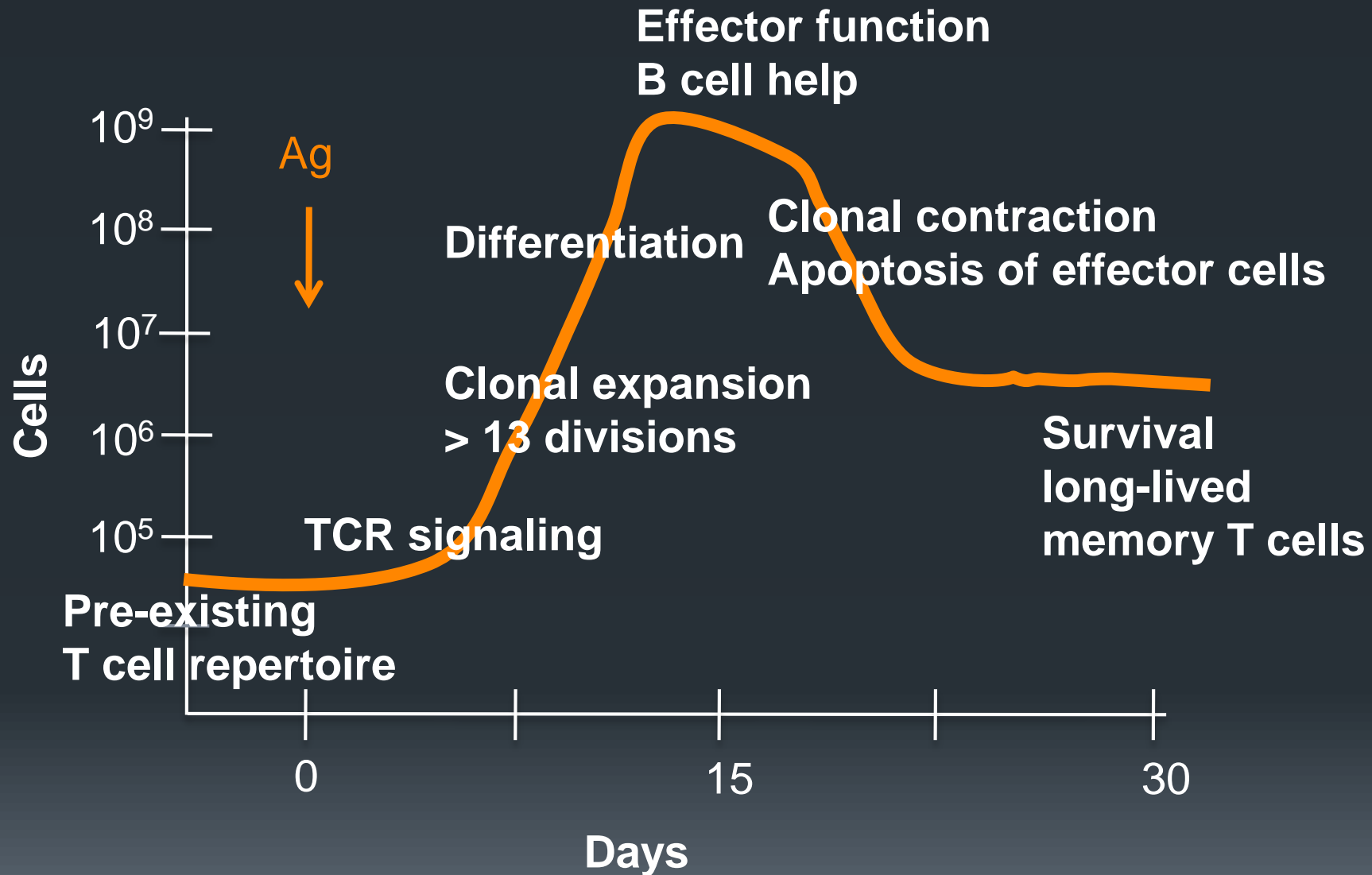


T-cells and Aging

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Stanford University School of Medicine

Kinetics of T cell responses after vaccination



Age and Vaccine Responses

What are the critical defects with aging that need to be prevented or repaired to improve vaccine responses?

- **Lack of players (# naïve T cells, # of antigen-specific memory T cells, T cell receptor diversity)**
- **Failure of T cell activation/signaling**
- **Failure to clonal expand and develop effector cells**
- **Failure to develop long-lived memory T cells**

Estimation of T Cell Diversity by Nexgen Sequencing

Naive and memory CD4 and CD8 T cells from young and elderly adults



Five aliquots of 1×10^6 cells each



Illumina MiSeq sequencing (150bp)

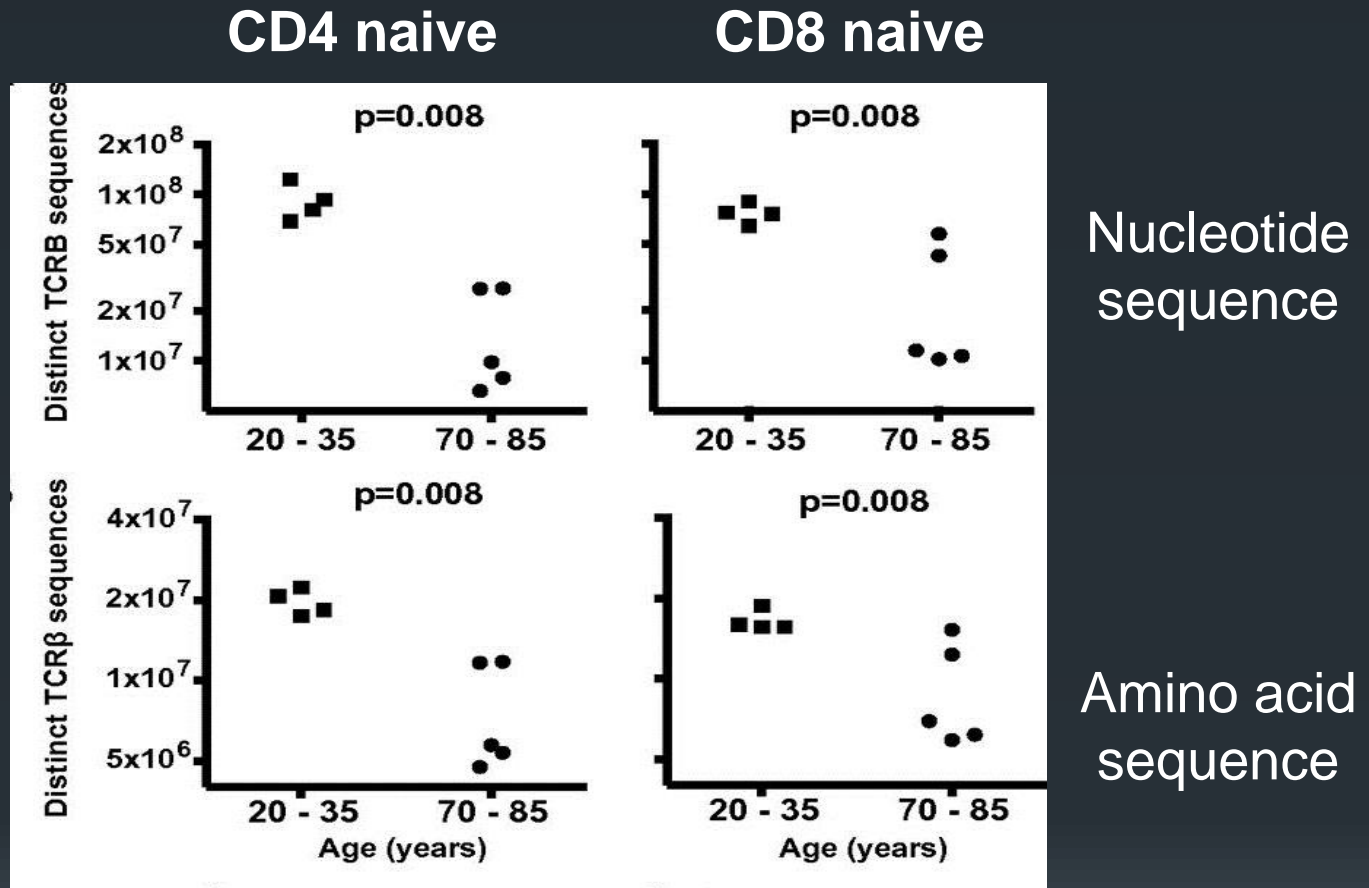


Estimates of **richness** (number of different TCR sequences):
Incidence-based non-parametric analysis using Chao 2 estimator

