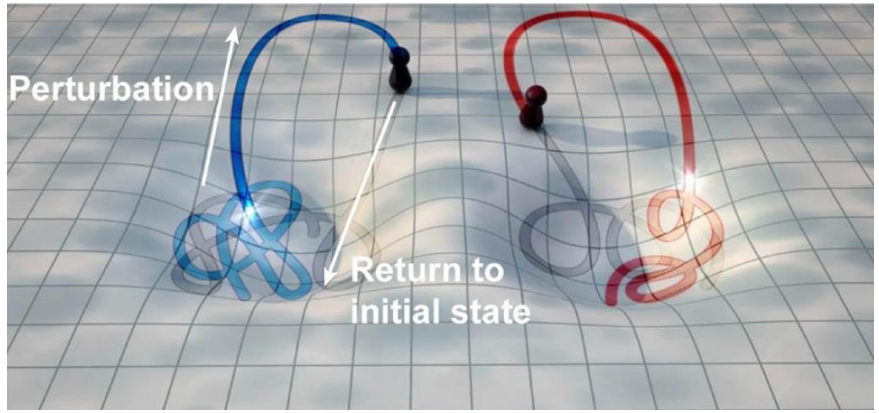
What is immunosenescence?

= age-dependent decrease in immunological competence

- Reduction in protective immune responses
- Inflammaging

What shapes a person's immune system?

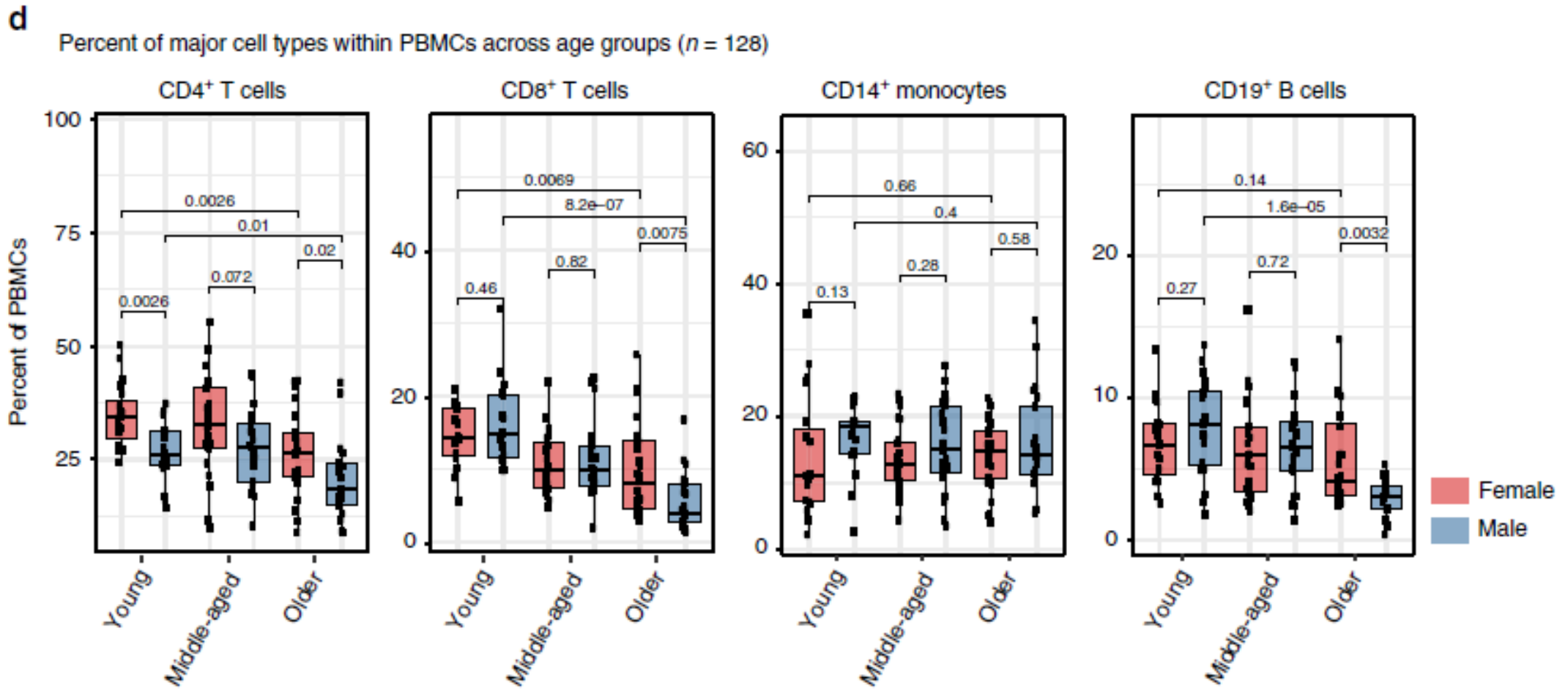
- The immune system is stable throughout life,
- An elastic response to immunological challenge



- Genetic variation contributes for 20-40%
- Remaining 60-80%:
  intrinsic (aging, male/female) & extrinsic factors (chronic infections, cohabitation …)

Liston A, Carr E, Linterman M. Trends in Immunology, 2016

The effect of Aging on the Immune System



- T cell percentages decline with age in both sexes
- Monocyte percentages are not significantly altered with age
- B cell proportion declines only in aging men

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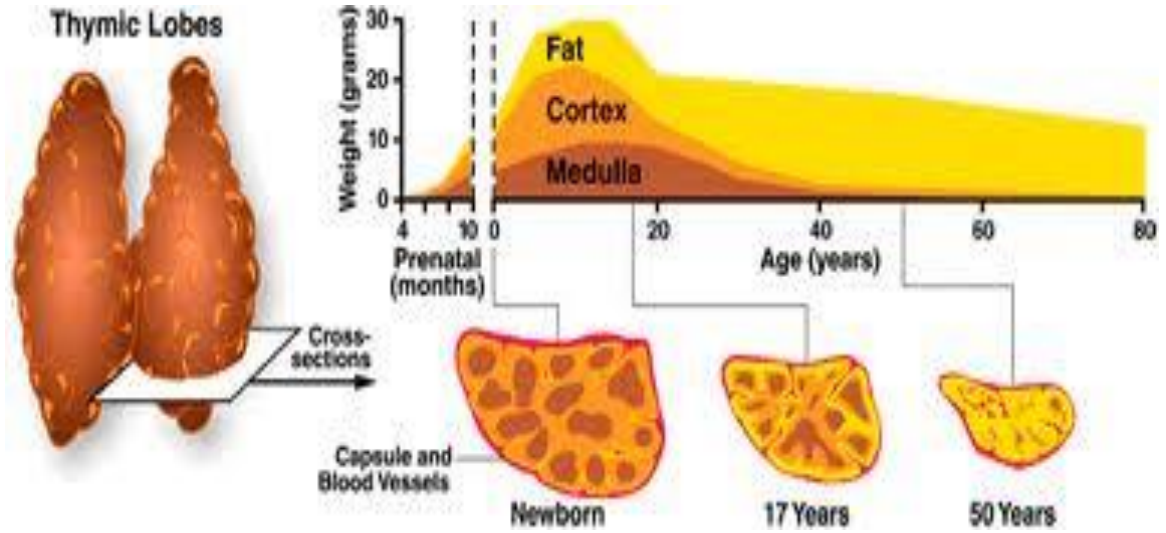
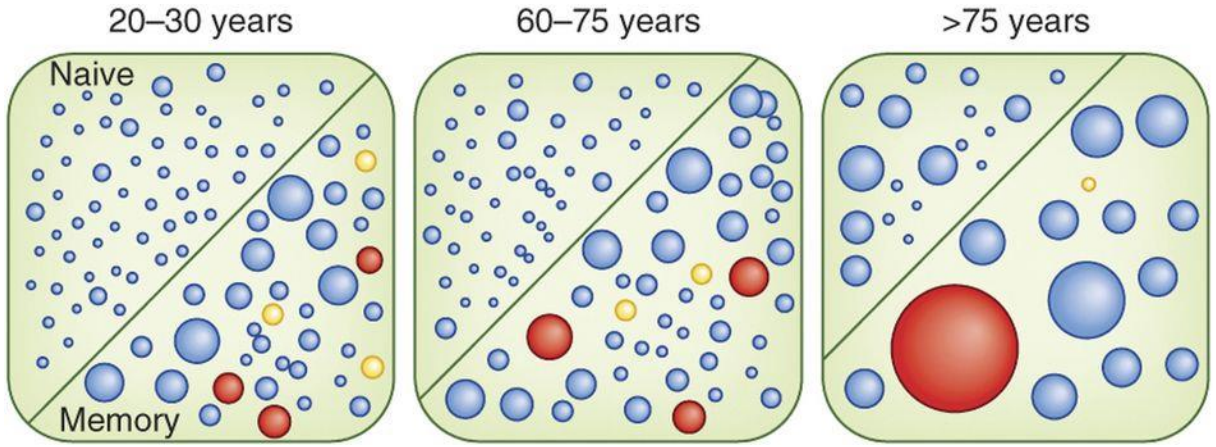
Márquez, E. J., et al.. Nat Commun. 2020

