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Healthspan extension, resistance to infection and the rules for immune aging

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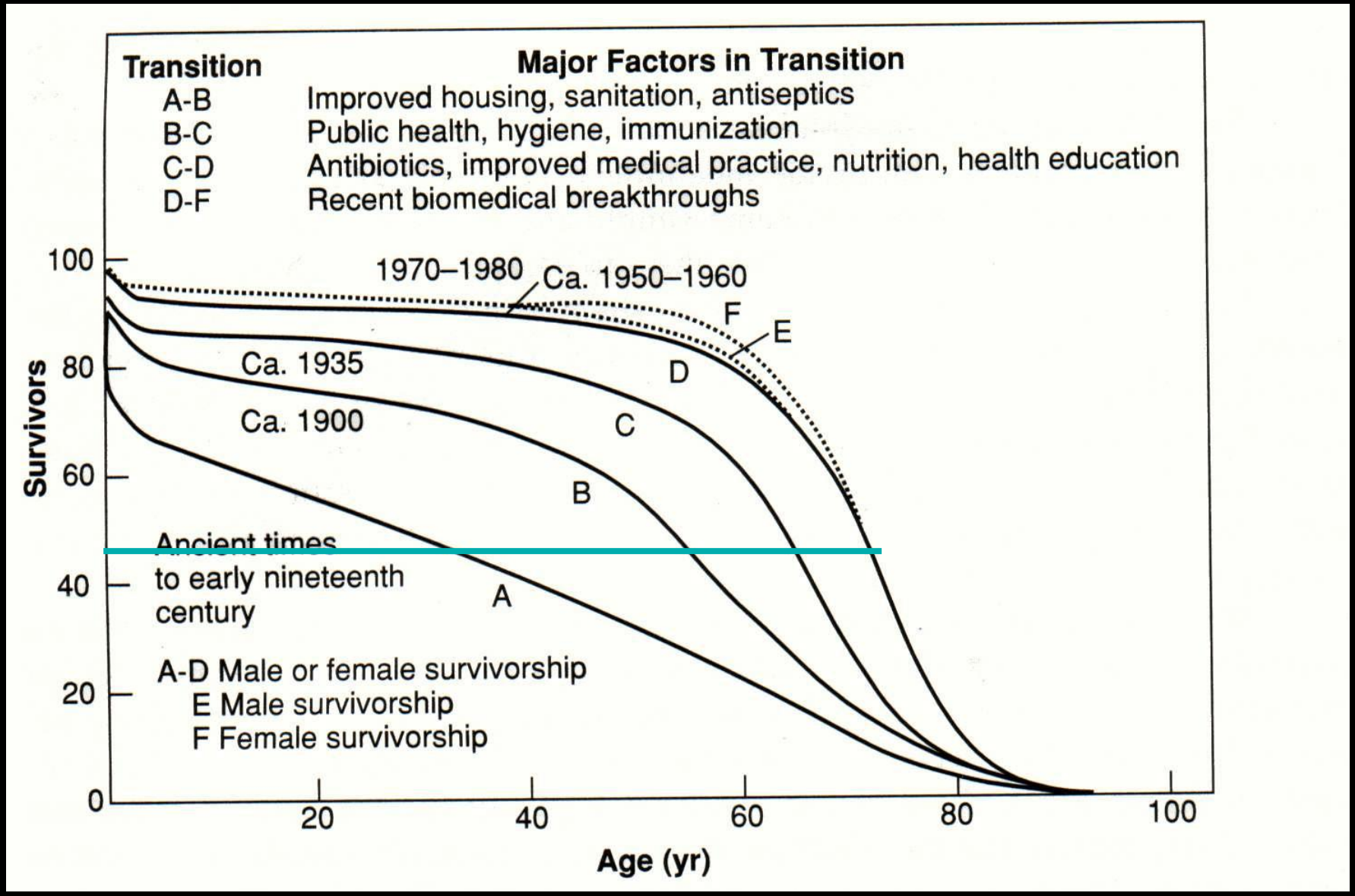
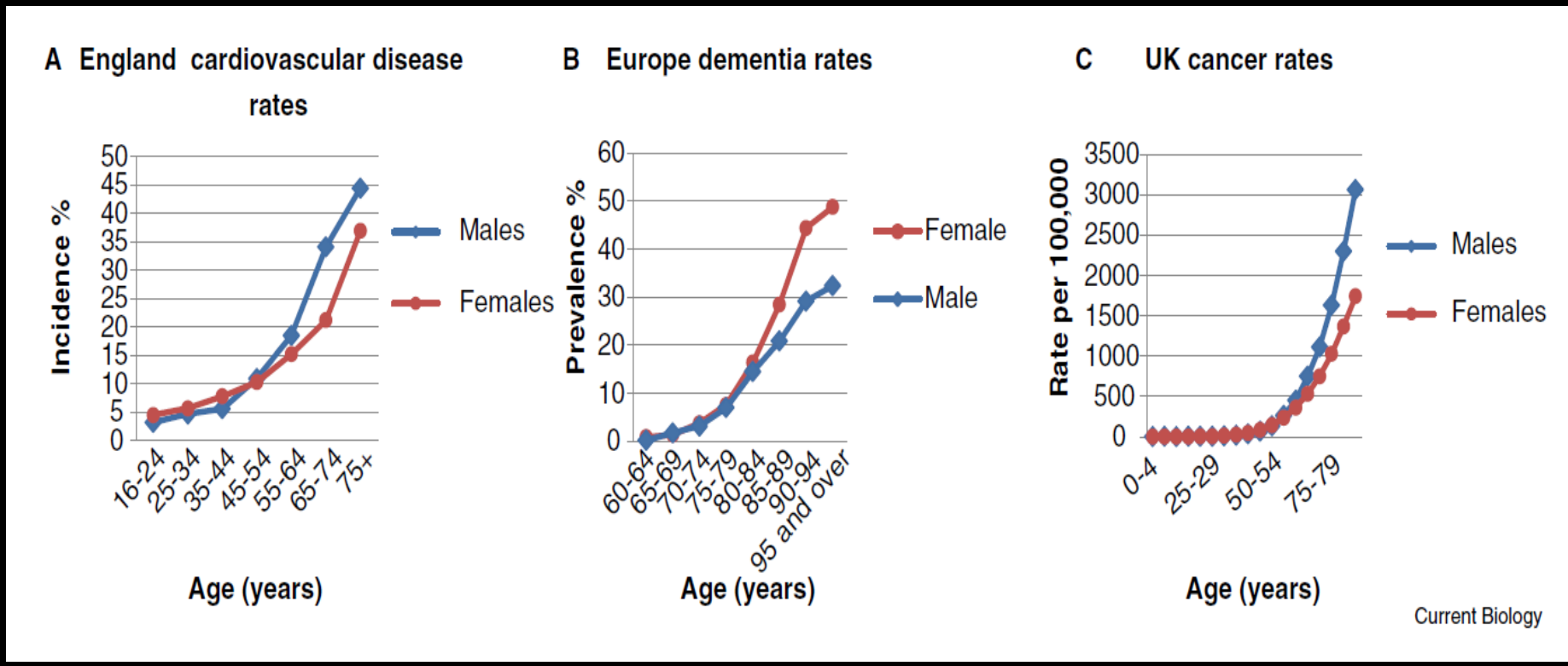
Brian Rudd