Estimates of **clonality** (unevenness in clonal size distribution):
Lymphclon (Liu, Olshen, Fire, Boyd)

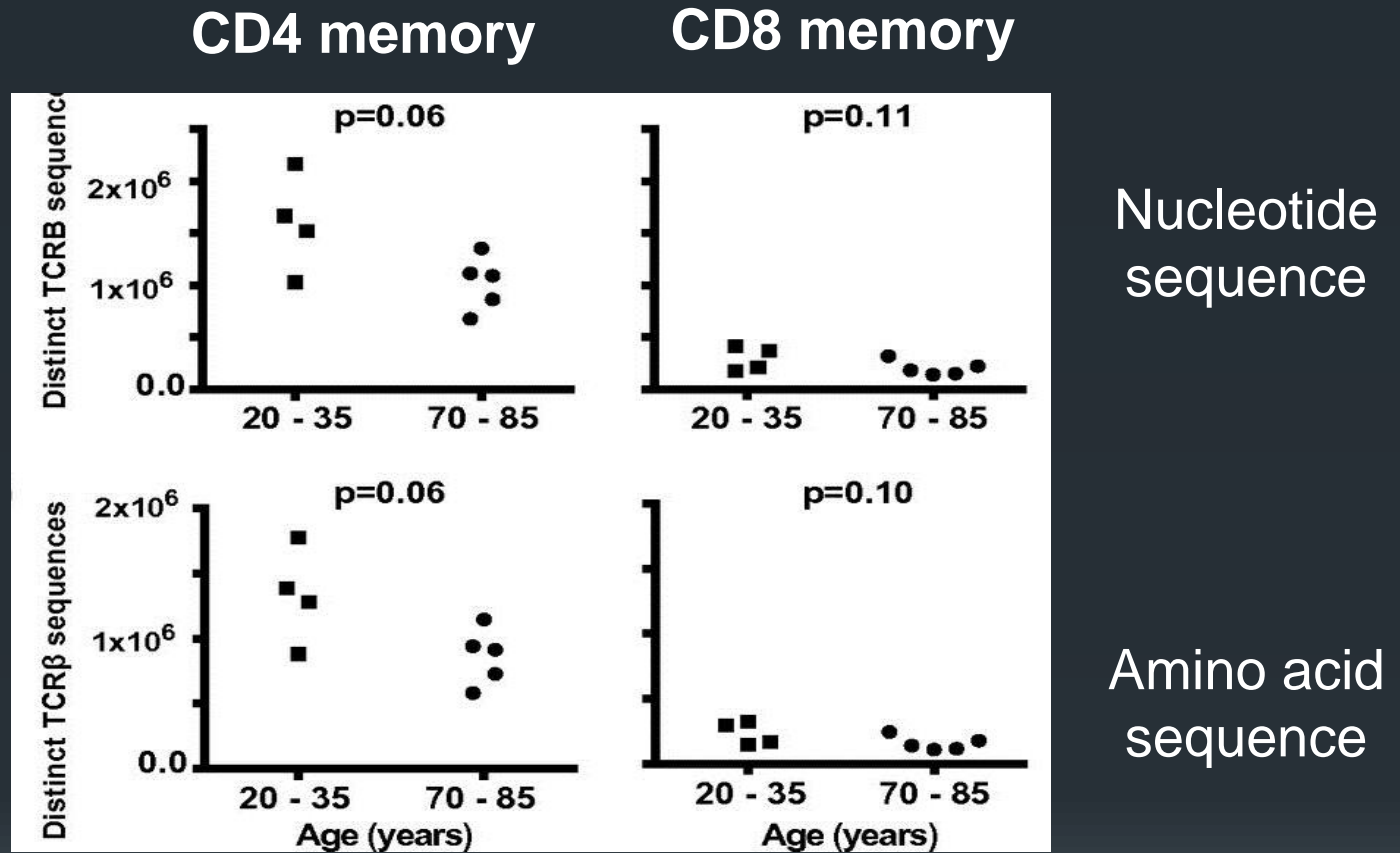
Age and T Cell Diversity

The naive T cell repertoire in older individuals continues to be very diverse



Age and T Cell Diversity

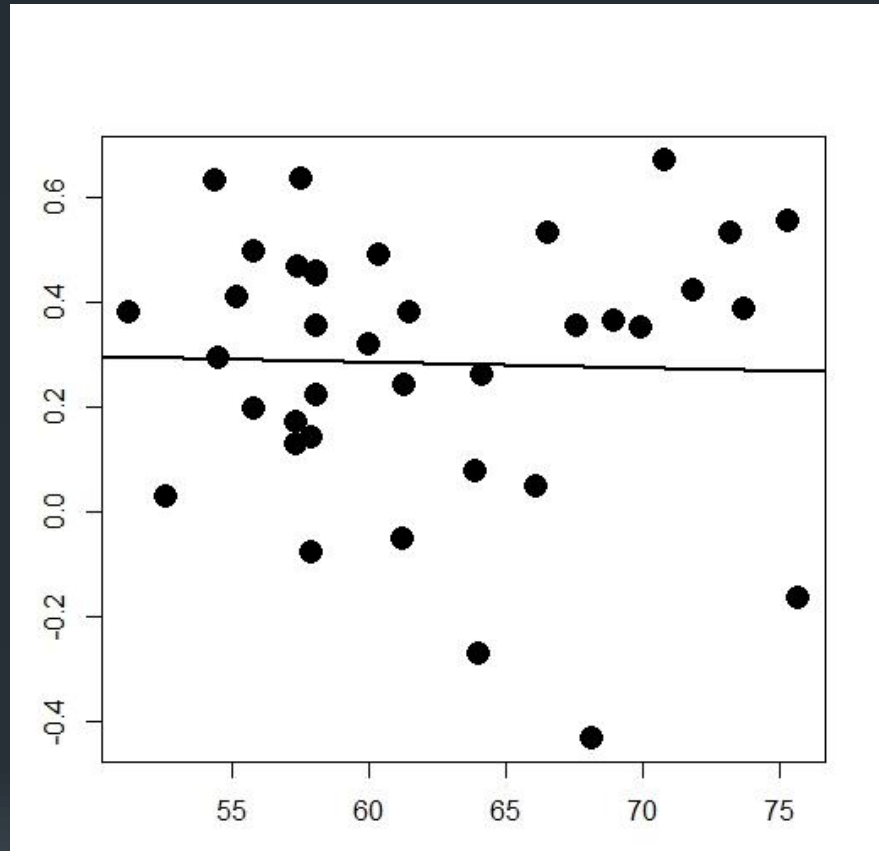
Richness in the memory T cell repertoire does not change with age



Age and Herpes Zoster Reactivation

VZV-specific antibodies do not decline with age

Log (VZV-specific antibody titers)