The effects of Aging on T lymphocytes

Thymic involution

- Cortex and medulla are replaced by adipose tissue
- Decline of naive T cells released from thymus
- Homeostatic proliferation of existing T cells





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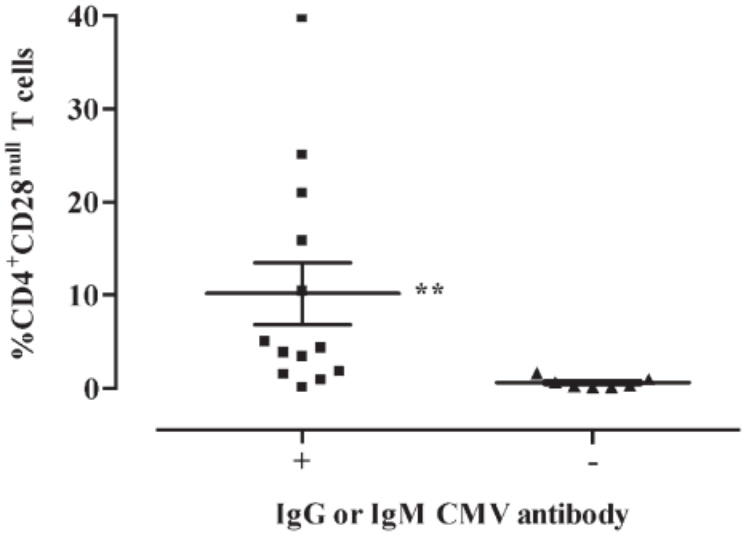
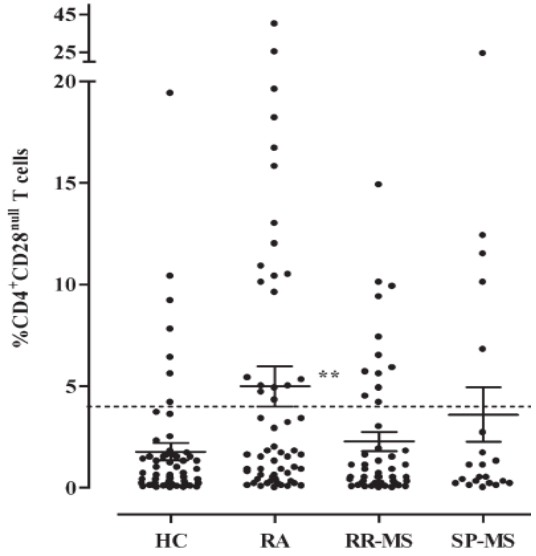
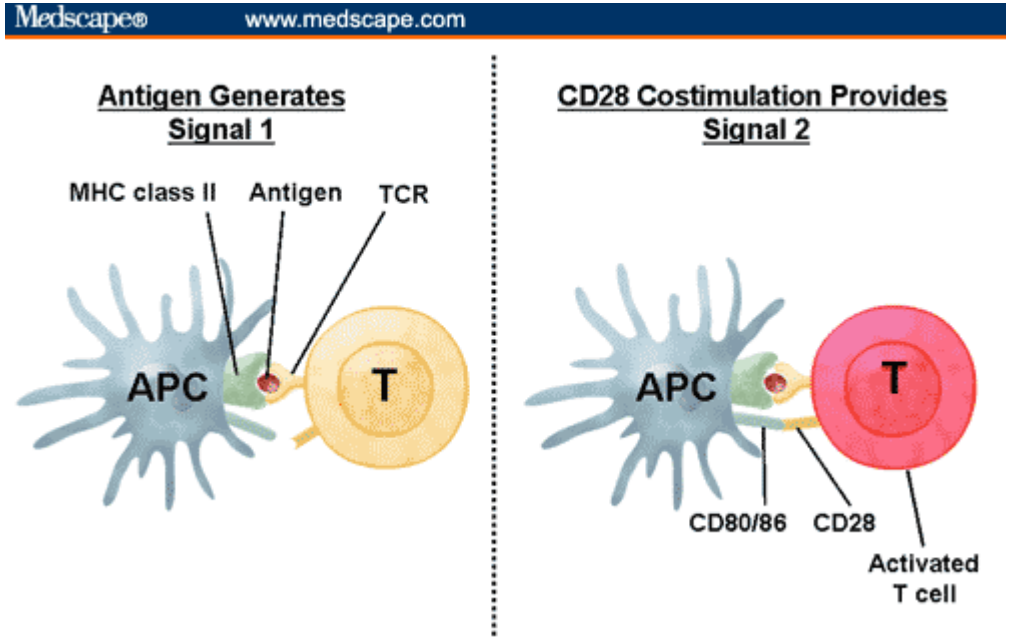
Nature Immunology, 2013

The effects of Aging on T lymphocytes

- Loss of co-stimulatory molecules CD28 and CD27
- Caused by proliferative stress after chronic antigen stimulation (e.g. CMV, autoimmune disease)
- **Immunosenescent T cells**







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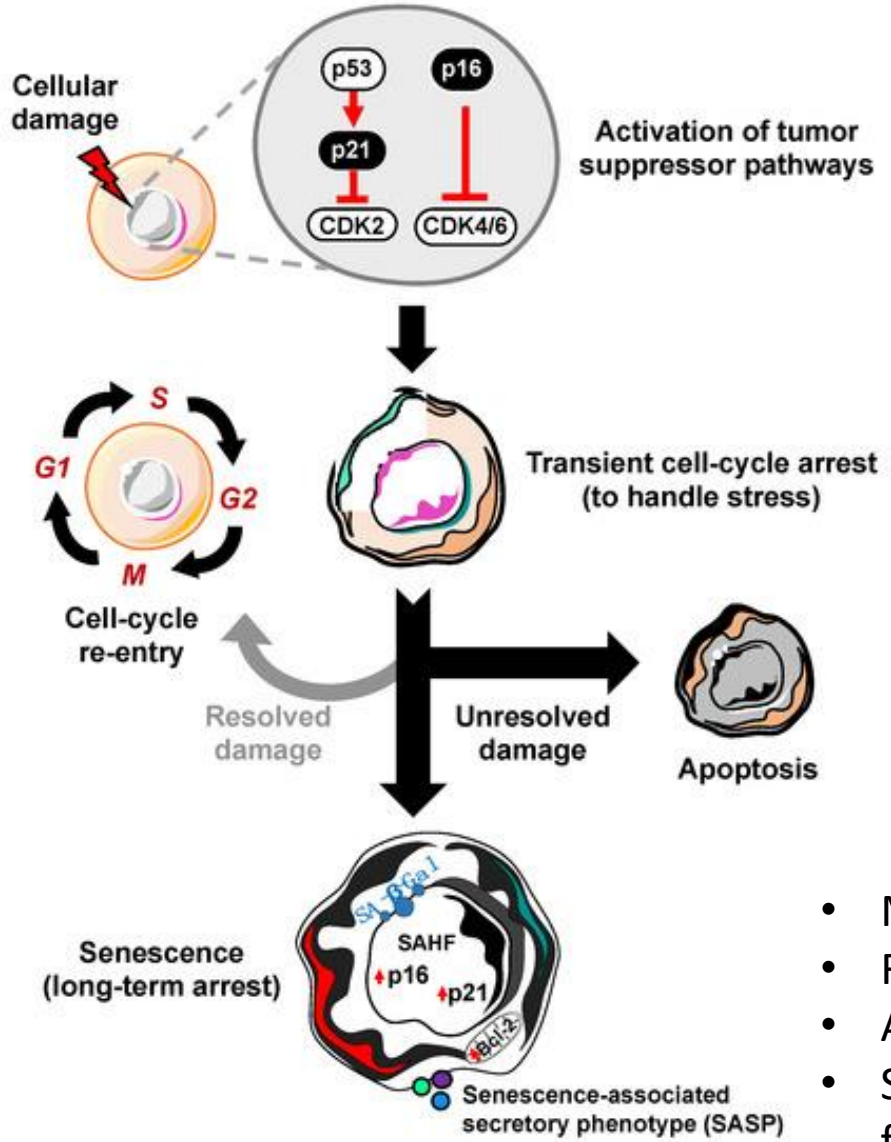
Thewissen et al, Clin Immunol 2007 ; Vanheusden et al, Trends in Mol Med 2015