"Rectangularization" of the Survival Curve:



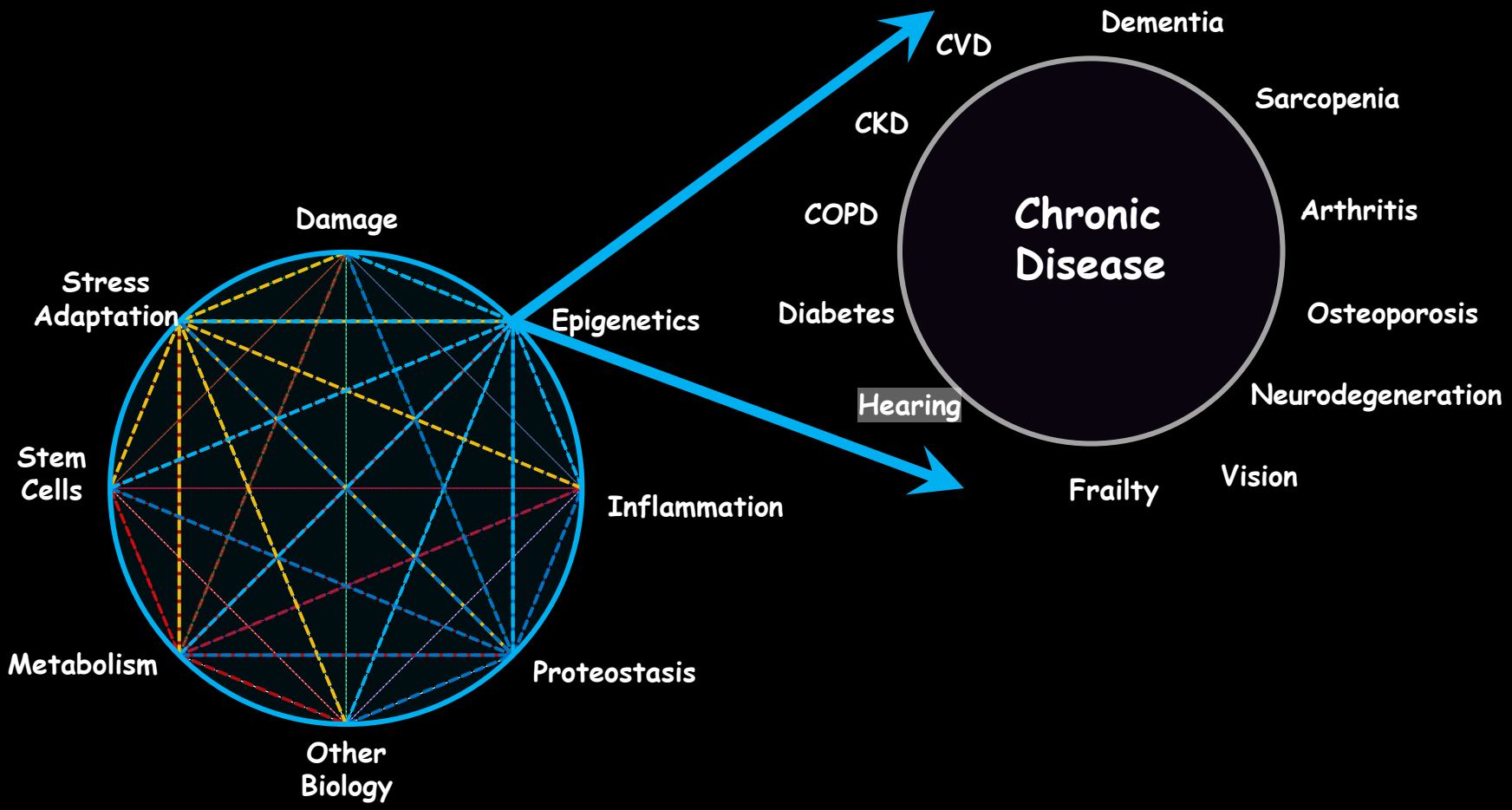
Slide courtesy of Neal Fedarko

Aging and incidence of CV disease, Dementia, Cancer in the general population



Current Biology 22, R741–R752, September 11, 2012