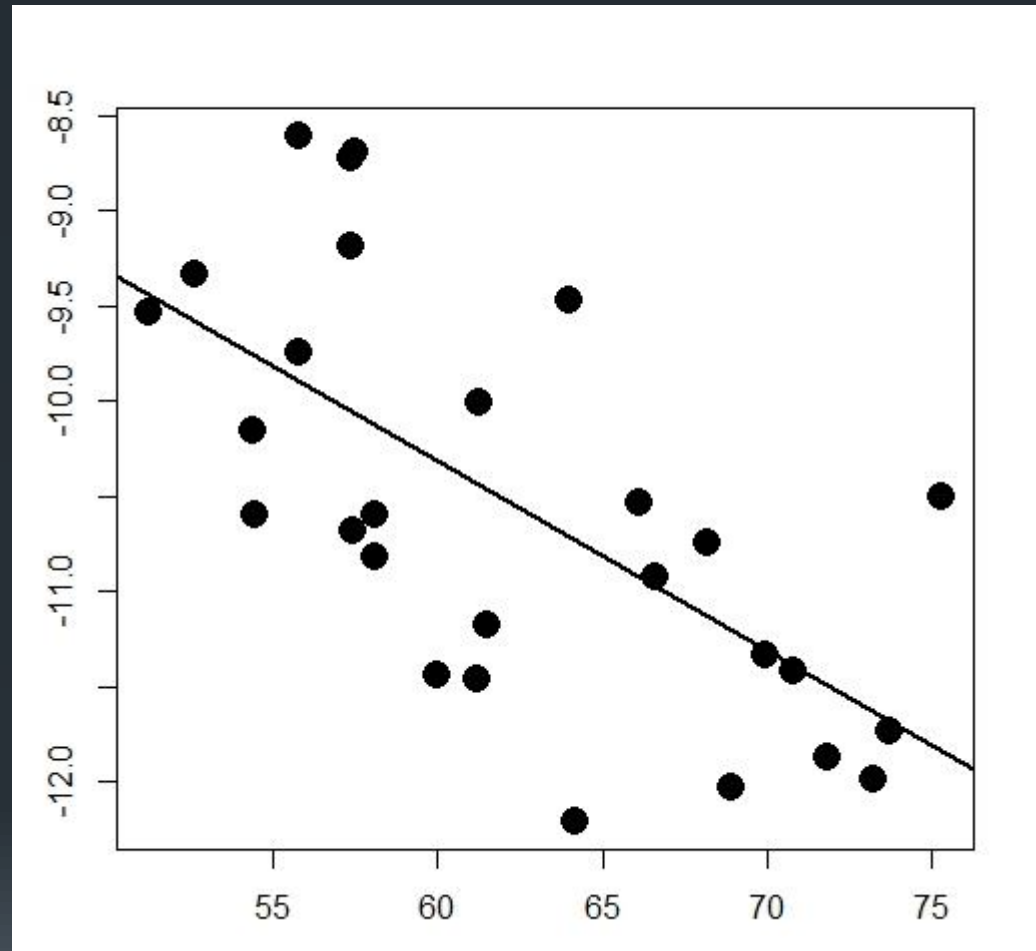


Age (years)

Age and Herpes Zoster Reactivation

Decline in VZV-specific CD4 T cells with age

Log (frequency IFN γ +
VZV-specific T cells)

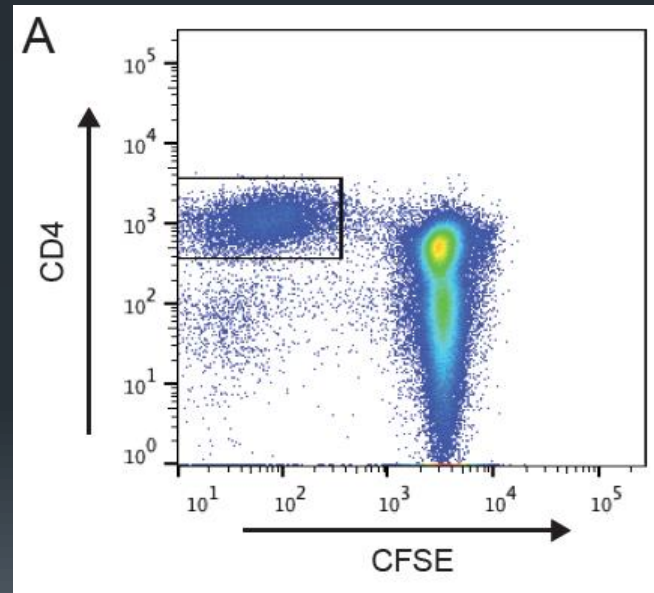


Age (years)

Repertoire analysis of VZV-specific T cells

Experimental Design

- CFSE-labelled PBMC stimulated with VZV lysate for 8 days in triplicate
- Triplicate samples of CFSE-low cells sequenced
- TCR considered specific for VZV if present in ≥ 2 replicates and enriched by at least 2-fold compared with total CD4