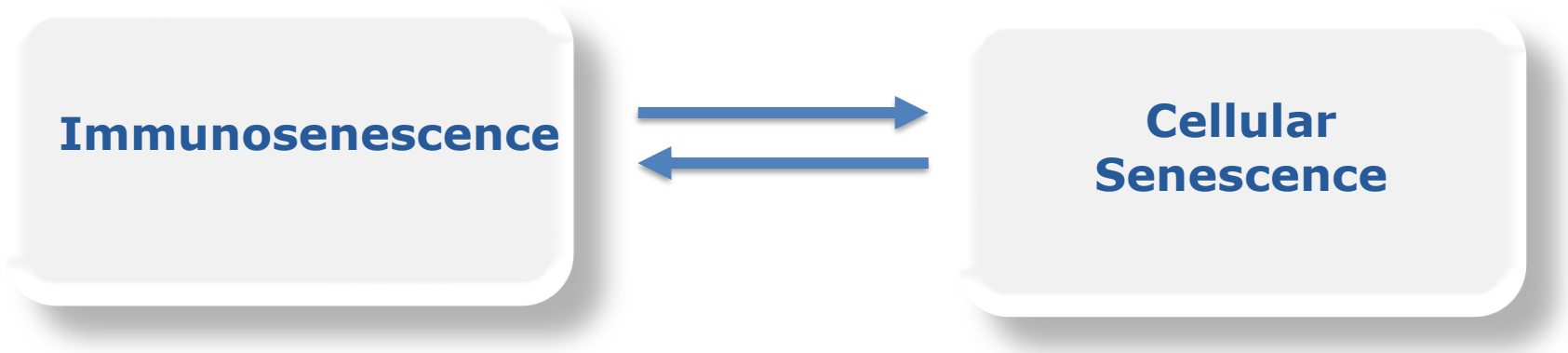
Cellular senescence



- Metabolic changes
- Resistant to apoptosis
- Altered gene expression
- Secretion of proinflammatory factors

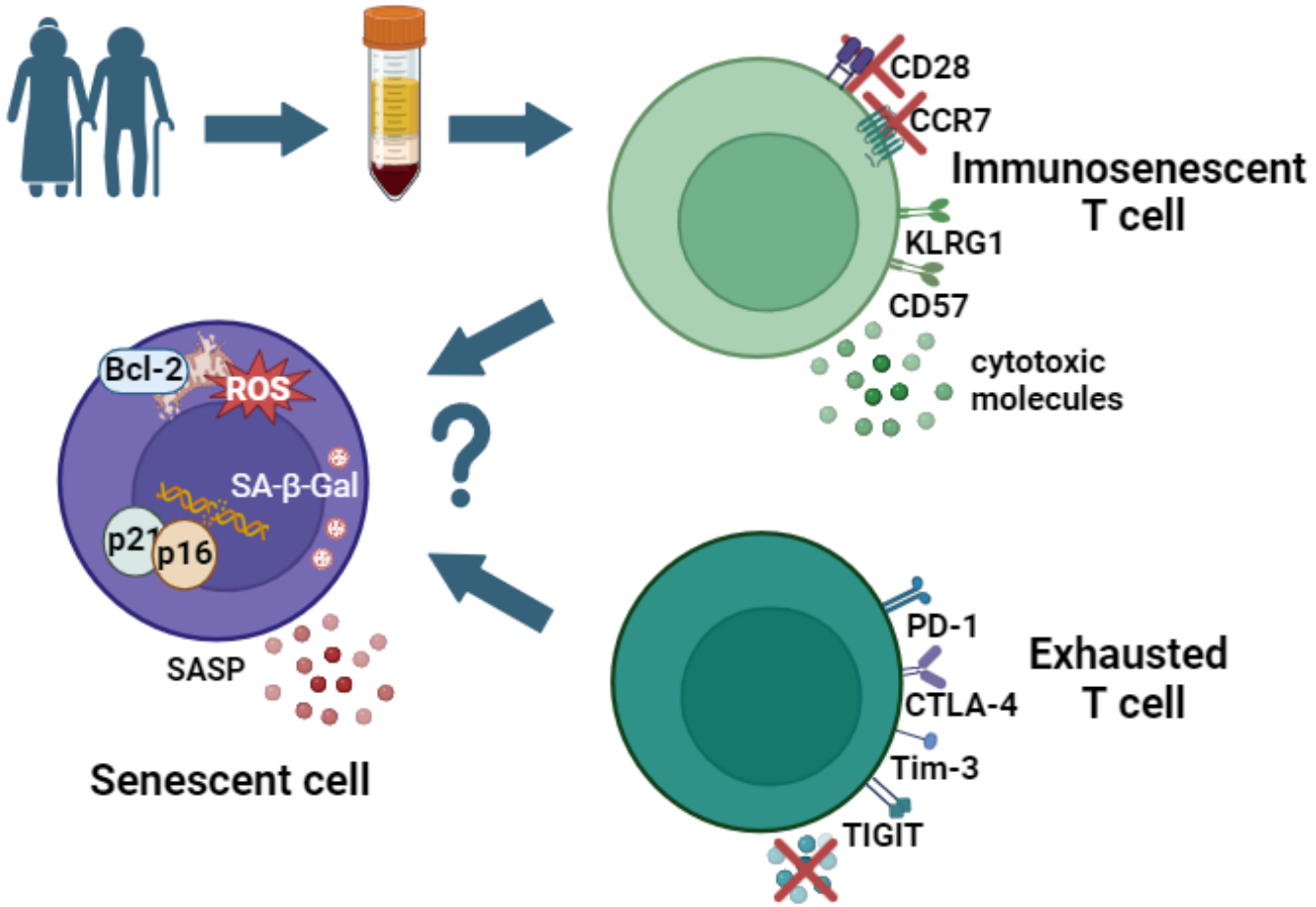
Prieto L et al; Cells 2020, 9(4), 954

Two different things…



The causal relationship and overlap between them is still poorly understood

Are Immunosenescent T cells really senescent?