Aging mechanisms link to the development of chronic disease



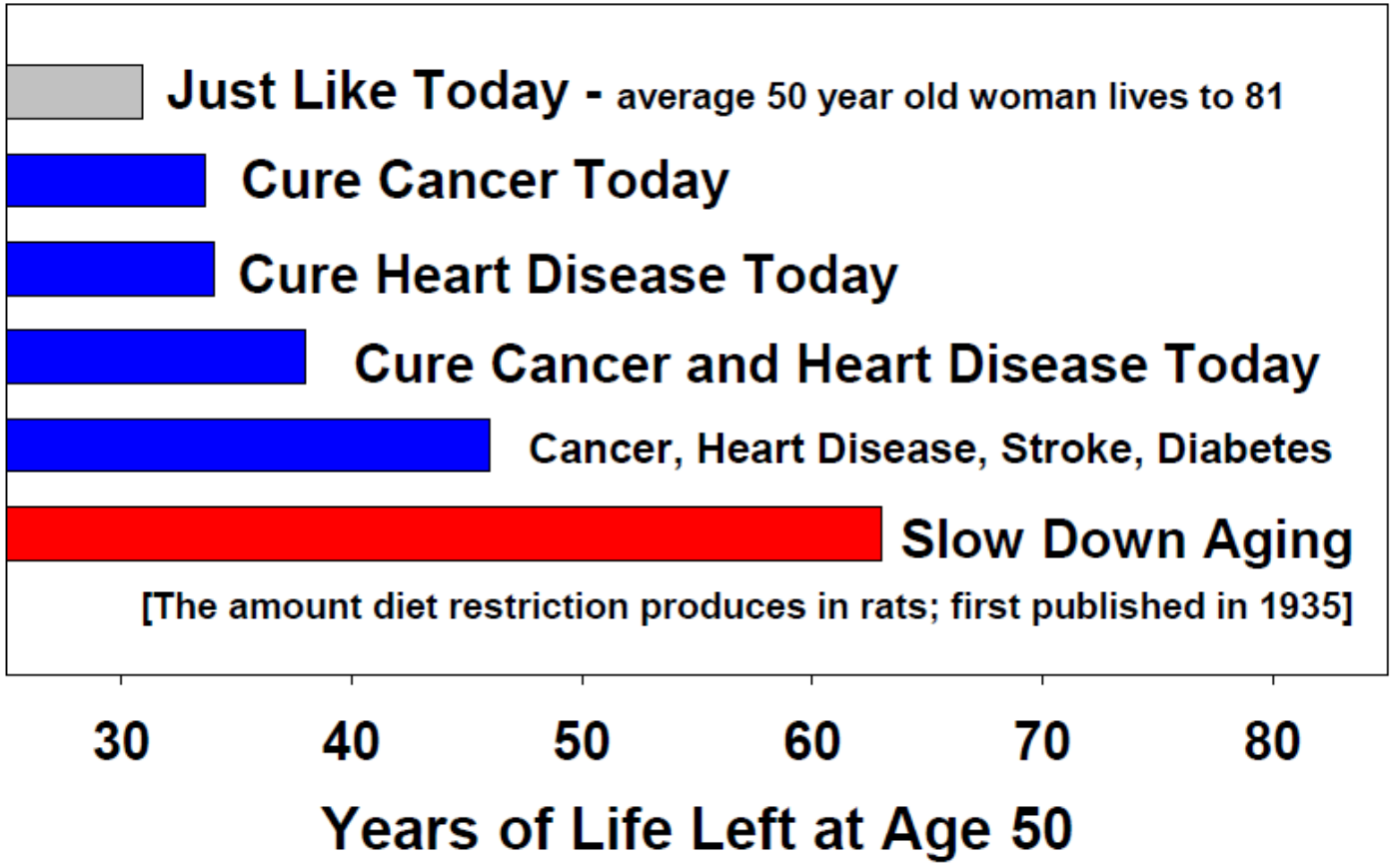
Slide courtesy Felipe Sierra, PhD

HEALTHSPAN

83 years old;
HTN, Hyperlipidemia, prior MI

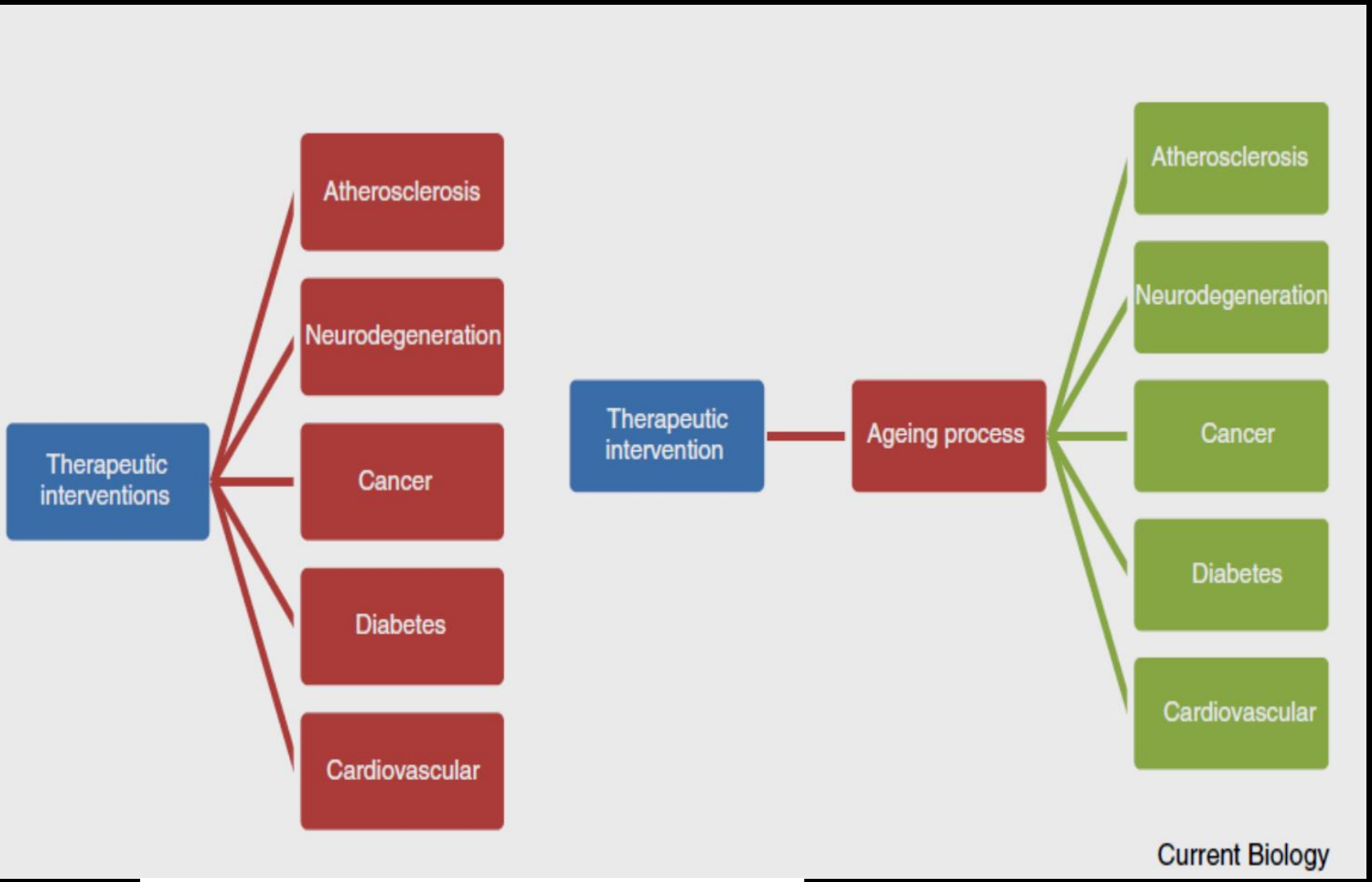
83 years old;
HTN, Hyperlipidemia, prior MI

Aging Research: Biggest Bang For the Buck?



Slide courtesy of Jeff Halter

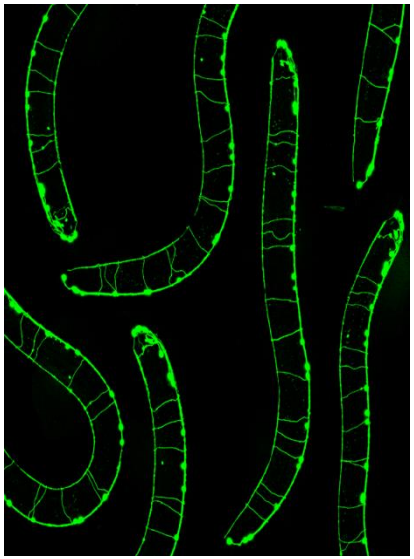
A new paradigm – address the most common risk factor for all chronic disease, simultaneously, not one at a time



Current Biology 22, R741–R752, September 11, 2012

Why we Age - Metabolic Magic!