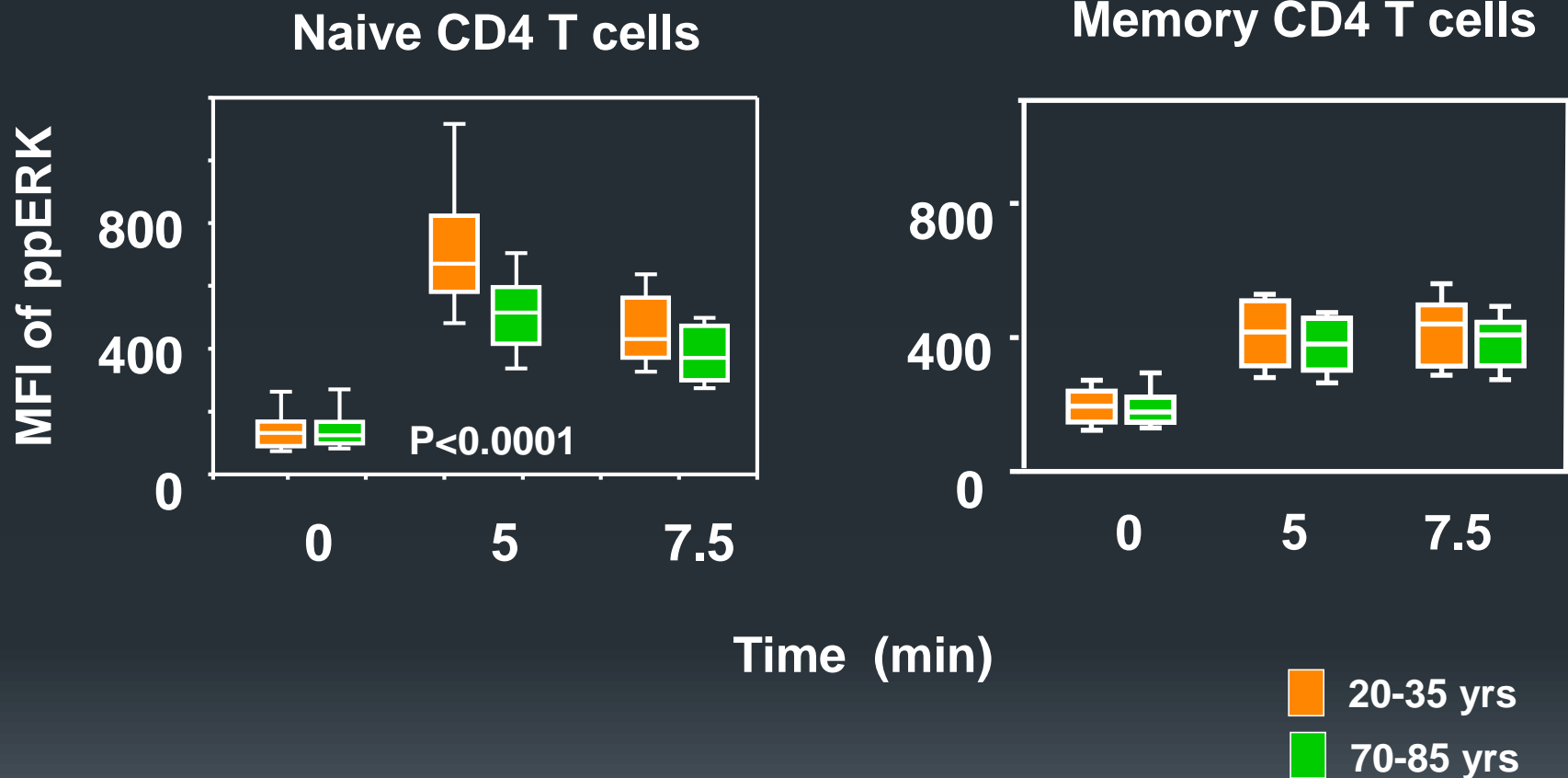
Age and Vaccine Responses

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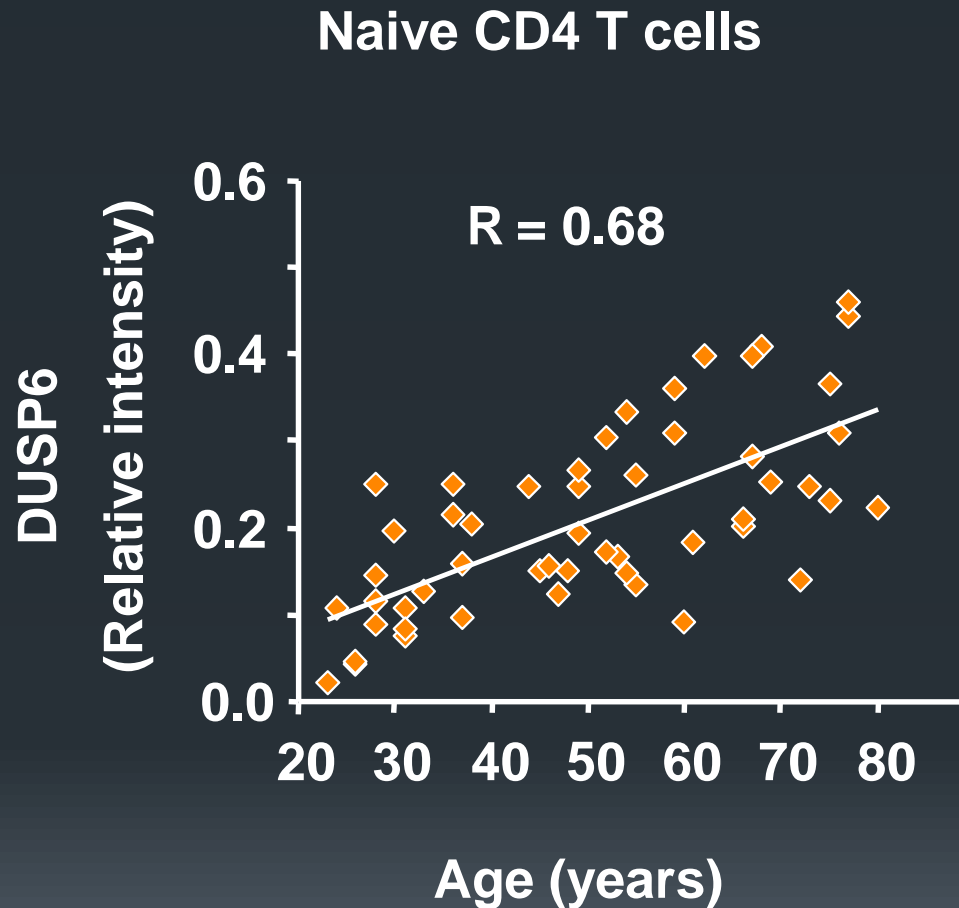
Functionality of CD4 T cells with age

T cell receptor signaling: defective ERK phosphorylation



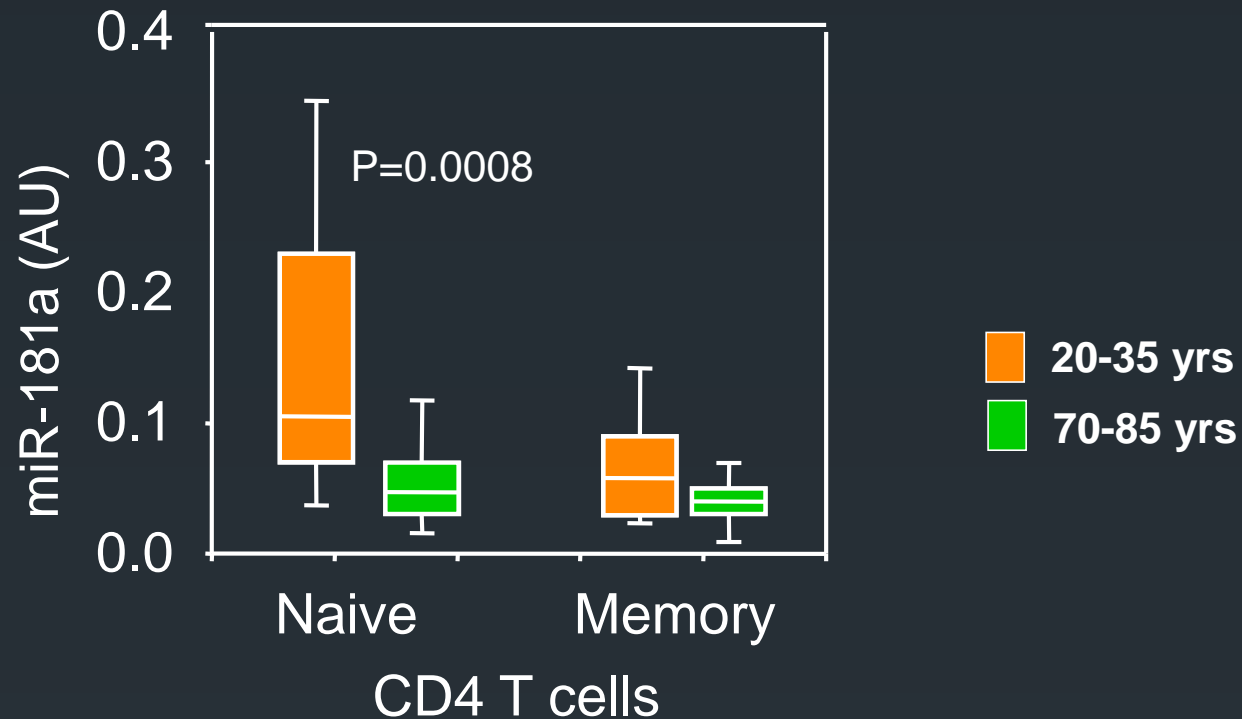
Aging and naive CD4 T cell activation

Increased expression of DUSP6



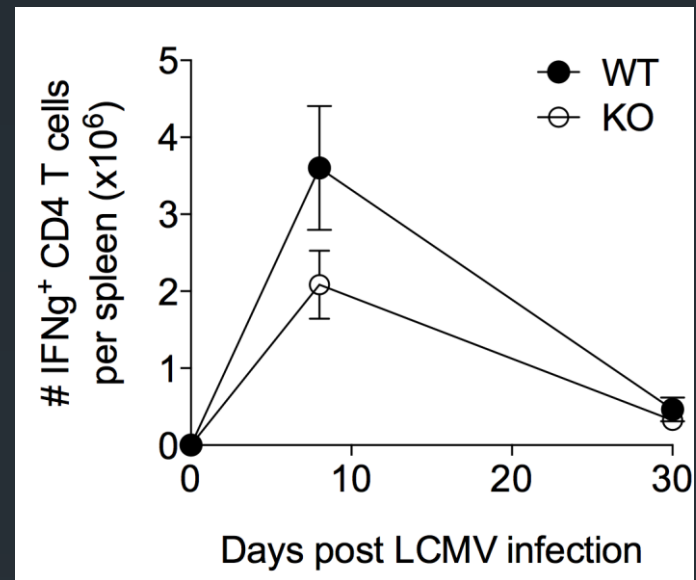
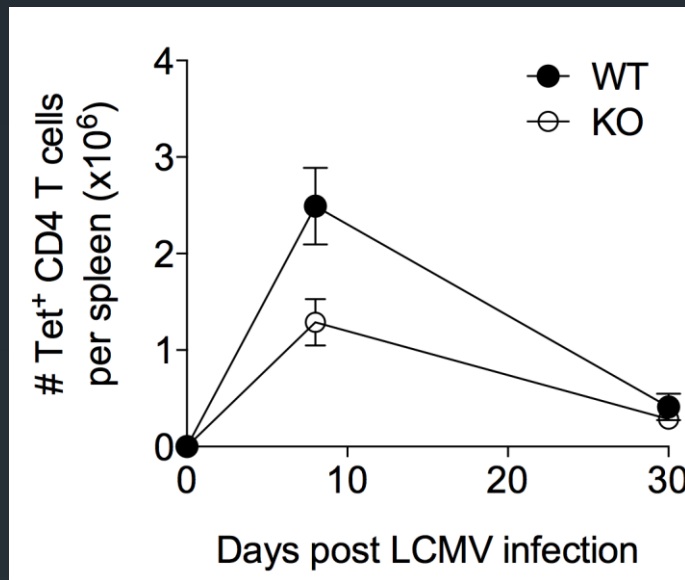
Aging and naive CD4 T cell activation

