

Biology of Immune Aging

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Immune deficiency

- Increase morbidity and mortality from infections
- Poor vaccine responses
- Cancer



Immune Aging

Chronic inflammation

- Coronary artery disease
- Alzheimer's disease
- Osteoporosis
- Frailty

Autoimmunity

- Autoantibody production
- Polymyalgia rheumatica
- Giant cell arteritis
- Rheumatoid arthritis

Aging and the Immune System

Intrinsic immune aging threats

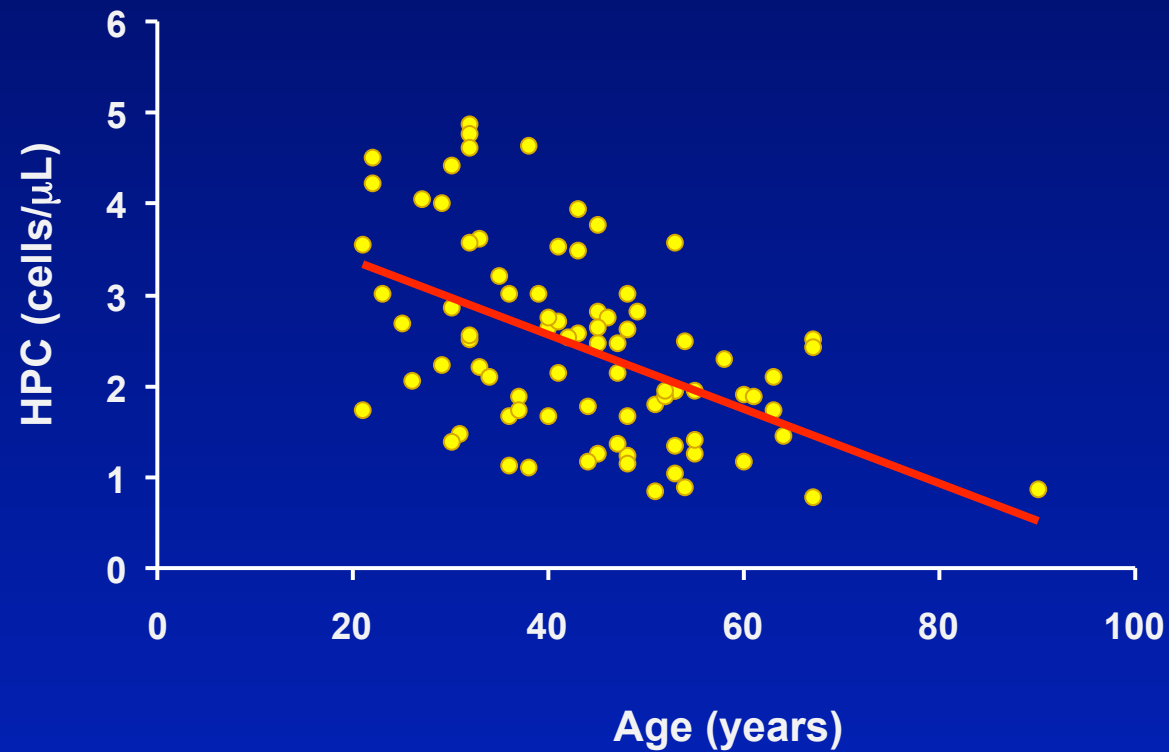
- Declining regenerative capacity, increased cell loss
- Failure of homeostatic mechanisms
 - Imbalance of functional cell subsets
 - Contraction in T and B cell receptor diversity
- Failure in cell proliferation - Cellular senescence
- Failure in cell activation
- Induction or repression of gene expression
 - Differentiation
 - Chronic stimulation and proliferation
 - Epigenetic changes