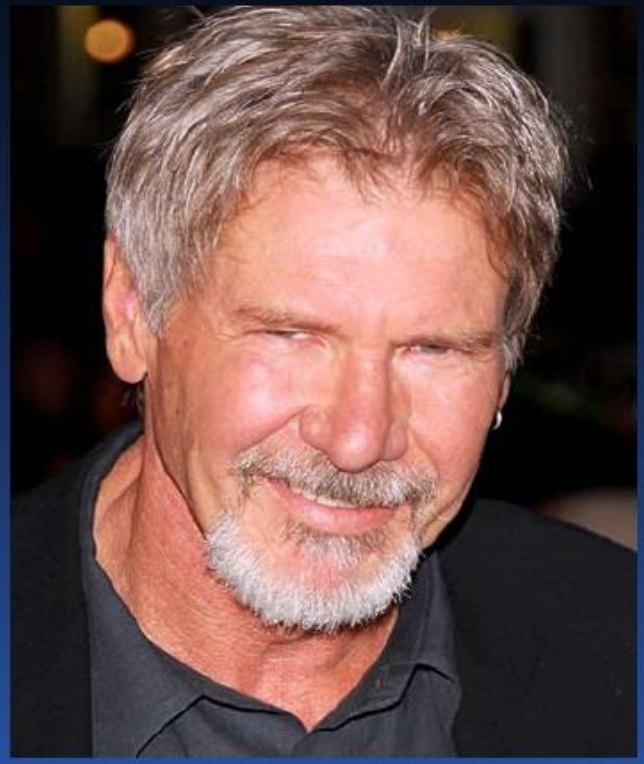
The same intervention(s) (Caloric restriction; rapamycin) and the same genes (insulin/insulin growth factor receptor pathway) control the aging/function *in the same manner* in some **very distant** cousins.

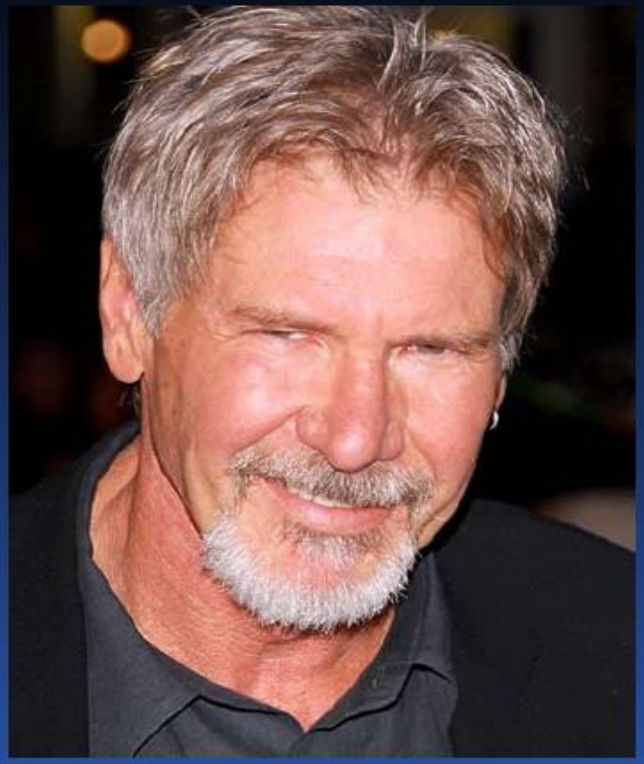


Why is this important?

- Long-lived worms, flies and mice are resistant to **many** kinds of stress.
- The stress resistance might be the **cause** of the successful aging **and** of delaying age-related diseases.
- Humans may react in a similar manner

The Goal of Aging Research: A New Kind of Old Person





Normal person, age 70

Normal person, age 114

Slide courtesy of Richard Miller, U Michigan

CR literature background

- Immune status
  - CR old mice & monkeys exhibit proportionally more naïve CD4 and CD8 T cells and increased thymic cellularity
  - CR creates a lymphopenic environment
  - CR splenocytes have increased in vitro responsiveness

- Response to Infection (Influenza A, IAV)
  - Old mice have impaired CTL activity
  - Old mice have impaired proliferation in vitro against IAV antigens, which is improved in old CR mice (i.p.)
  - CR increases early adult and old mouse mortality, perhaps due to impaired NK cell activity; adaptive immmune status unclear

CR believed to operate at least in part via the mTORC1 complex inactivation, which is phenocopied by rapamycin treatment.