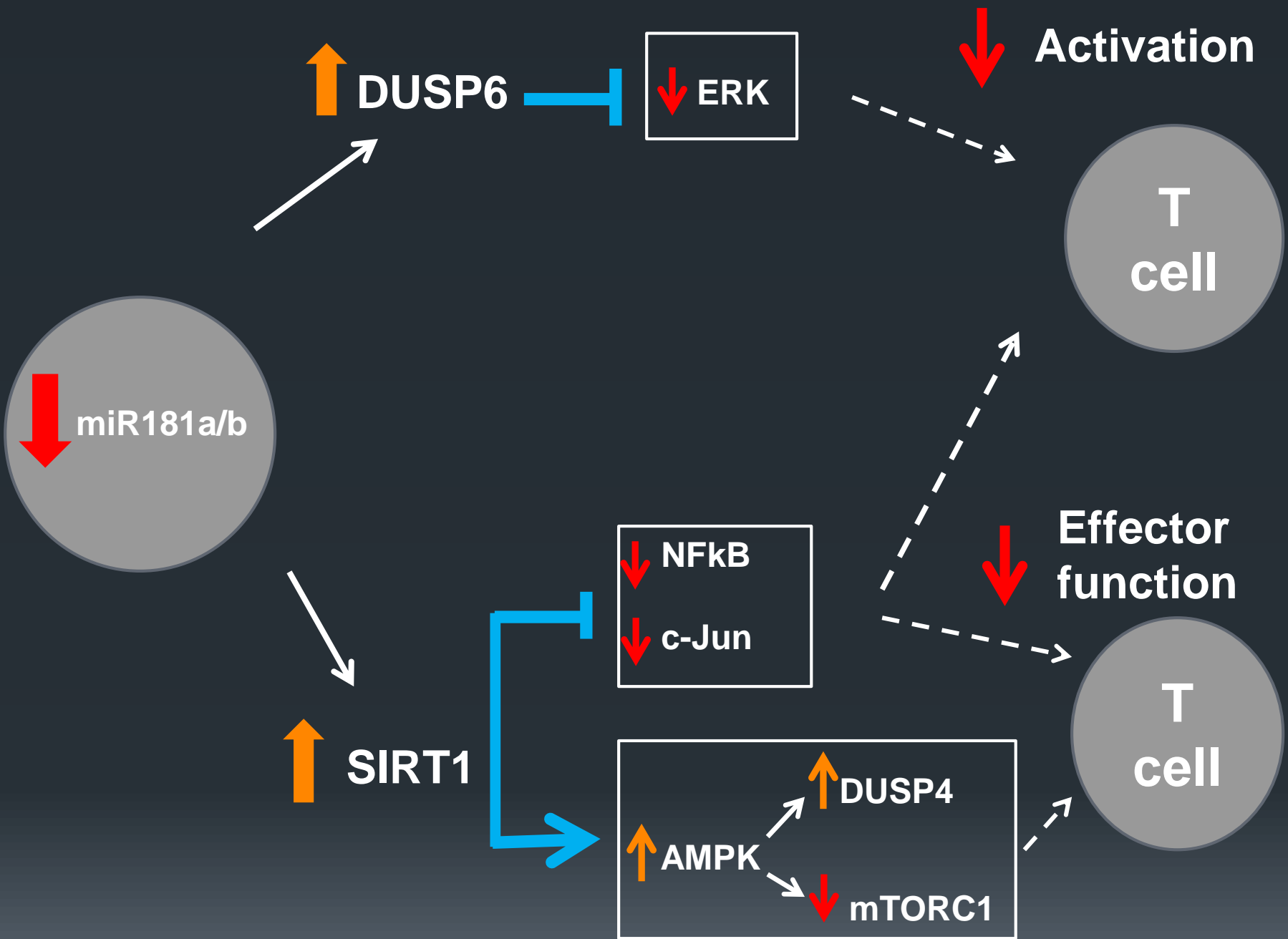
Age-related decrease in miR-181a expression



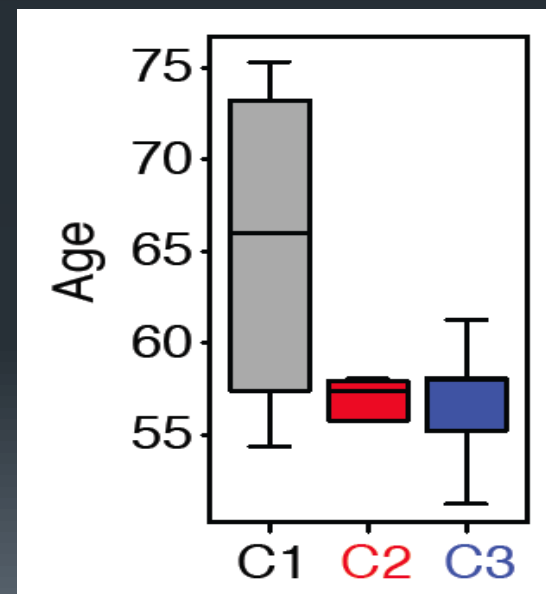
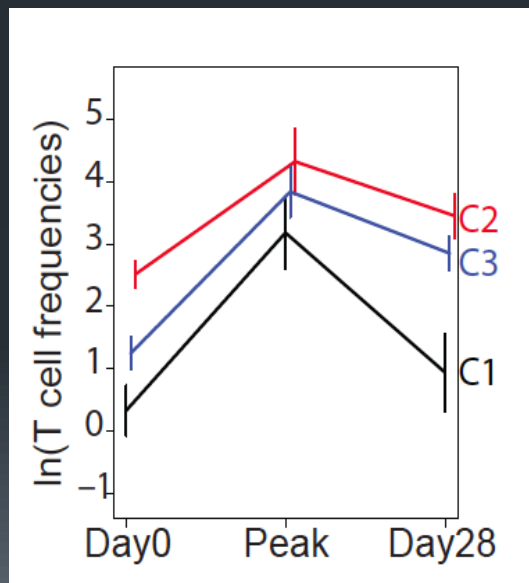
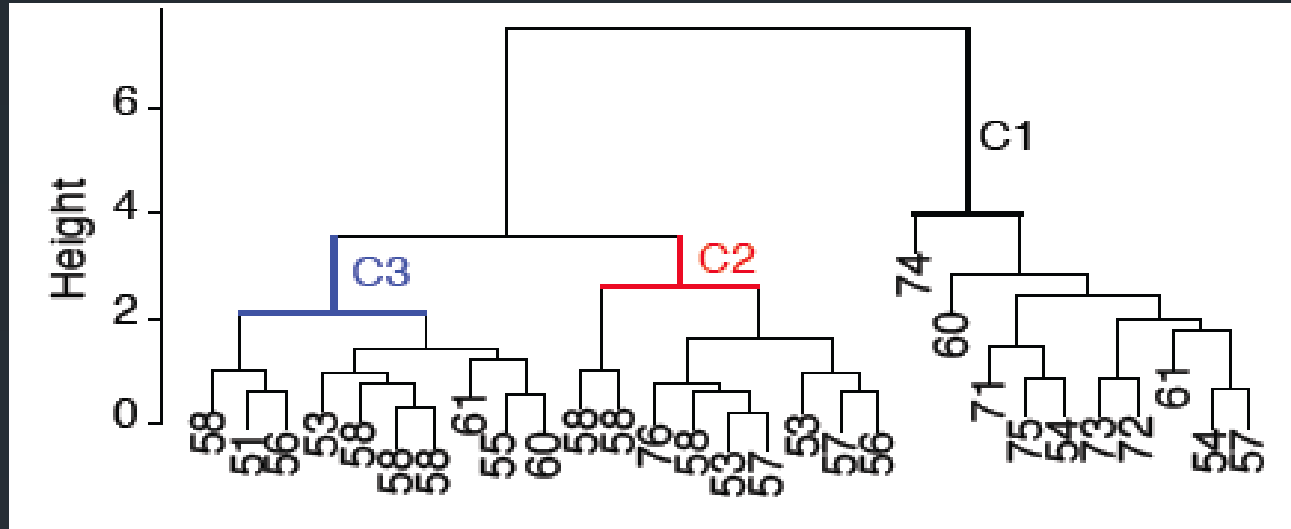
Nature Medicine 18, 1518–1524 (2012)