Aging and the Immune System

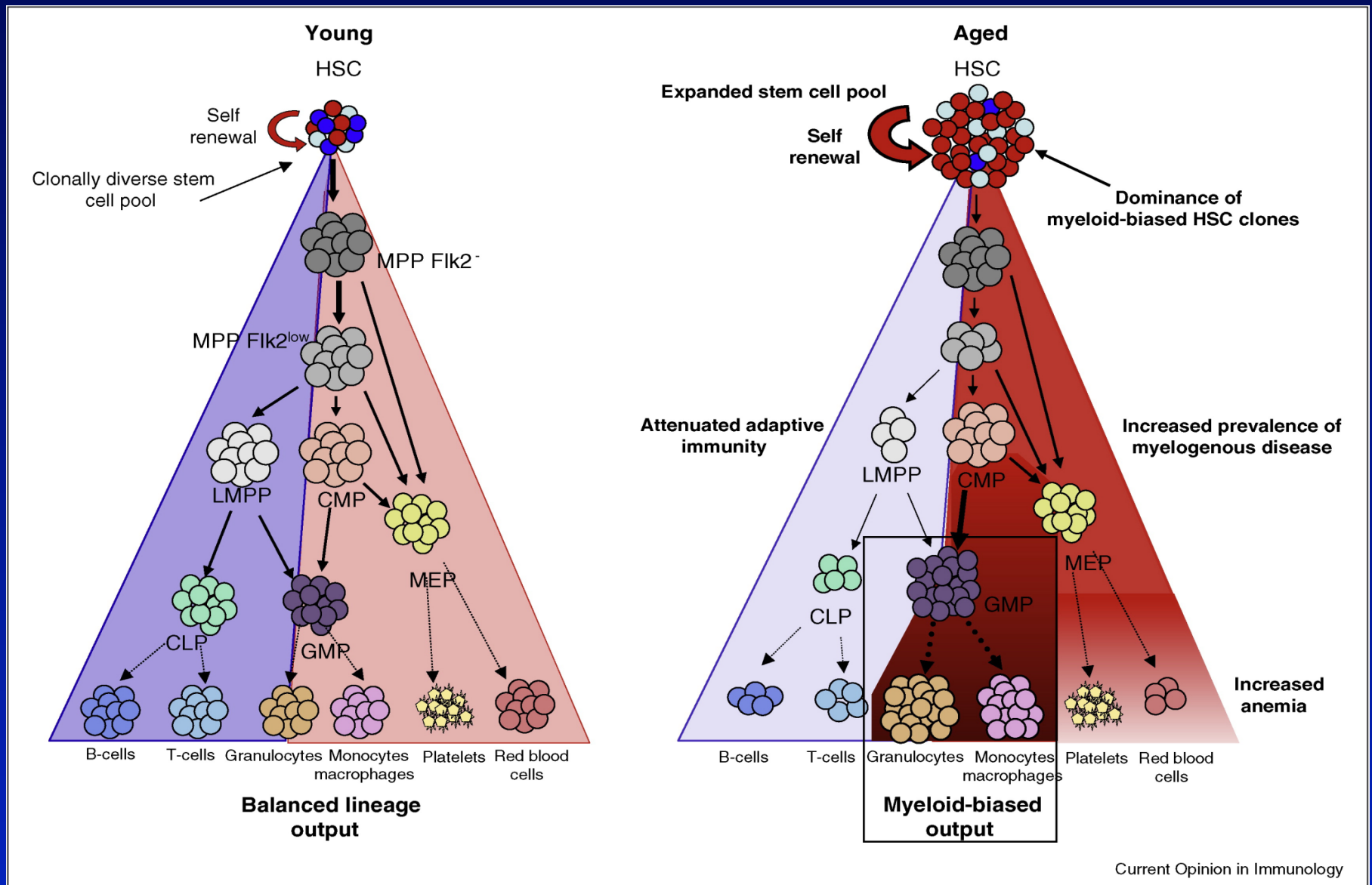
Extrinsic immune aging threats

- Declining barrier function
- Chronic infections (CMV)
- Cumulative antigenic experience over lifetime
- Tissue injury and repair

Decline in peripheral hematopoietic progenitor cells



Imbalanced lineage commitment of HPC



Rossi et al., Dorshkind et al.

Aging and Innate Immunity

Inflamm-aging

Pro-inflammatory

- No reduction in neutrophil or monocyte numbers
- Increased serum IL-6, IL-18, TNF
- Constitutive activation of signaling pathways (STAT)

Anti-inflammatory

- Reduced activation-induced neutrophil chemotaxis, phagocytosis, oxidative burst
- Reduced TLR and cytokine responses in monocytes

Aging and Innate Immunity

? Chronic innate activation due to

- Defective barrier function
- Defective adaptive immunity
- Degenerative tissue damage

? Defective innate responsiveness

- Cell-intrinsic defects (e.g. physical membrane properties)
- Attenuation to inflammatory environment (e.g. induction of negative regulatory SOCS pathways)

The T-cell compartment – A highly dynamic system

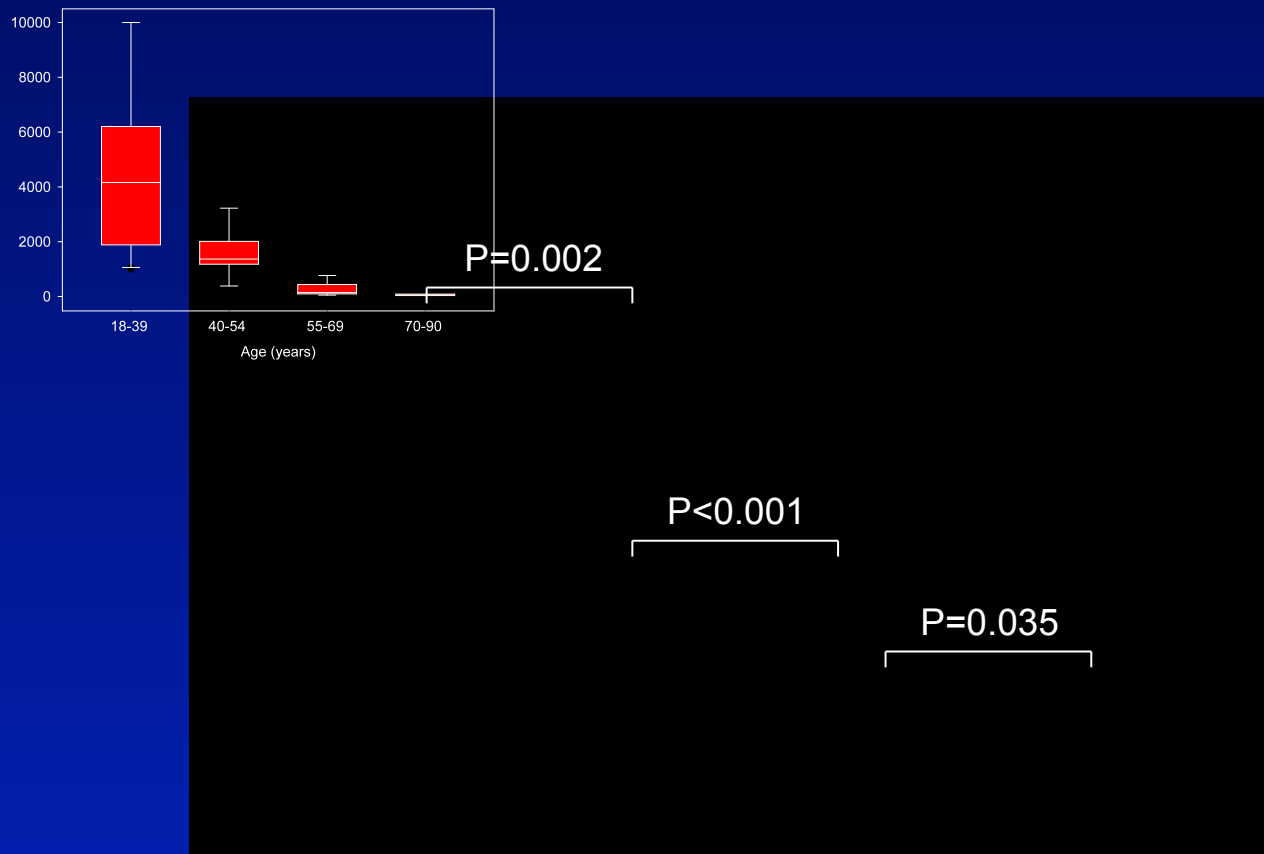
Estimates of T-cell kinetics in humans

Cell type	Pool size (no. of cells)	$T^{1/2}$ (days)	Daily production rates (cells/day)
CD4	2×10^{11}	87	$\sim 1.3 \times 10^9$
CD8	1×10^{11}	77	$\sim 0.8 \times 10^9$
			$\sim 2.1 \times 10^9$
			= $\sim 1\%$ of the pool

Hellerstein, M. et al. Nat Med. 1999 Jan;5(1):83-9.