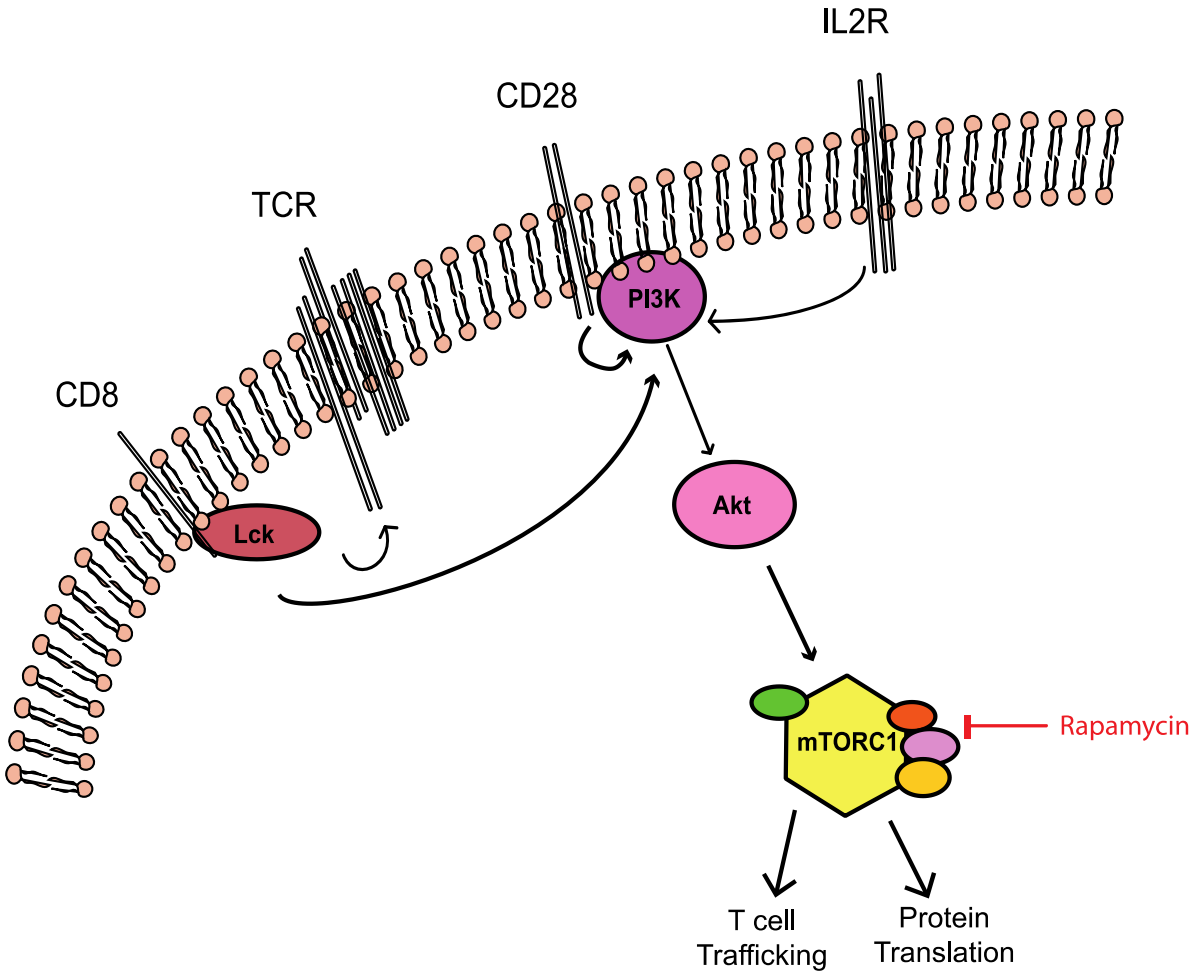
Aging, metabolism and immune responses

Rapamycin a mTORC1 inhibitor, can extend lifespan in mice even if administered in the last third of life; also reported to improve immunological memory upon short-term administration.

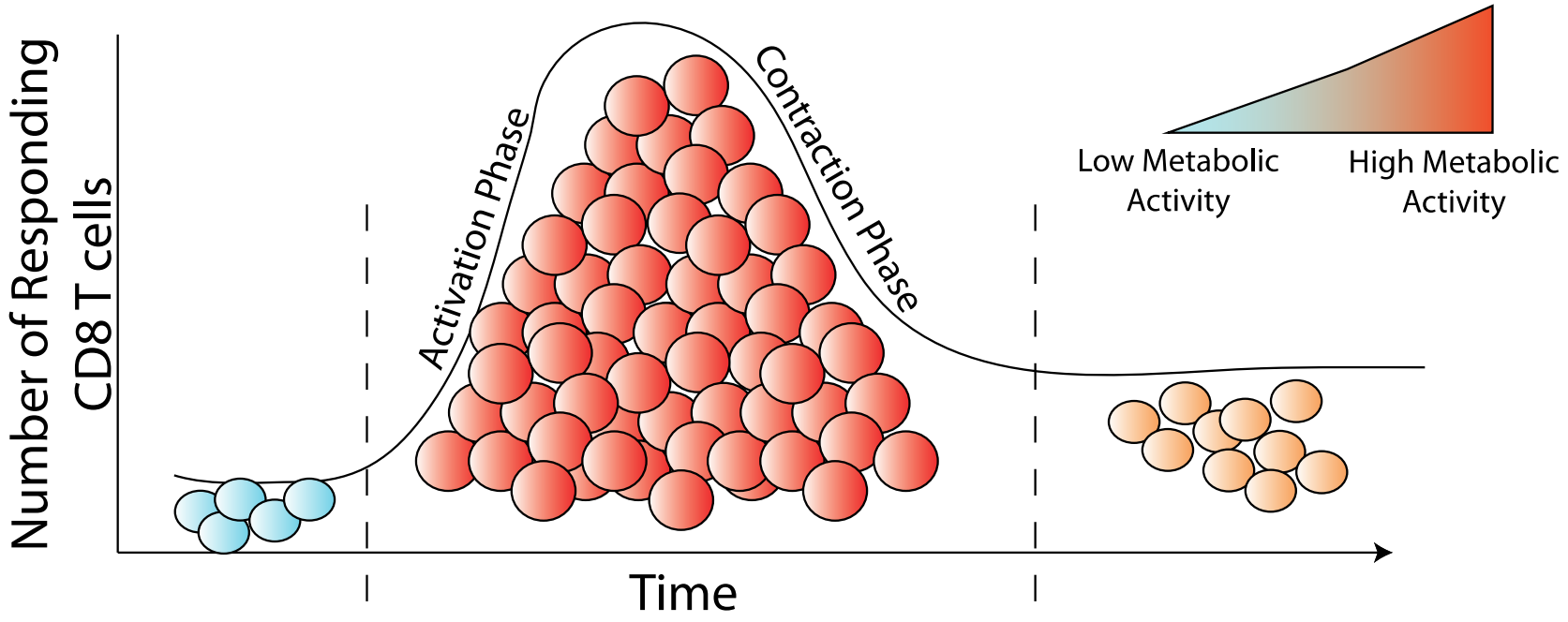
mTOR integrates growth factor signals (IGF, Insulin; CD28 in T cells) and nutrient (amino acid and glucose) availability signals to determine whether the cell will enter macromolecular synthesis and cell cycle