Slaets et al; Aging Cell, 2024

Strategy for the assessment of cellular senescence in lymphocytes

- Spectral flow cytometry panel
- N=100 individuals
- Senescence-associated β-Galactosidase

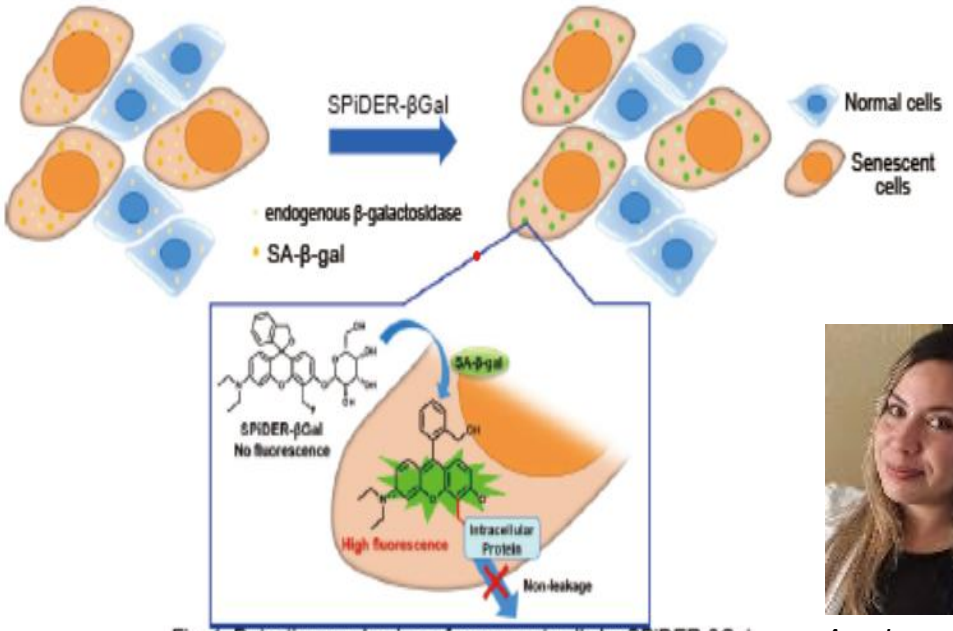


Fig. 1 Detection mechanism of senescent cells by SPiDER-βGal

Ana Laura Kouri

	Marker
Senescence	SPiDER-b-gal
	Ki67
T cells	CD3
	CD8
	CD4
	CD45RA
	CD197 (CCR-7)
	CD28
	CD57
	CD95
	CD152 (CTLA-4)
	CD279 (PD-1)
	KLRG1
B cells	CD27
	CD19 (B)
	IgD
	CD38
NK cells	CD56
	CD16
Monocytes	HLA-DR (CD74)
Live/Dead	Zombie

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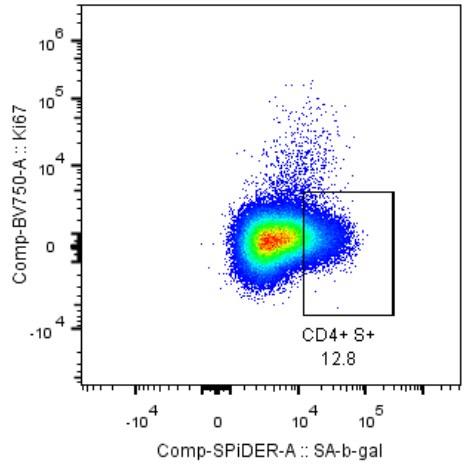
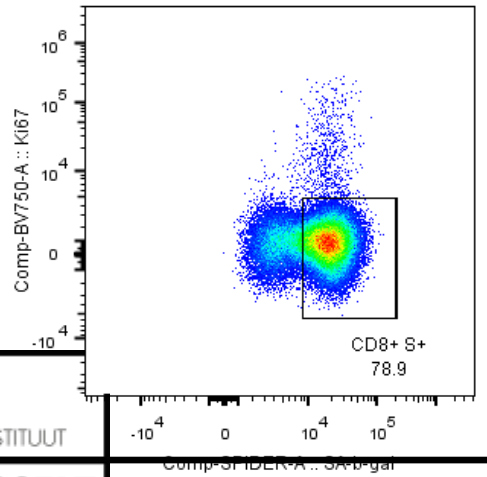
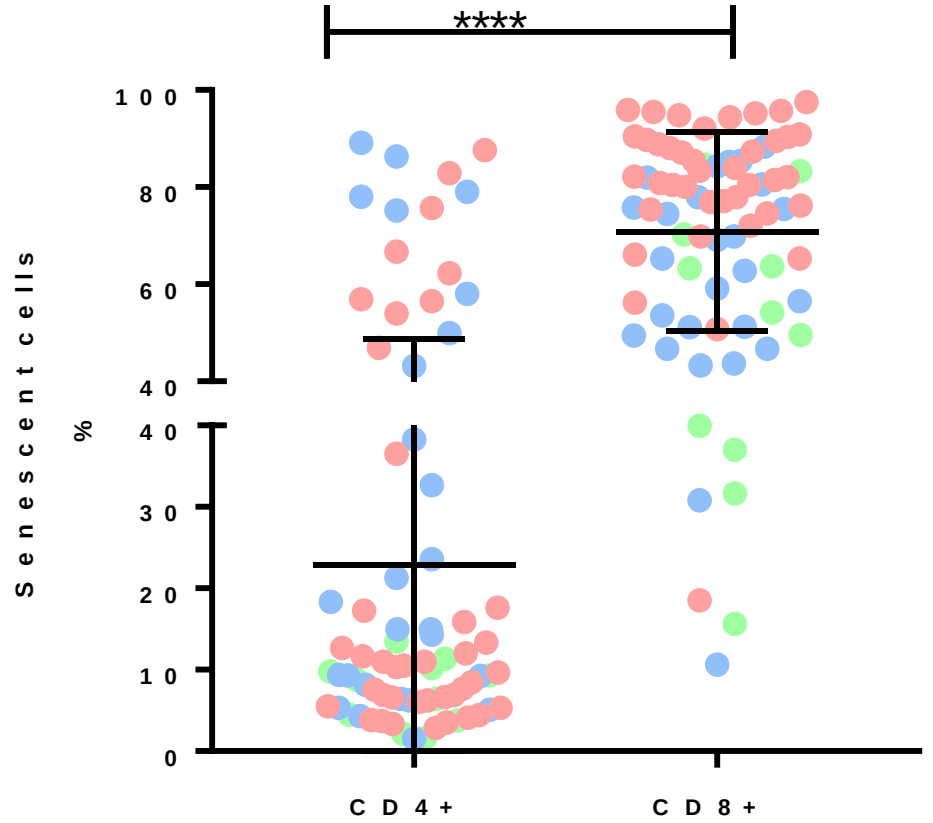
High expression of cellular senescence markers in CD8+ T lymphocytes