Aging and T Cell Homeostasis

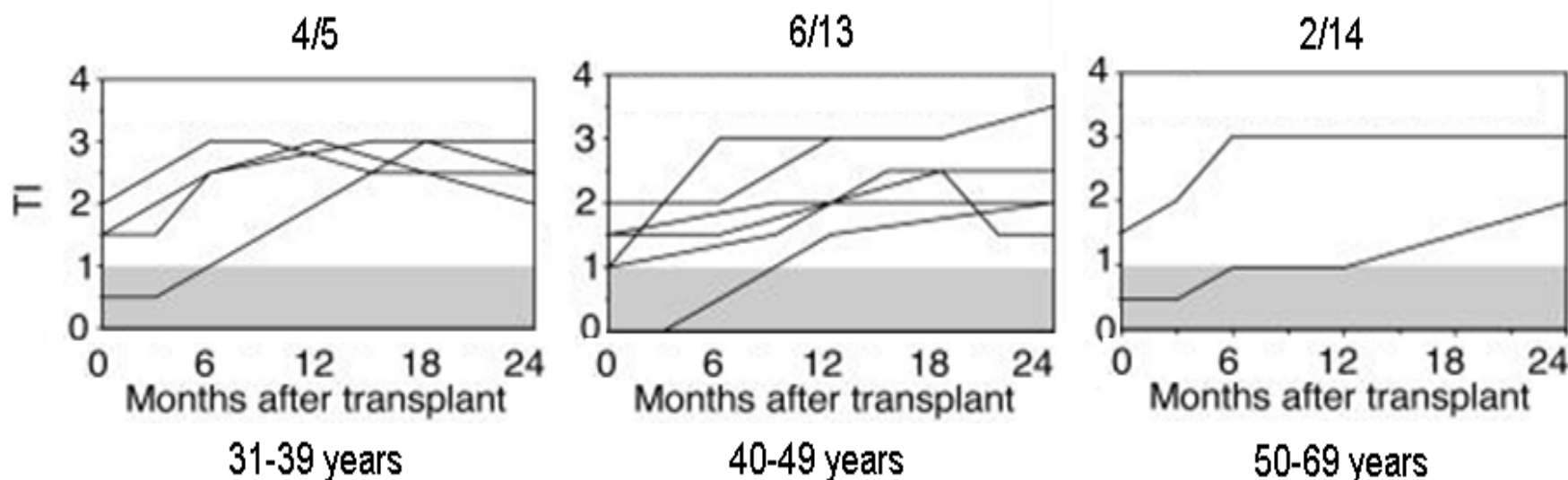
Age-dependent decline in thymic output



Naylor, K et al. J Immunol. 2005 Jun 1; 174(11):7446-52

Aging and T Cell Homeostasis

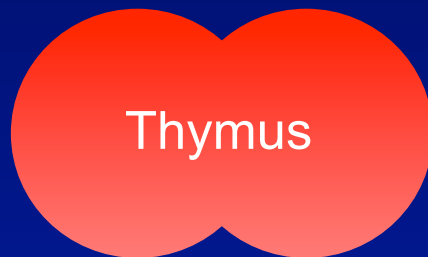
Age-dependent decline in thymic output



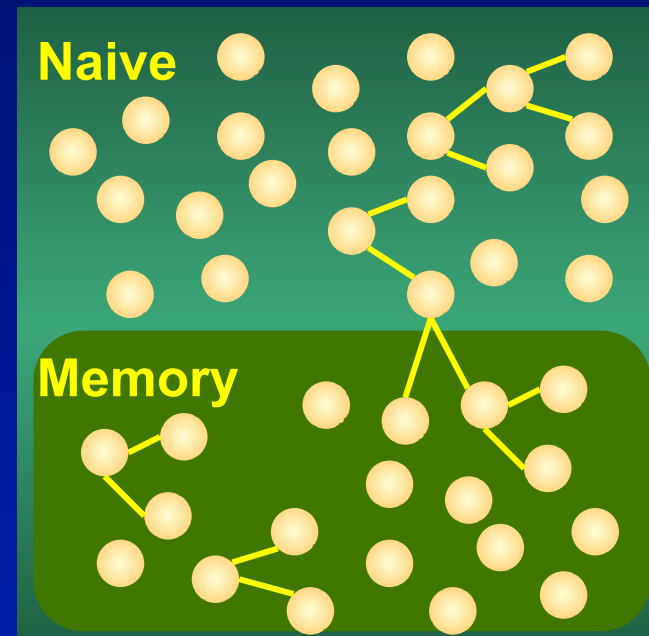
Hakim, FT et al. J Clin Invest. 2005 April 1; 115(4): 930–939