How do CR and Rapa interface with the need of T cells to expand in response to infection?

T cell nutrient sensing

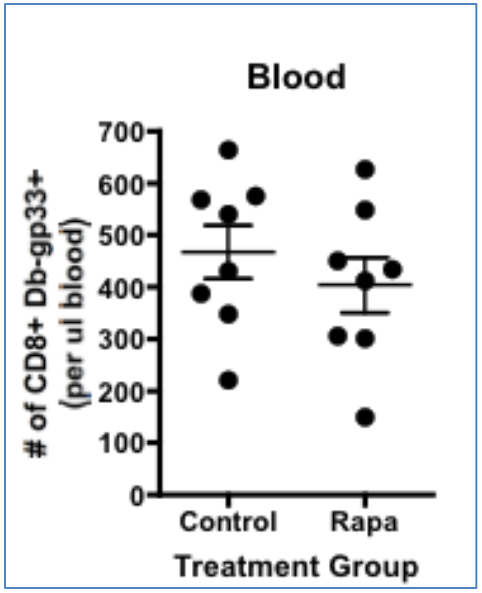


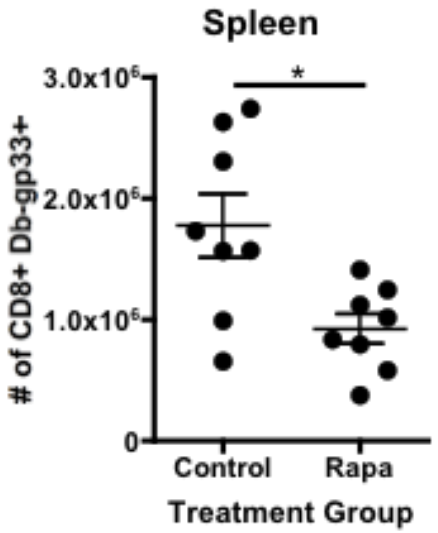
T cell Metabolism: Current Paradigm

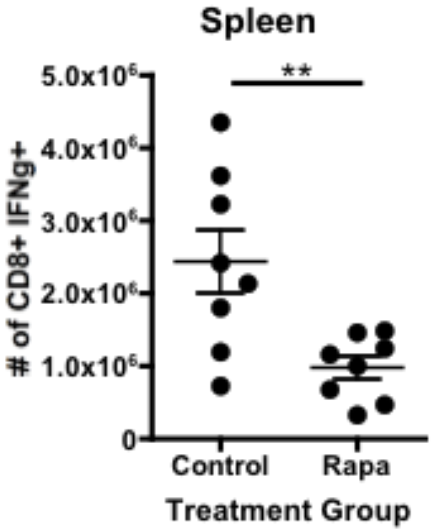


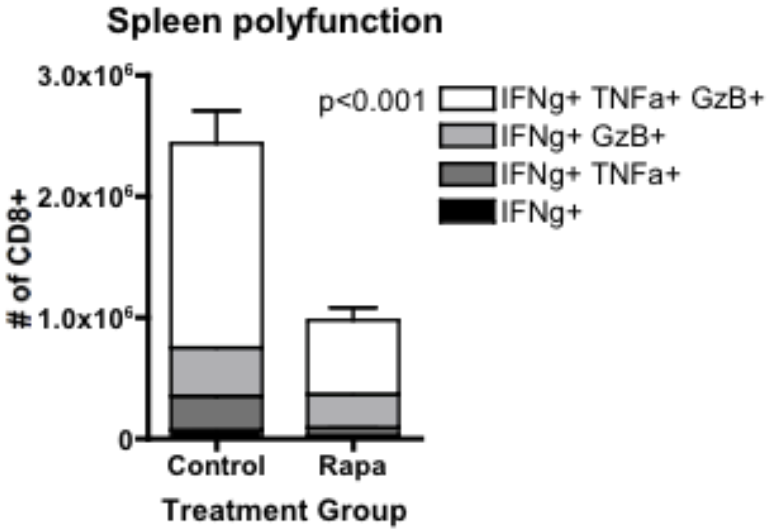
Naive T cells	Effector T cells	Central Memory T cells
Oxidative Phosphorylation	Glycolytic ATP Production	Oxidative Phosphorylation
Catabolic Metabolism	Anabolic Metabolism	Catabolic Metabolism
Minimal Energy Requirements	Maximal Energy Requirements	Low Energy Requirements