CD4+ T cells



CD8+ T cells





CD8+ T cells show a significantly higher frequency of senescent cells

Young
Middle Age
Elderly

*Mann Whitney test

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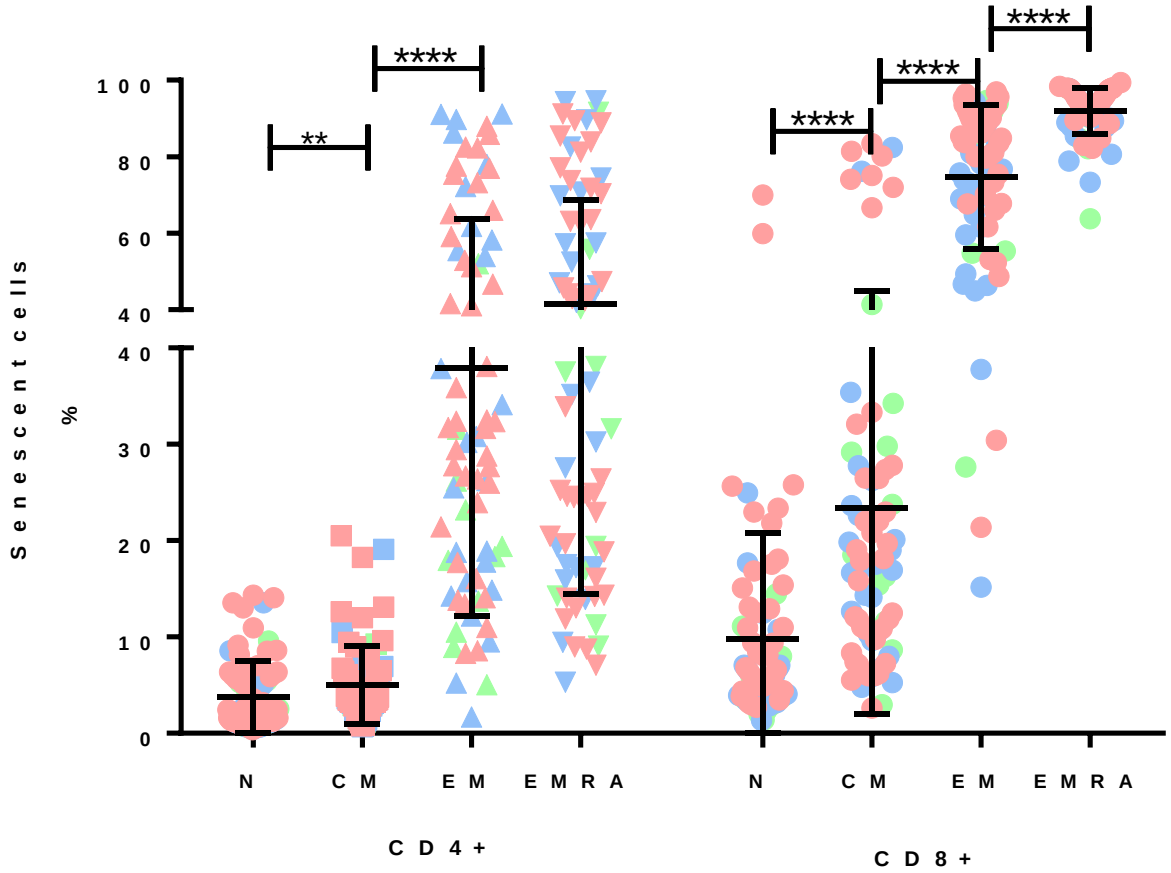
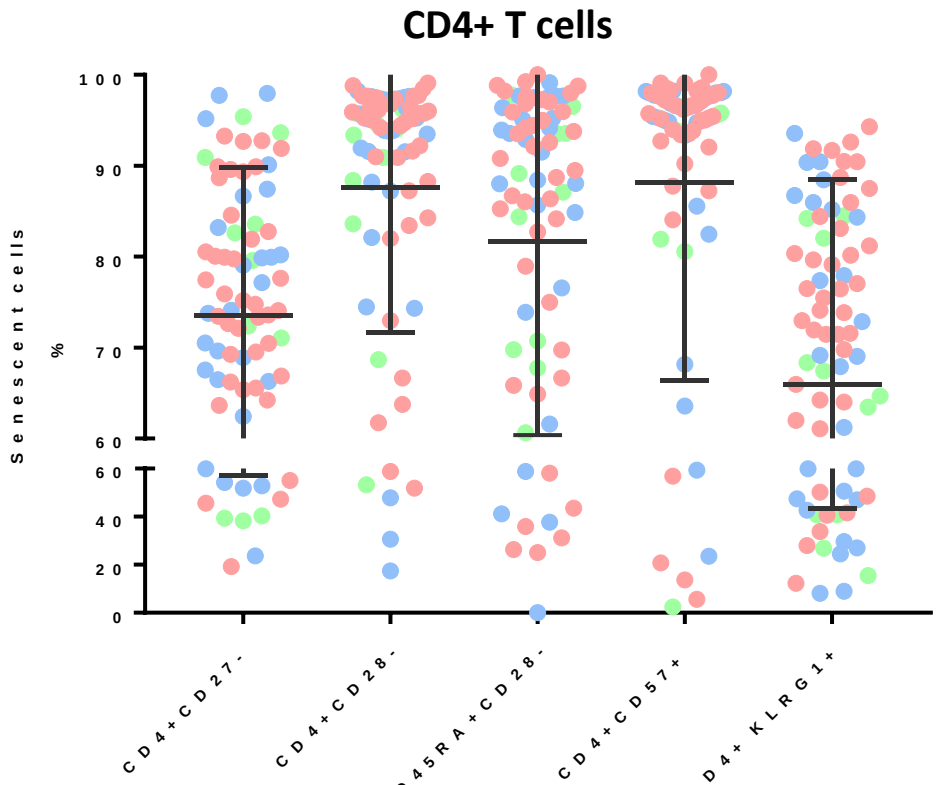
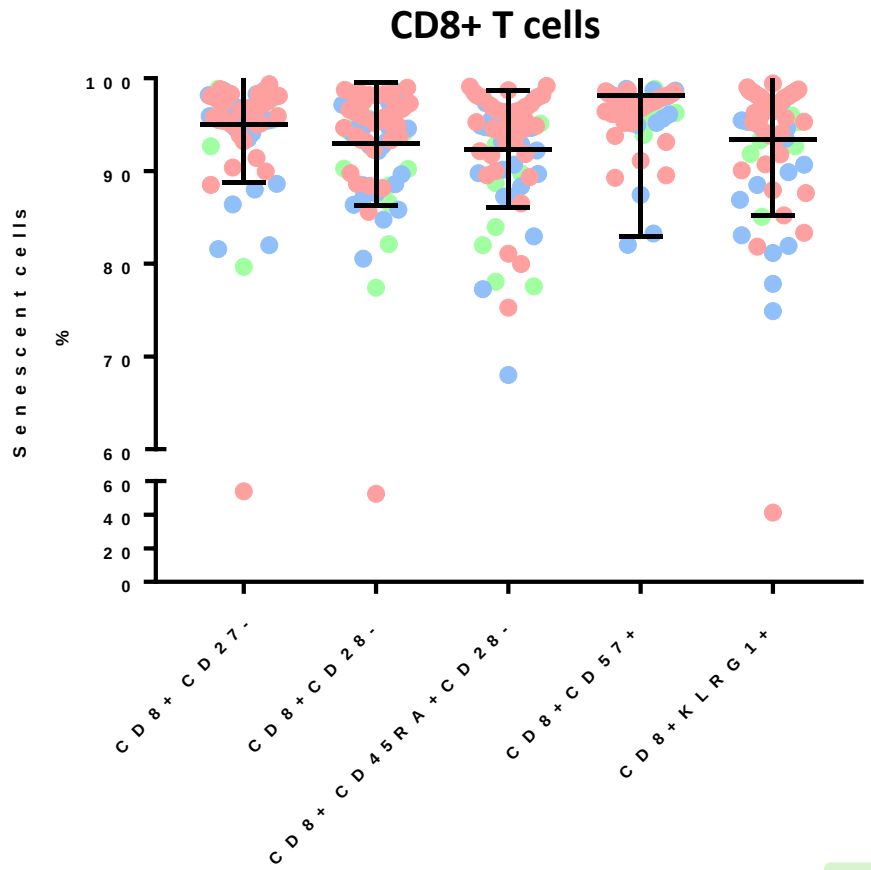
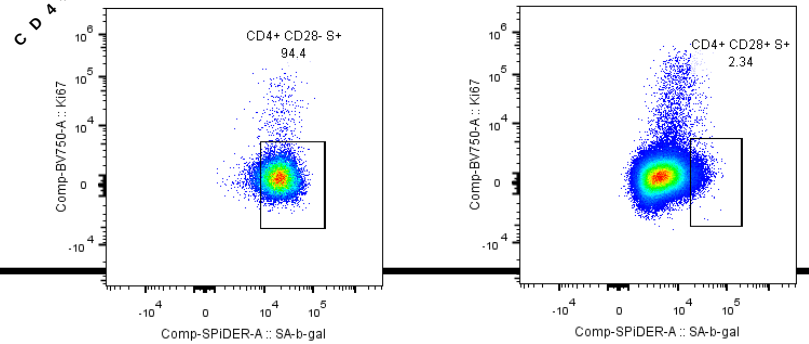
Cellular senescence increases with T lymphocyte stage of differentiation