Aging and T Cell Homeostasis

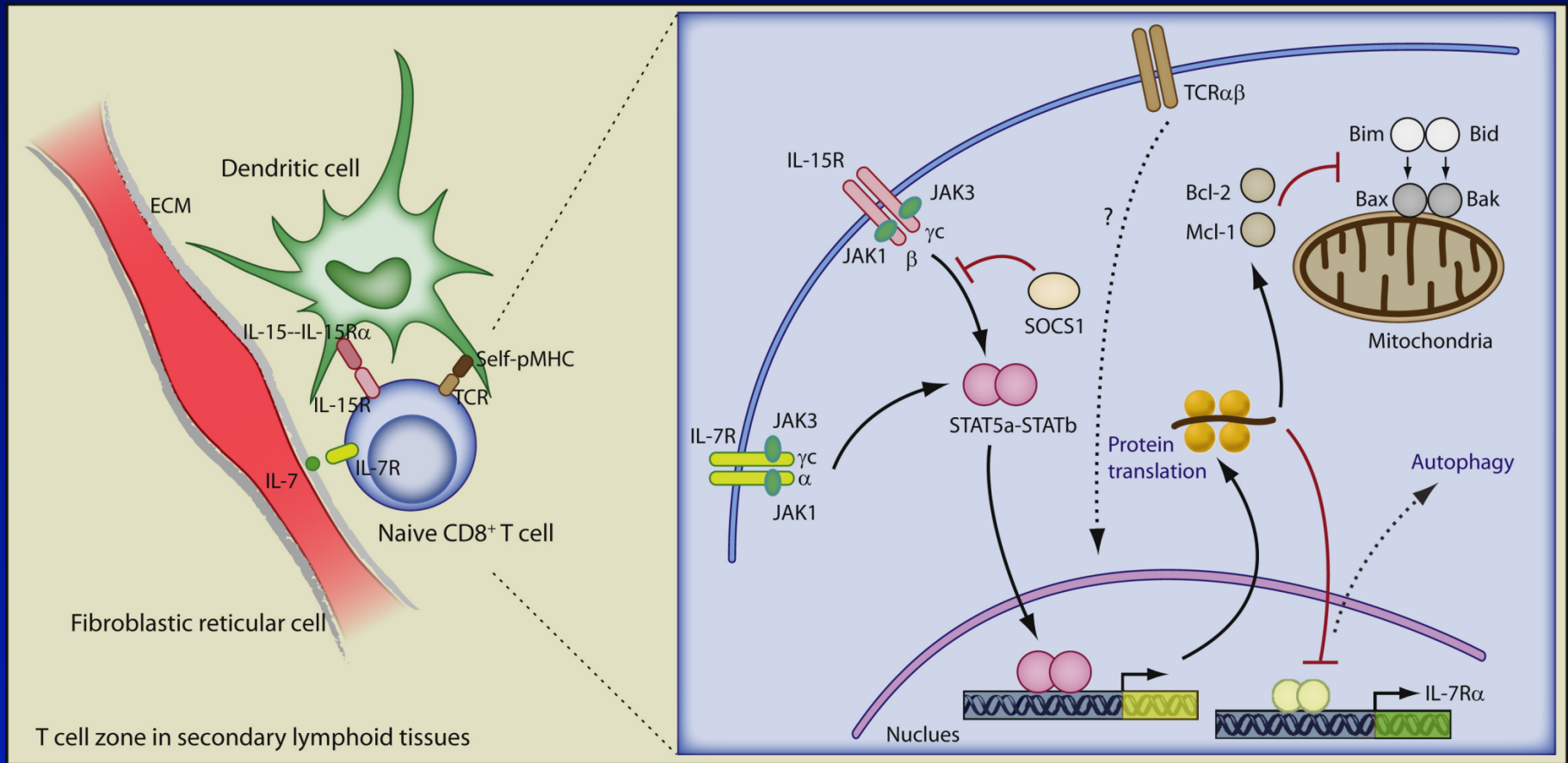
Decline in thymic
T cell generation



Increased homeostatic
T cell proliferation



Homeostatic T Cell Proliferation



Surh, Sprent. Immunity 2008, 29, 848

Mouse Models of Homeostatic Proliferation

Lymphopenia-induced proliferation

- Response to acute lymphopenia
- Response to self-MHC
- Slow turnover
- Transition into memory-like cells

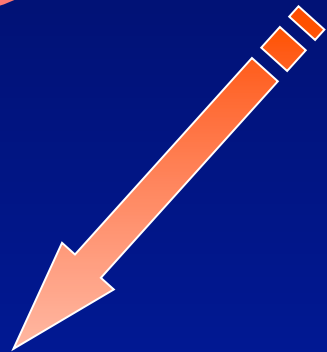
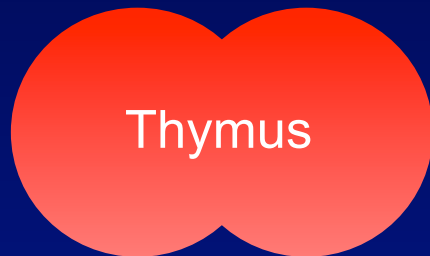
Chronic lymphopenia-induced proliferation

- Response to chronic lymphopenia
- Response to microbial antigen
- Fast turnover
- Differentiation into effector cells

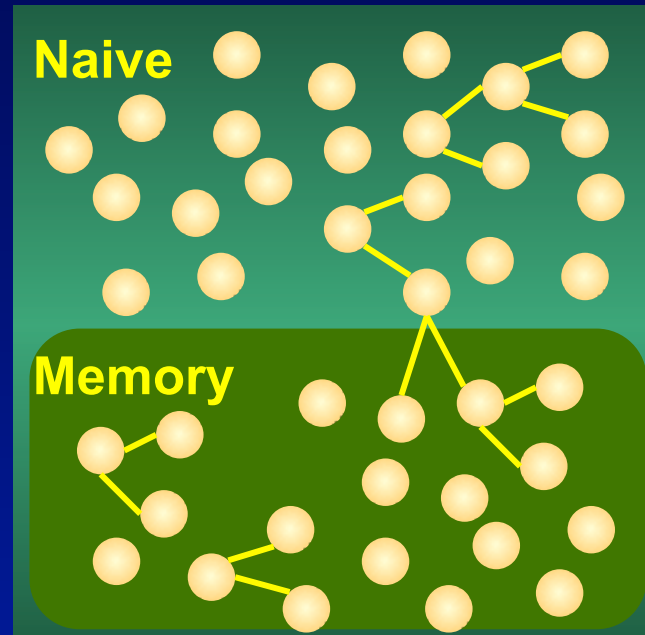
Cytokine-induced proliferation

- Response to elevated cytokines
- Response to self-MHC
- Fast turnover
- Transition into memory or effector T cells