miR-181a is required for T cell clonal expansion and effector differentiation





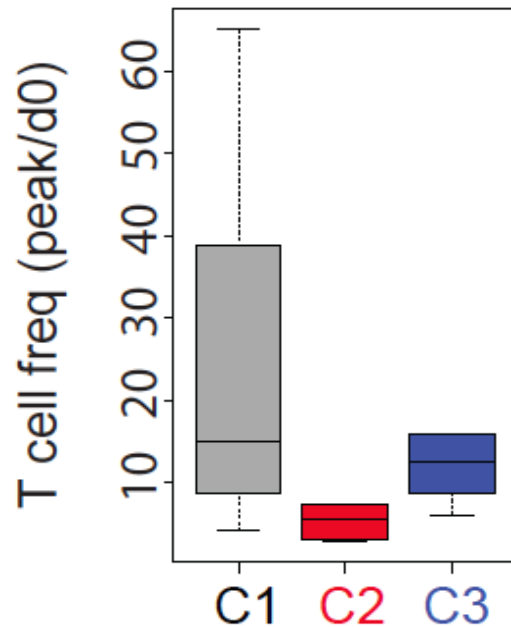
Cluster analysis of T cell responses after varicella zoster vaccination



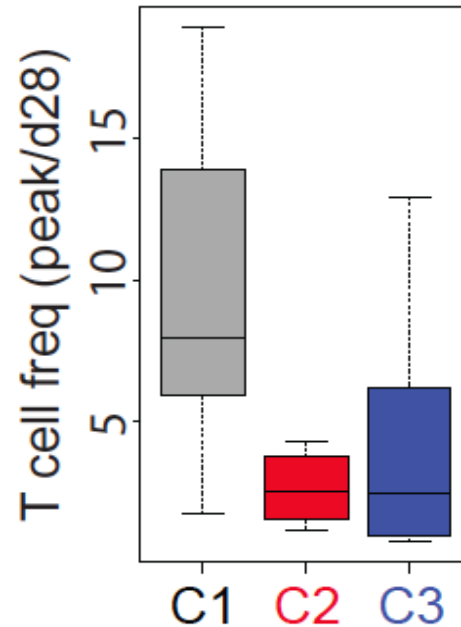
Age-associated defects in T cell responses