Immunosenescent T cells: not all of them are senescent







Young
Middle Age
Elderly

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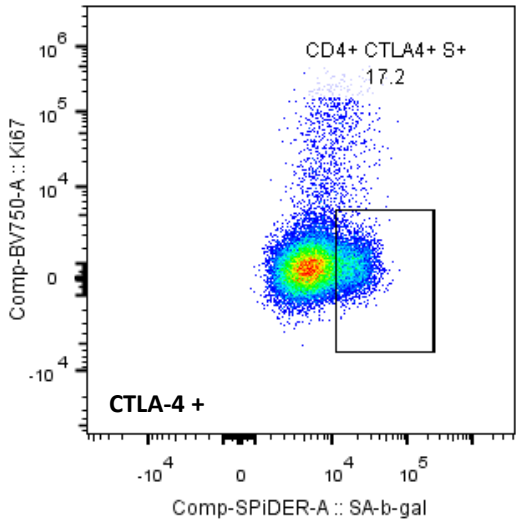
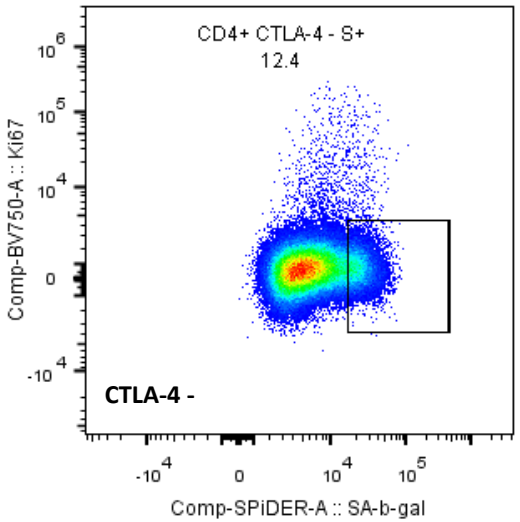
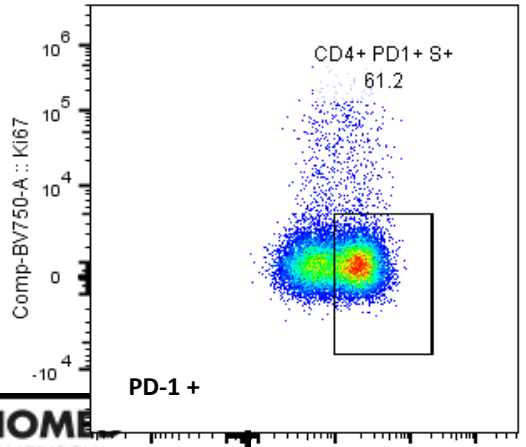
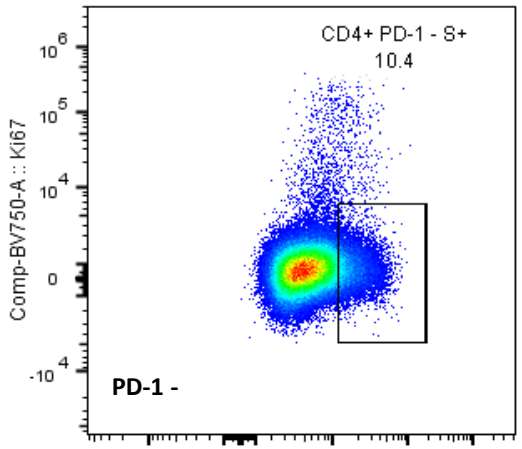
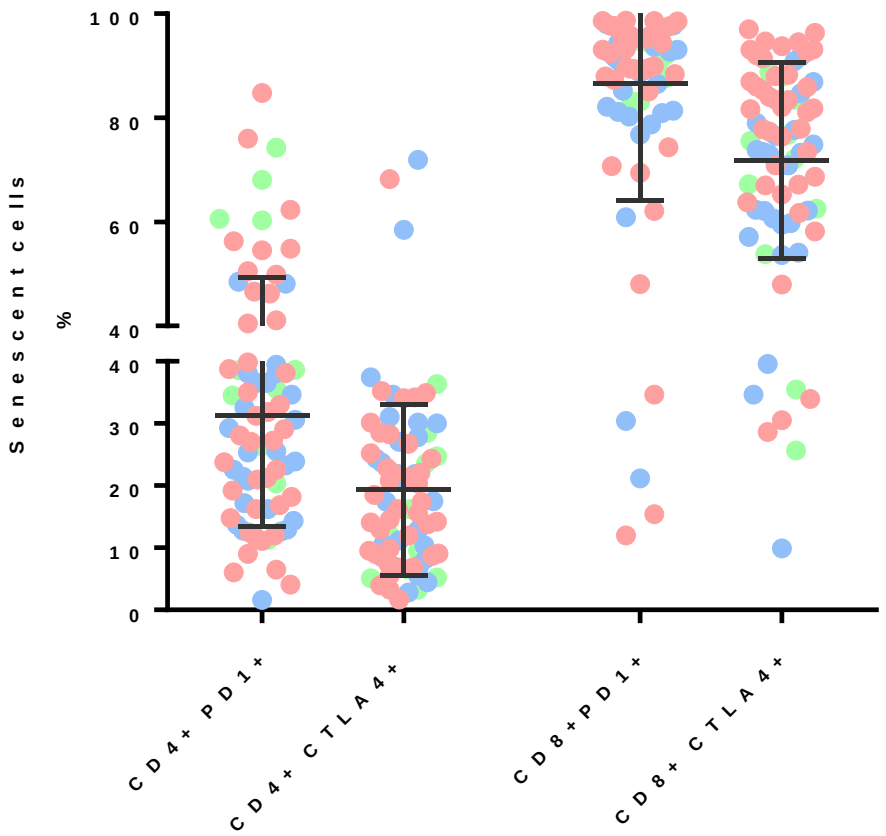
Expression of cellular senescence markers in exhausted T cells











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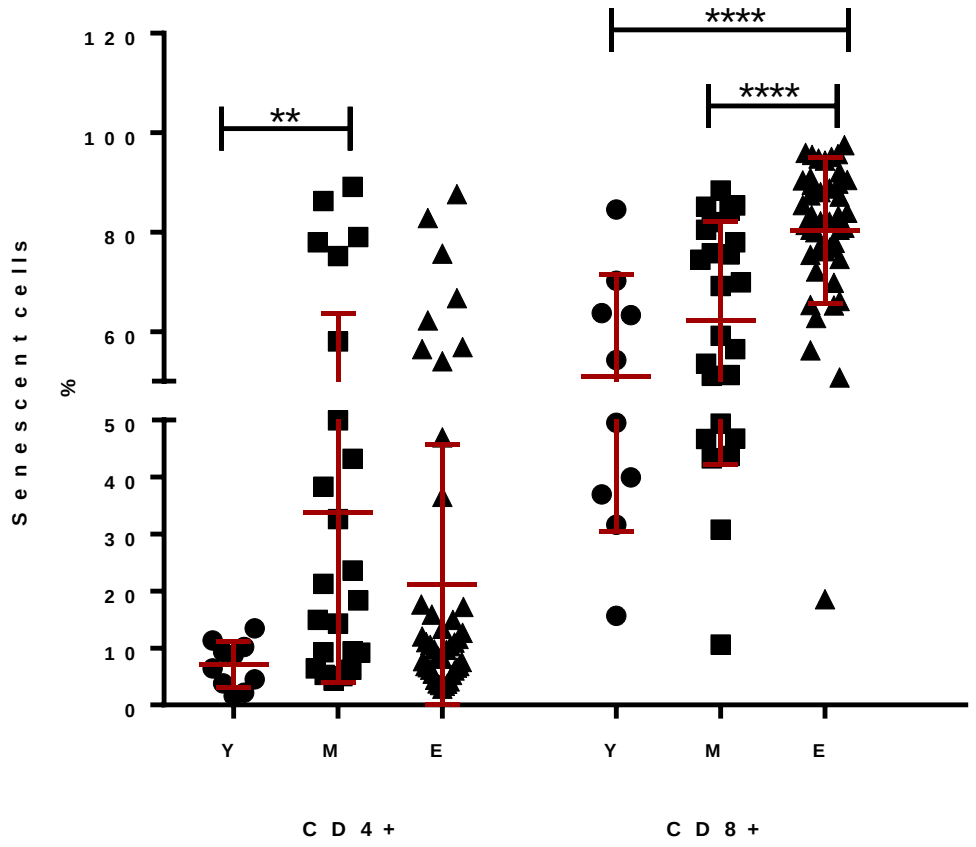
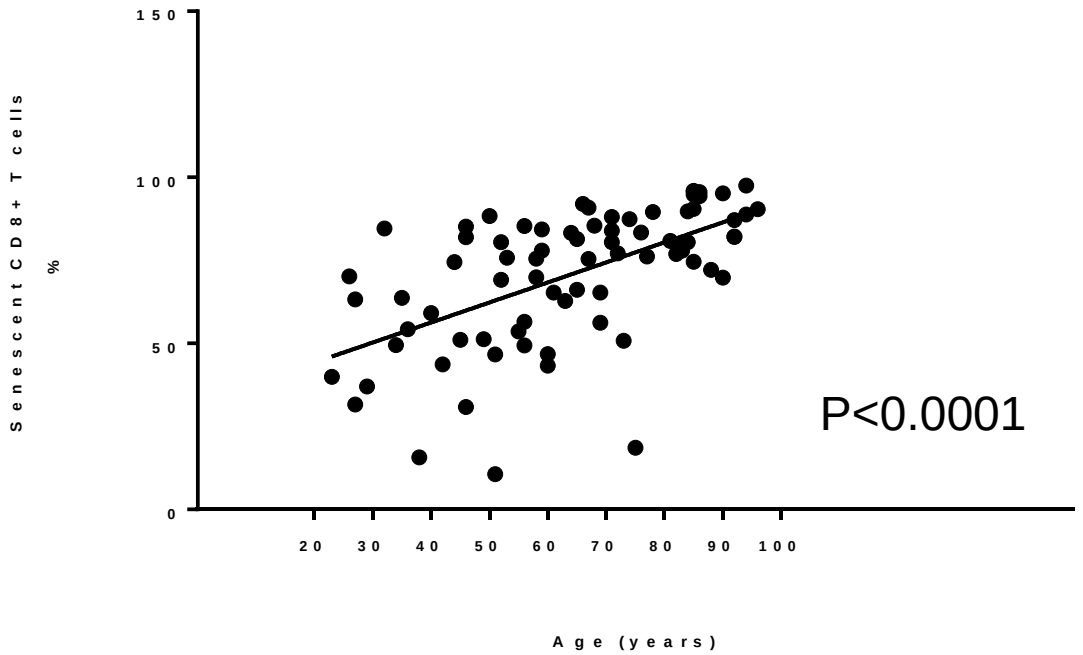
Senescent T cells increase with age