Decline in thymic
T cell generation



Increased homeostatic
T cell proliferation



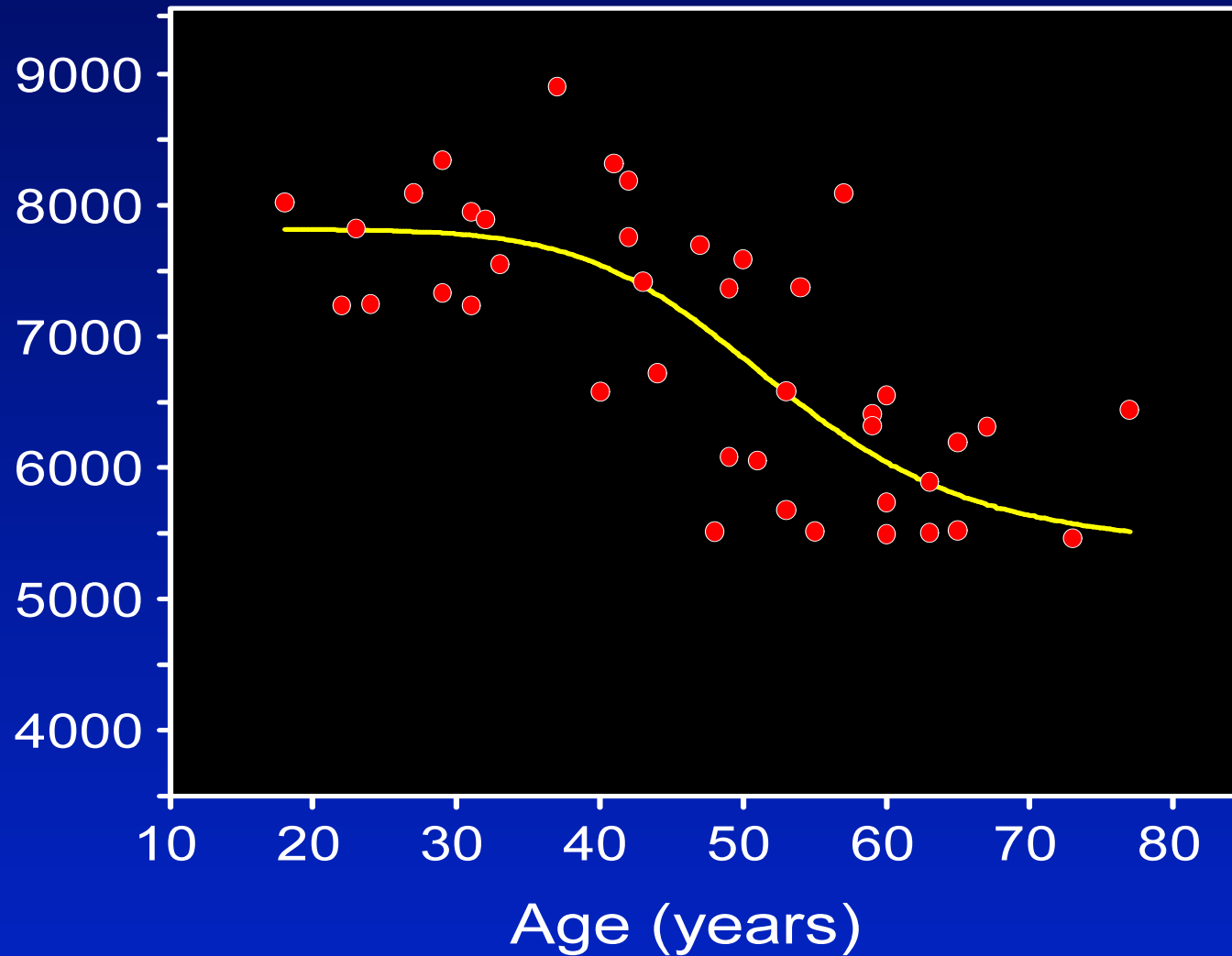
Peripheral selection of T cells

- Recognizing self with above average affinity
- Recognizing neoantigens (e.g. citrullination)
- Lowered T cell receptor activation thresholds
- Hyperresponsive to growth factors



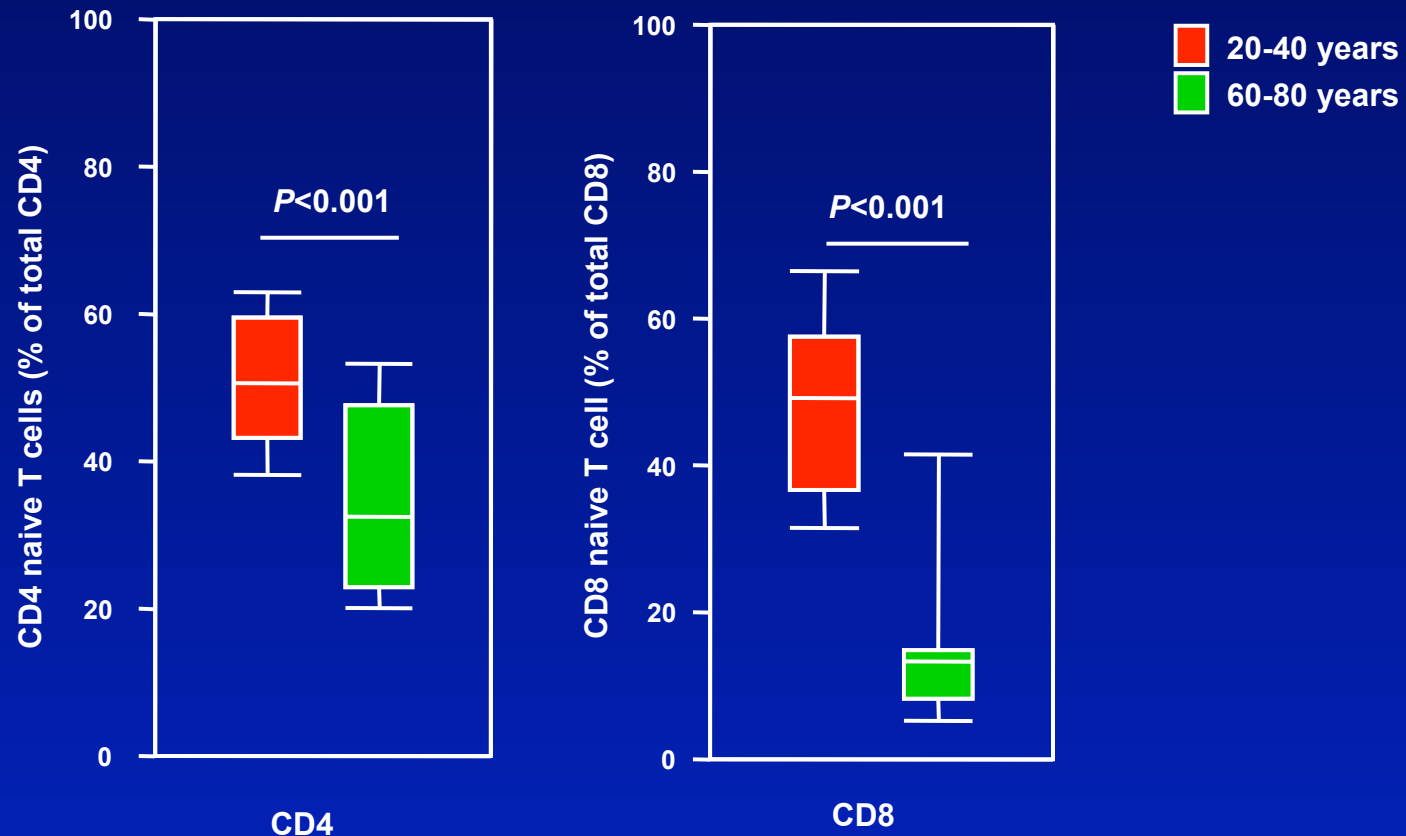
- Differentiation into memory-like or effector T cells
- Oligoclonal expansion
- Increased autoreactive potential