Increased cell loss during clonal contraction

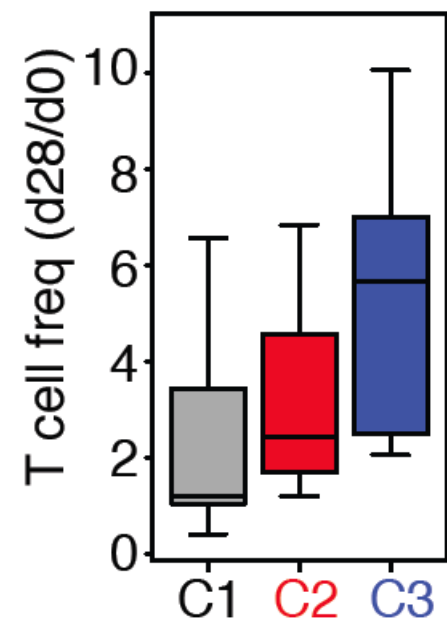
Expansion



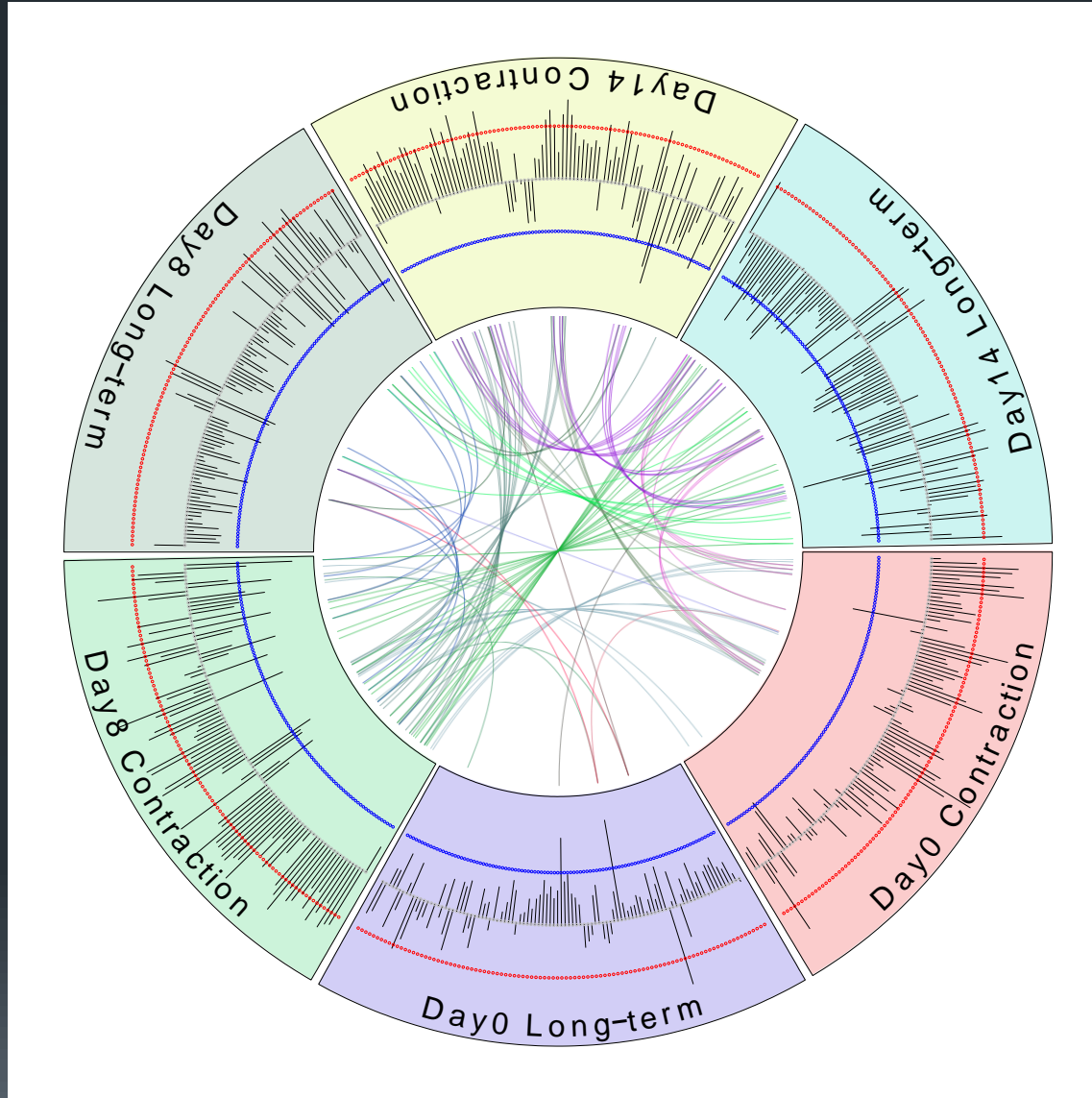
Contraction



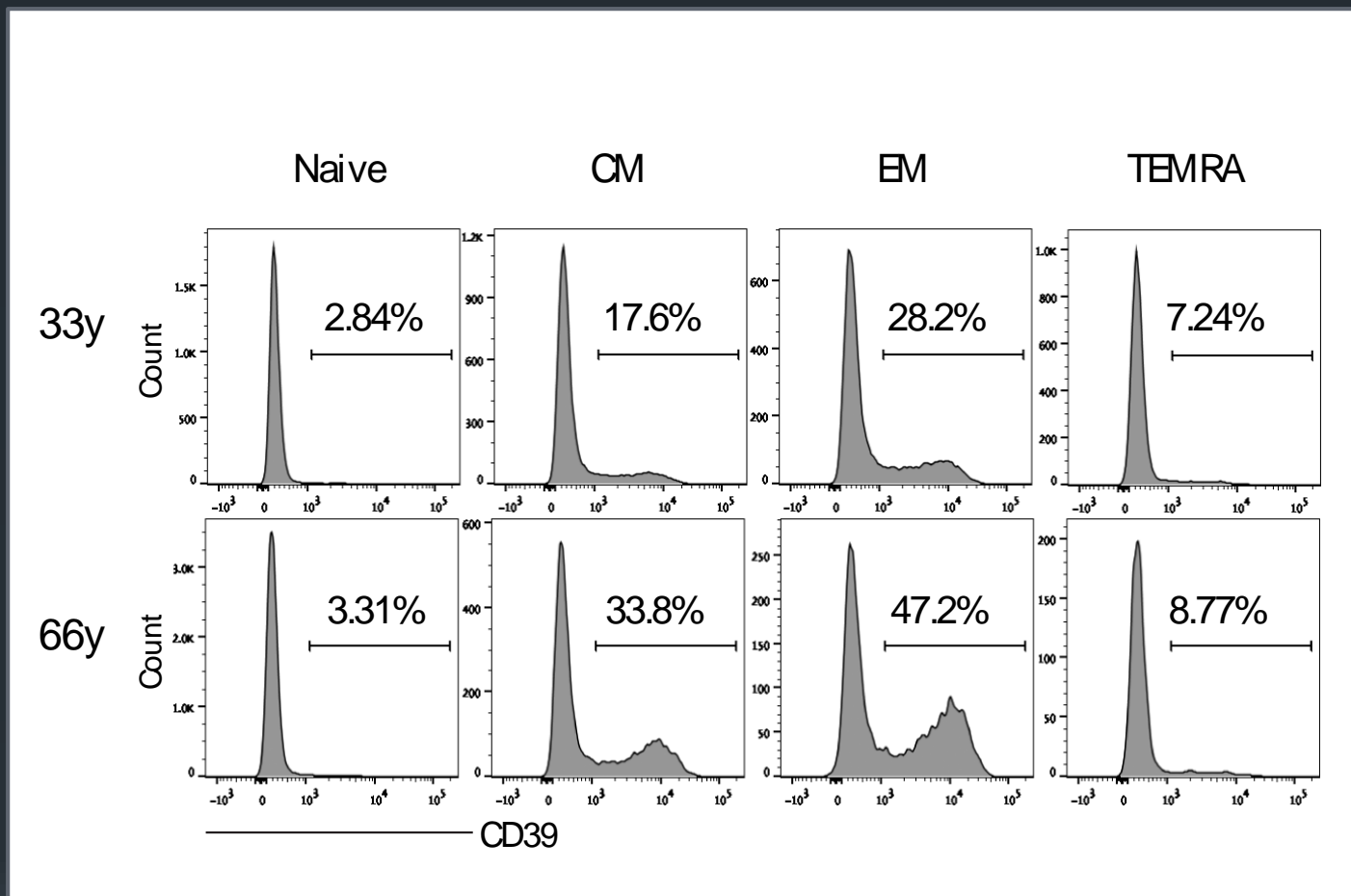
Net Long-lived



Gene expression in activated CD4 T cells correlates with contraction and generation of long-lived memory T cells