Y: Young < 40
M: Middle Age: 40-64
E: Elderly: ≥ 65

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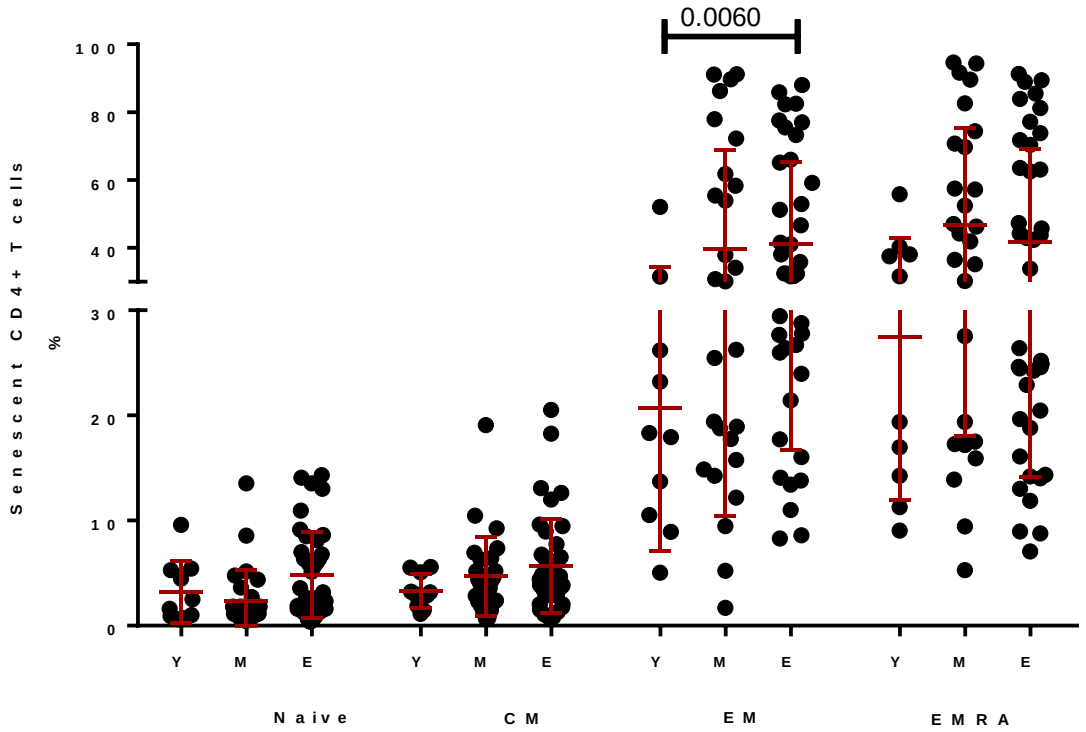
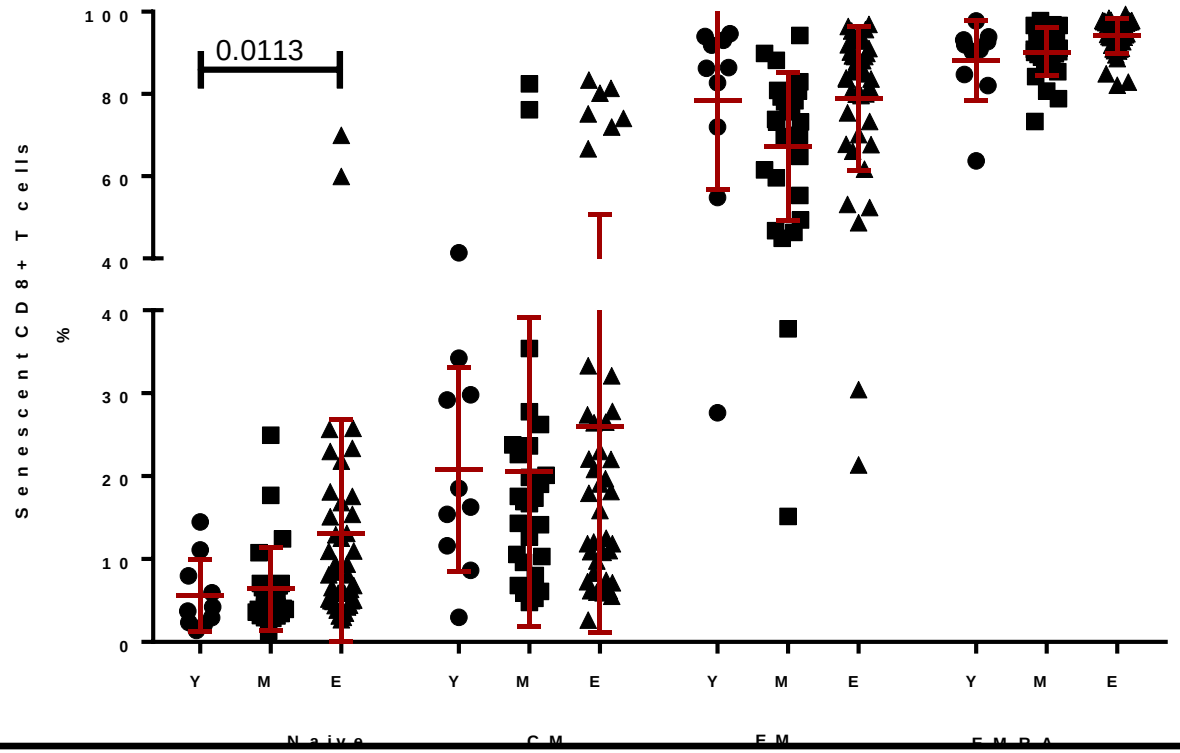
Cellular senescence in T cell differenation stages with increasing age