Aging and T Cell Telomeres



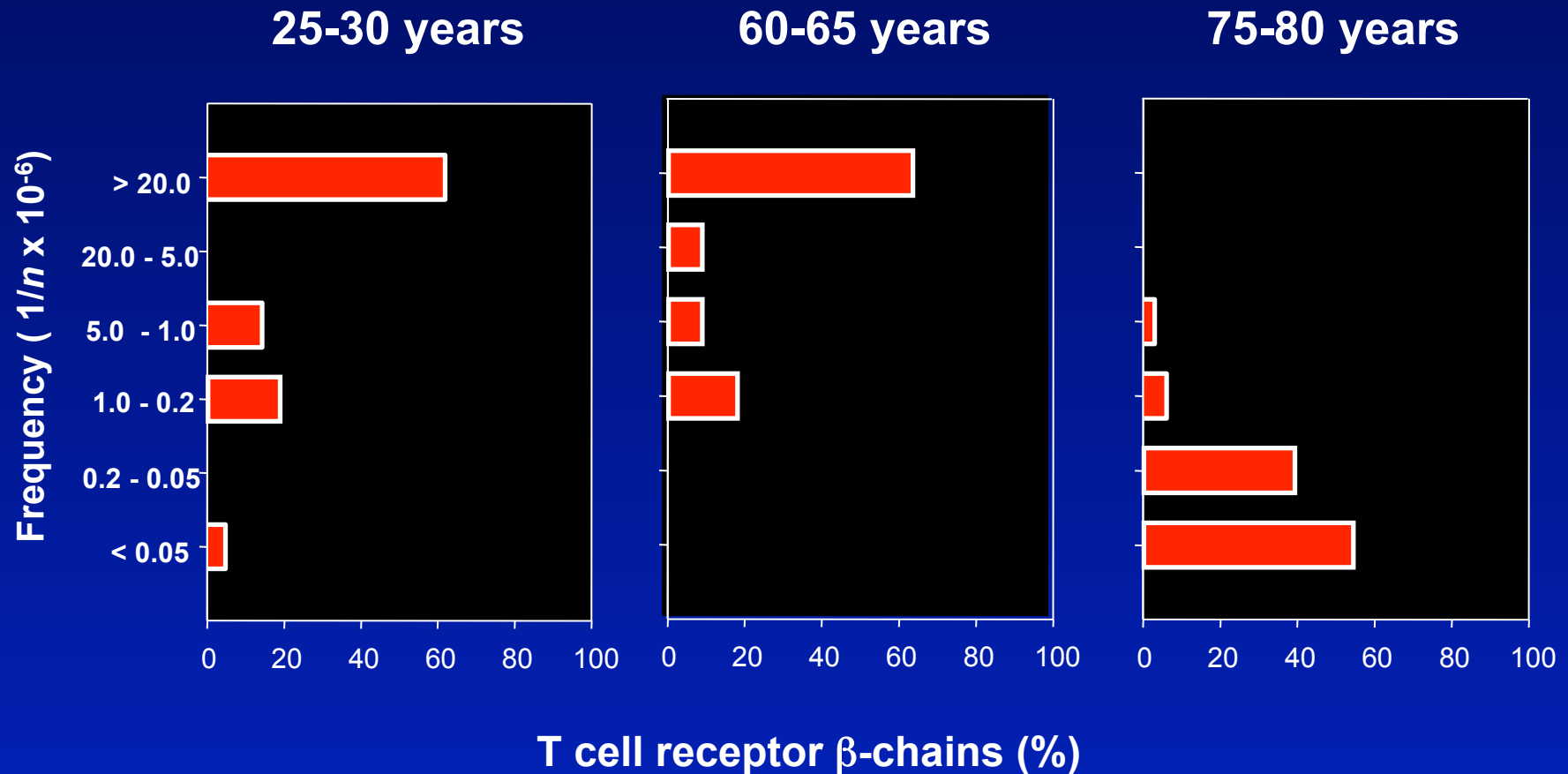
Aging and T Cell Homeostasis

Robustness of the CD4 T cell compartment to homeostatic failure



Aging and CD4 T cell diversity