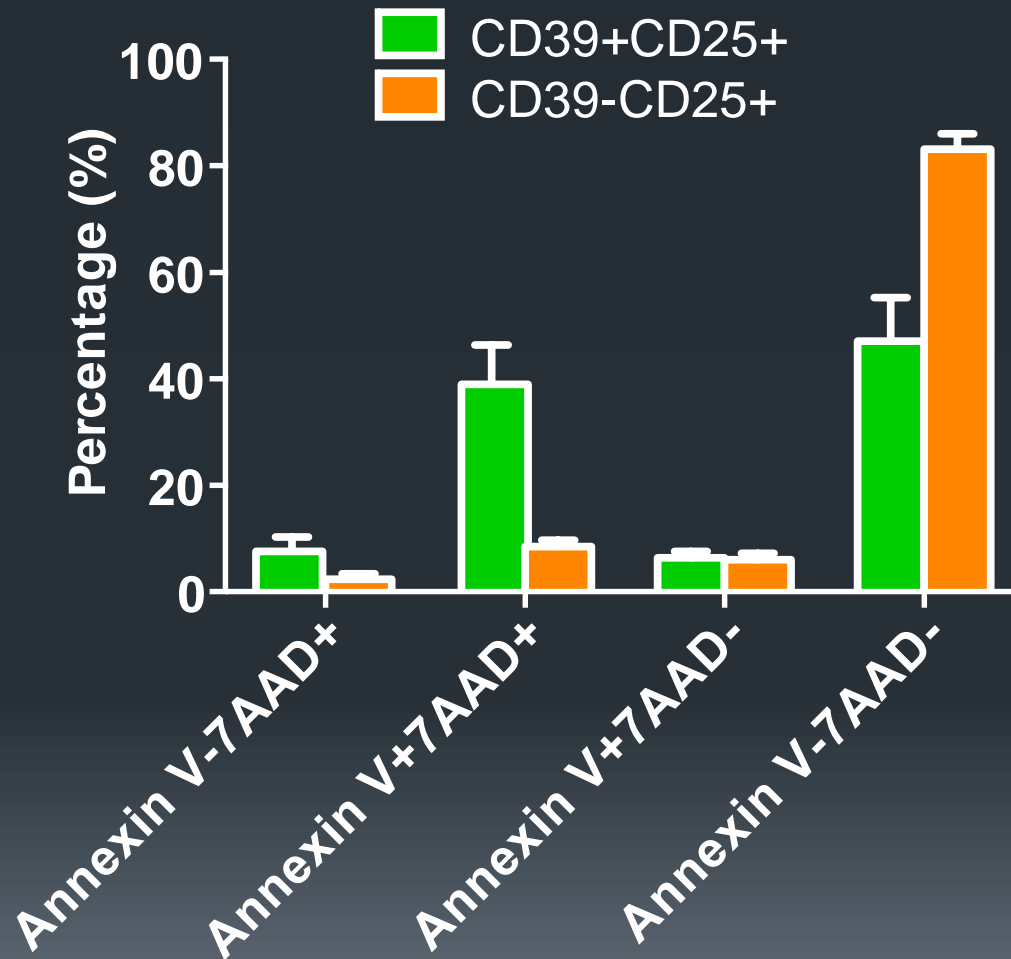


Increased expression of CD39 in CD4 T cell responses from older individuals

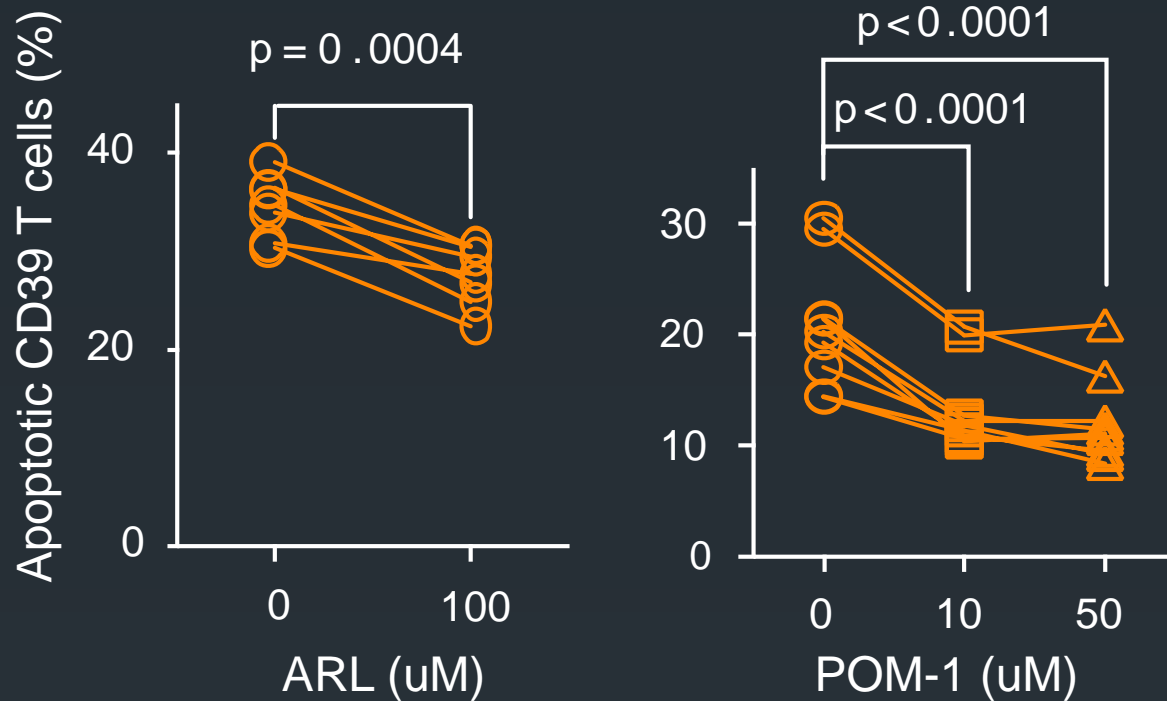


Cell Reports, in press

Increased apoptosis rates in activated CD39+ CD4+ T cells

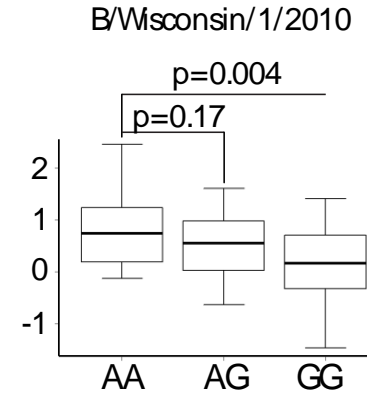
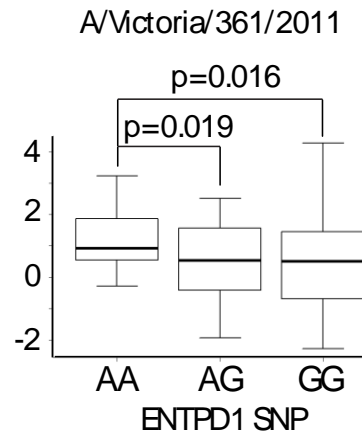
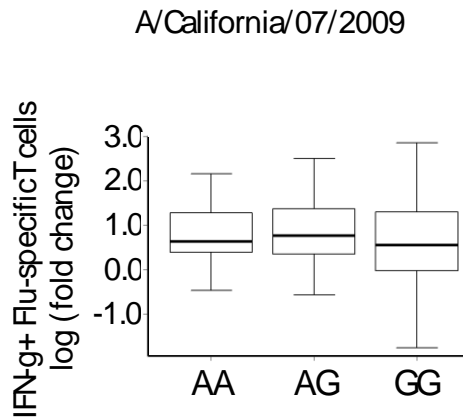
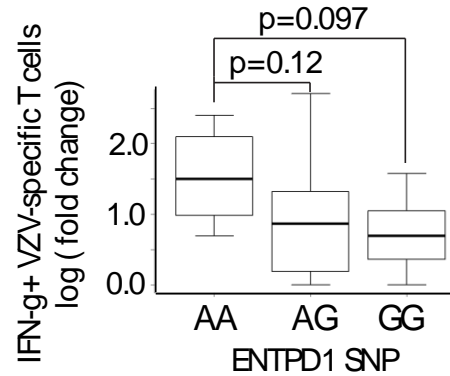


Inhibition of CD39 ATPase activity improves effector T cell survival

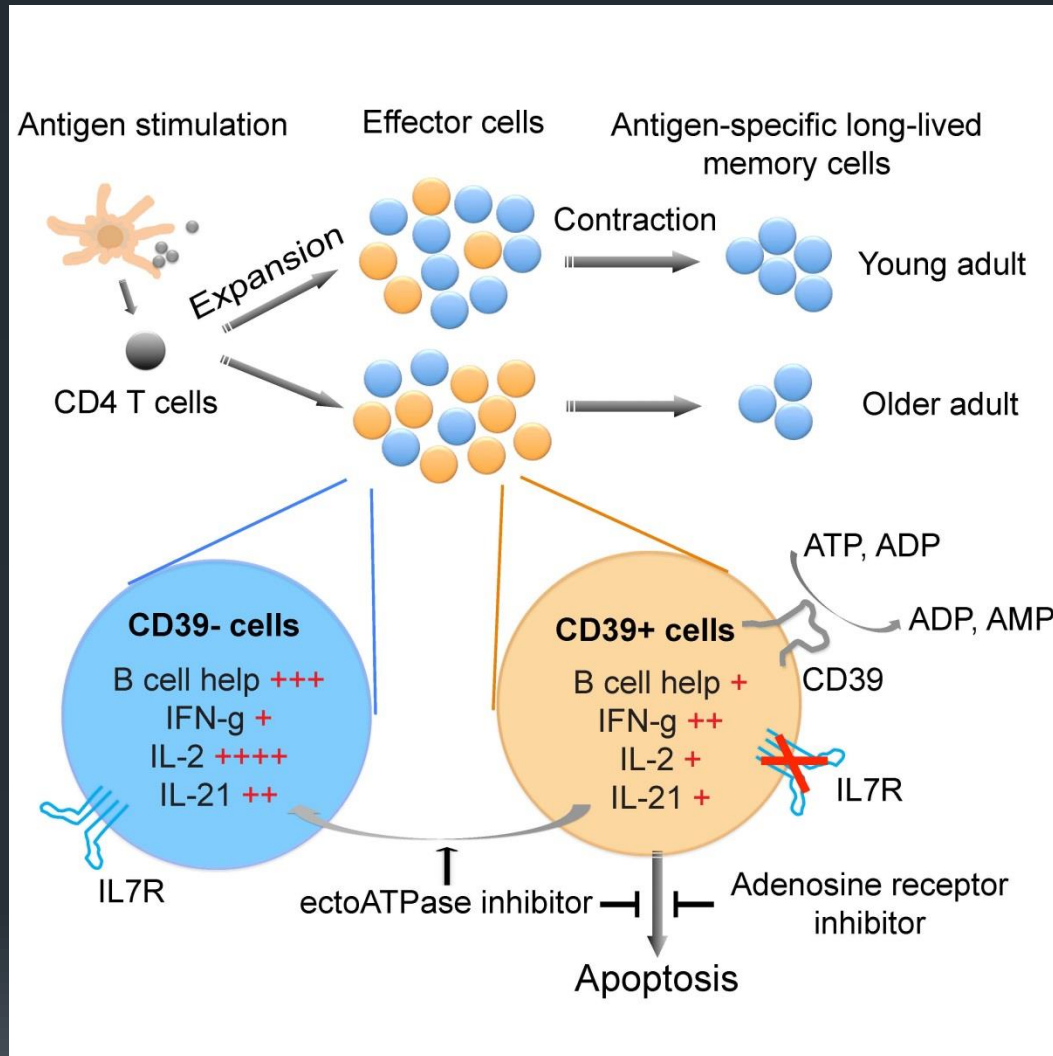


Cell Reports, in press

Promoter polymorphisms of the ATPase ENTPD1 (CD39) correlates with generation of memory T cells in vaccine responses



Age-associated increased CD39 expression impairs generation of long-lived memory T cells



Conclusions

- The naïve T cell receptor repertoire contracts with age, but remains very rich making holes in the repertoire unlikely.
- The breadth of the VZV-specific repertoire differs markedly between individuals irrespective of age and genetic make-up.
- The diversity of VZV-specific CD4 T cell repertoire increases after vaccination due to the expansion of infrequent clones, new recruitment of naïve T cells into the memory repertoire and the exhaustion of previously dominant clones.
- Since vaccination preferentially expands small VZV-specific T cells, their clonal sizes remain small even after vaccination.

Conclusions

- Activation of naive T cells in older individuals is compromised due to the loss of age-associated loss of miR181a and associated attenuation of signaling pathways.
- The major age-associated defect in VZV-specific CD4 T cell recall responses is a failure of effector cells to survive and develop into long-lived memory T cells.
- The propensity of effector T cells to survive and differentiate into long-lived memory cells is determined by the ecto-ATPase CD39 and purinergic signaling.
- Expression of CD39 is increased in T cell responses from older individuals leading to increased loss of antigen-specific T cells.

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