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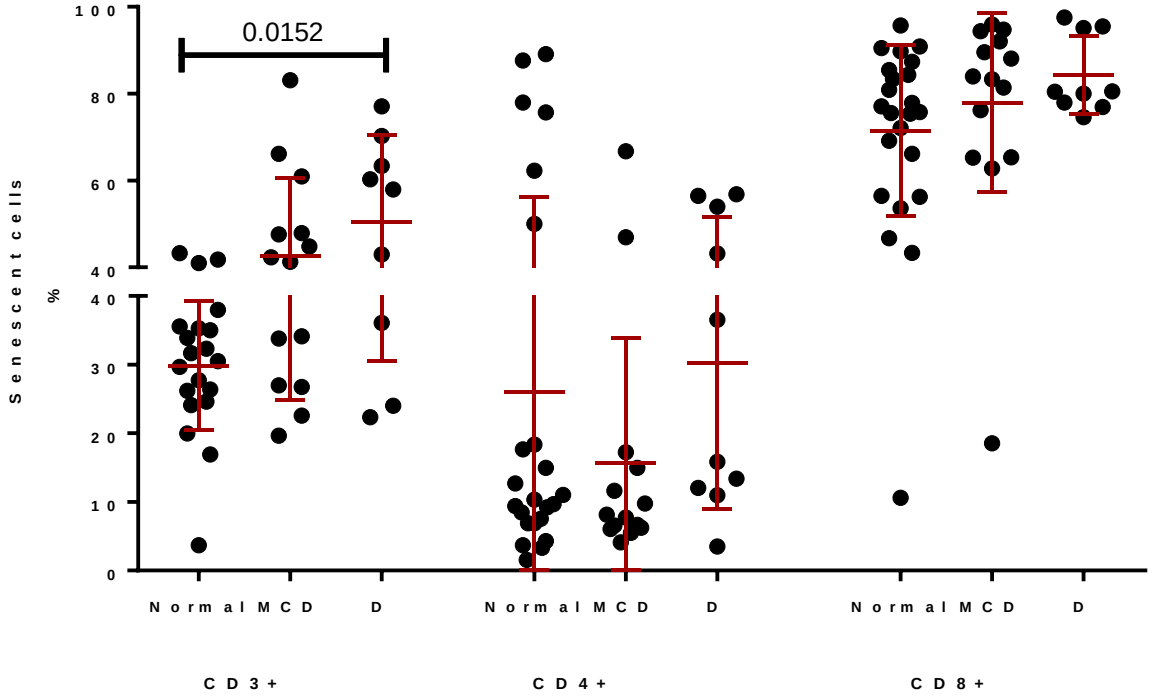
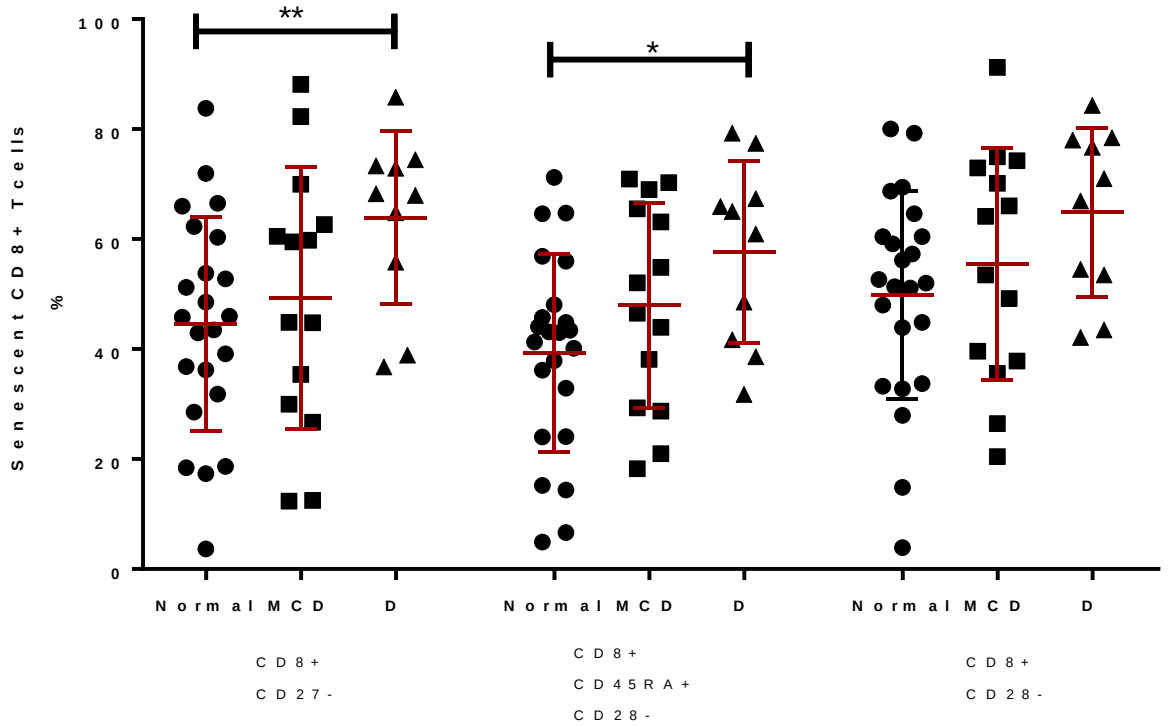
Association between immune aging and cognitive decline in elderly subjects





MCD: Mild Cognitive Decline
D: Dementia

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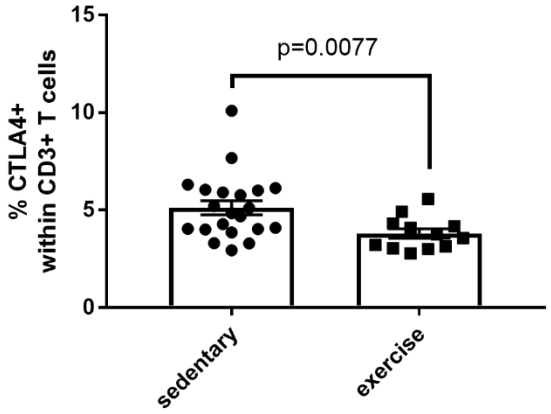
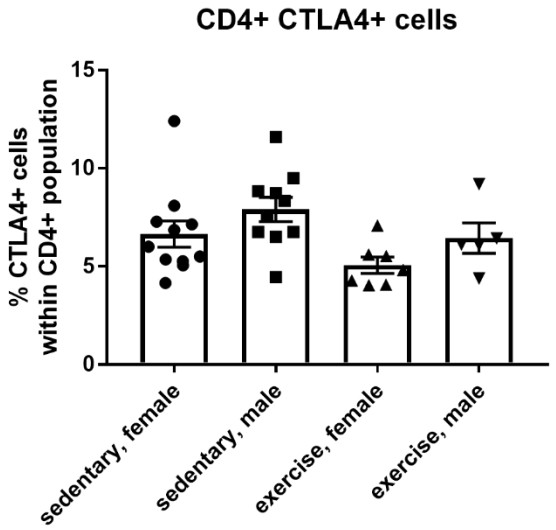
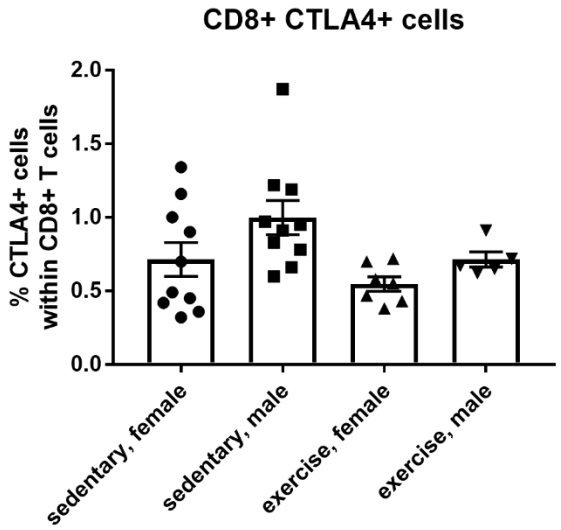
Can immune aging be prevented?

Exercise

- lower numbers of immunosenescent and exhausted T cells
- lower circulatory levels of inflammatory cytokines ("inflammaging")
- increased neutrophil phagocytic activity & NK-cell cytotoxic activity
- Increased antibody production after vaccination







Lena Fonteyn

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Slaets et al; Brain, Behaviour & Immunity, 2023

Take home messages

- Immunosenescence is not the same as cellular senescence
- Cellular senescence increases with the stage of differentiation in T lymphocytes
- CD8+ T cells more prone to senescence than CD4+ T cells
- Immune aging markers are associated with cognitive decline in elderly subjects
- High inter-individual differences → need for individualized approaches & multiple biomarkers

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Healthy Aging Research Consortium

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