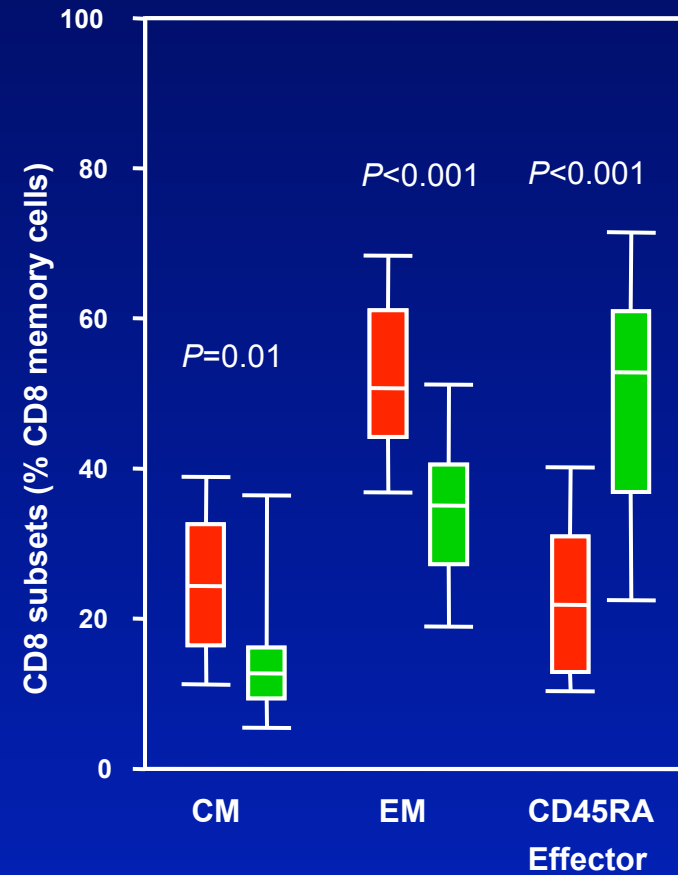
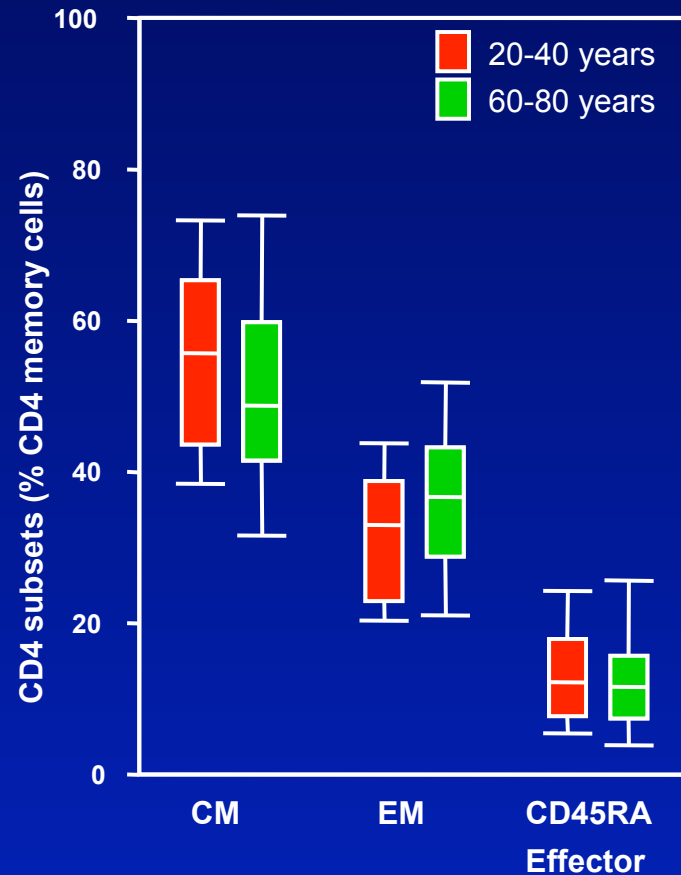
Naive CD4 T cells



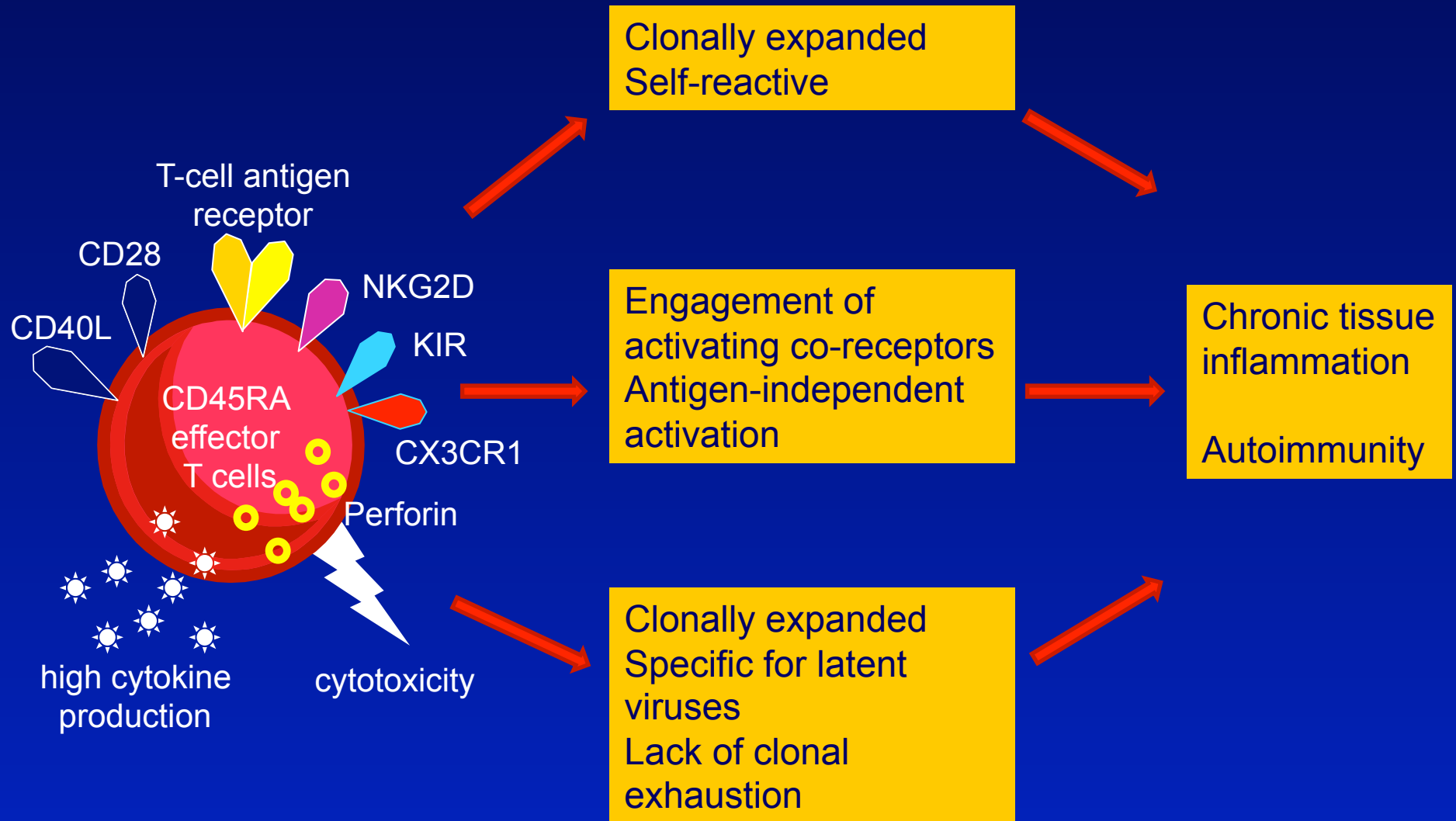
Naylor, K et al. J Immunol. 2005 Jun 1; 174(11):7446-52

Aging and T Cell Homeostasis

CD4 and CD8 T memory subsets

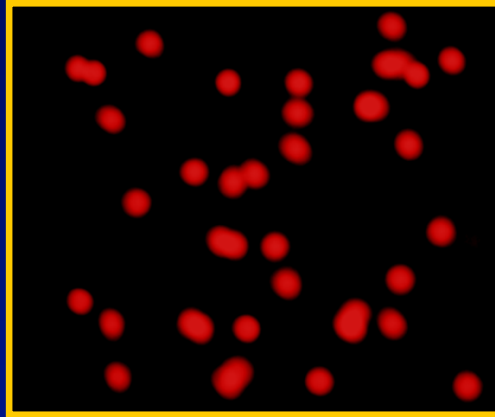


Terminally Differentiated CD45RA Effector T Cells

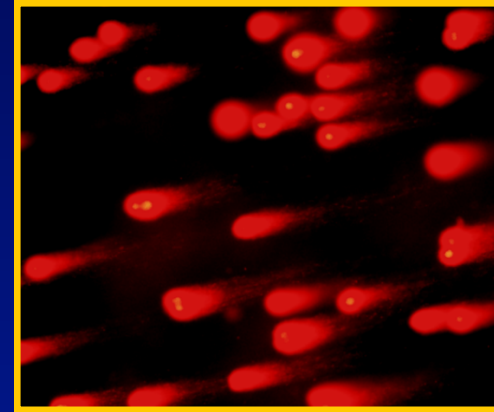


Aging and DNA Damage in T Cells

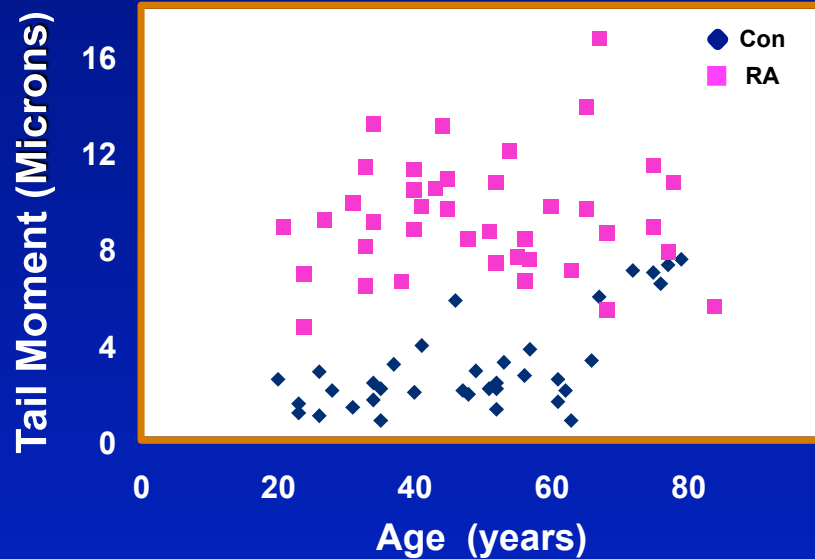
Con



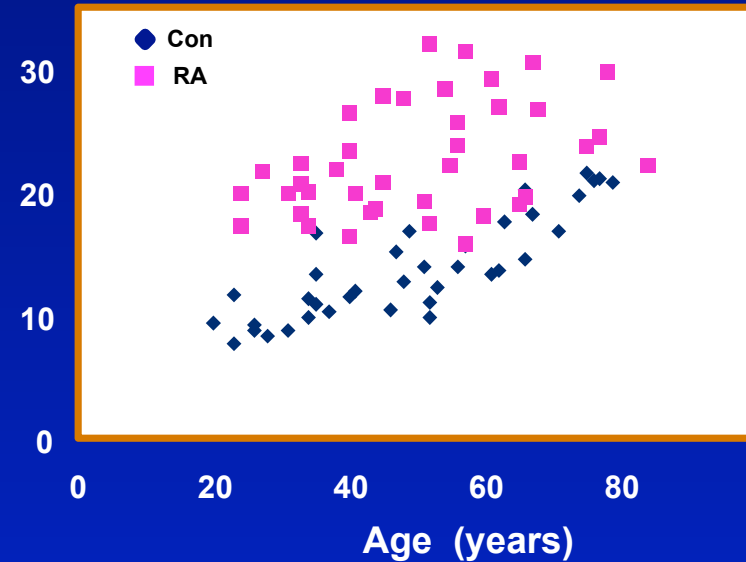
RA



Naïve ($CD4^+CD45RO^-CCR7^+$)



Memory ($CD4^+CD45RA^-CCR7^-$)



Immune Aging and Inflammation

Preferential generation of myeloid cells

Increased constitutive activation

- defective barrier
- increased systemic cytokines
- degenerative tissue damage
- viral reactivation due to defective adaptive immunity
- DNA damage

Peripheral selection of pro-inflammatory T cells

- self-reactive
- low TCR threshold
- increased cytokine sensitivity
- differentiated into memory-like or effector T cells with homeostatic proliferation in the absence of exogenous antigen
- clonally expanded end-differentiated effector T cells