Day 8 LCMV CD8 T cell function is impaired by rapa treatment during LCMV infection

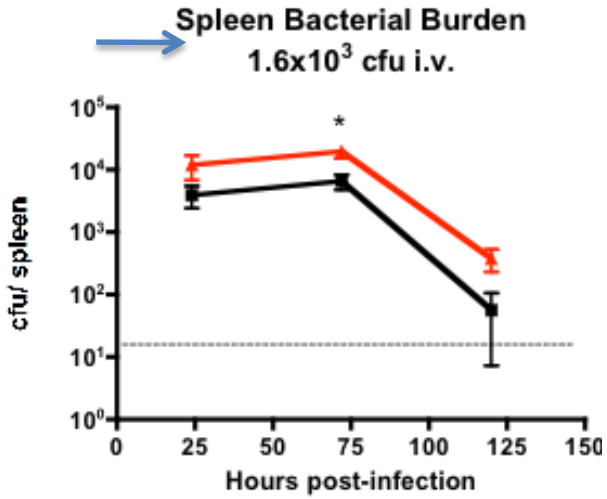


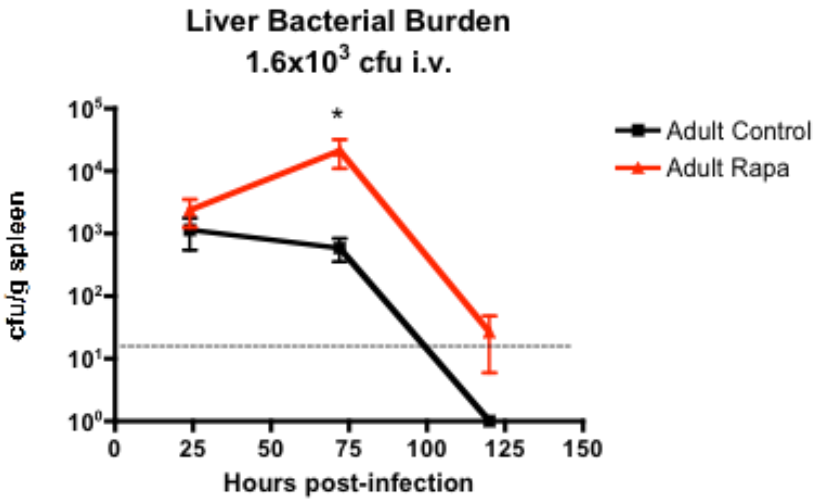


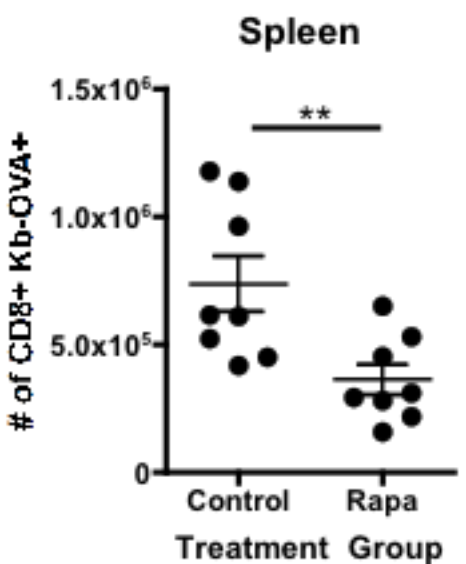


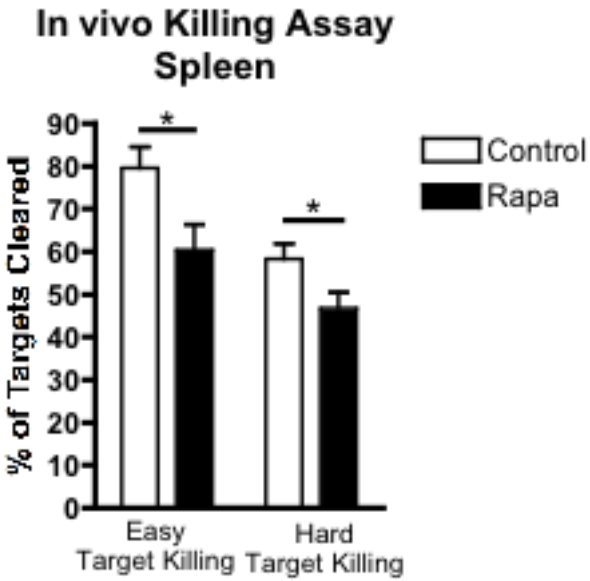


Rapa impairs both innate and adaptive immune responses to L. monocytogenes

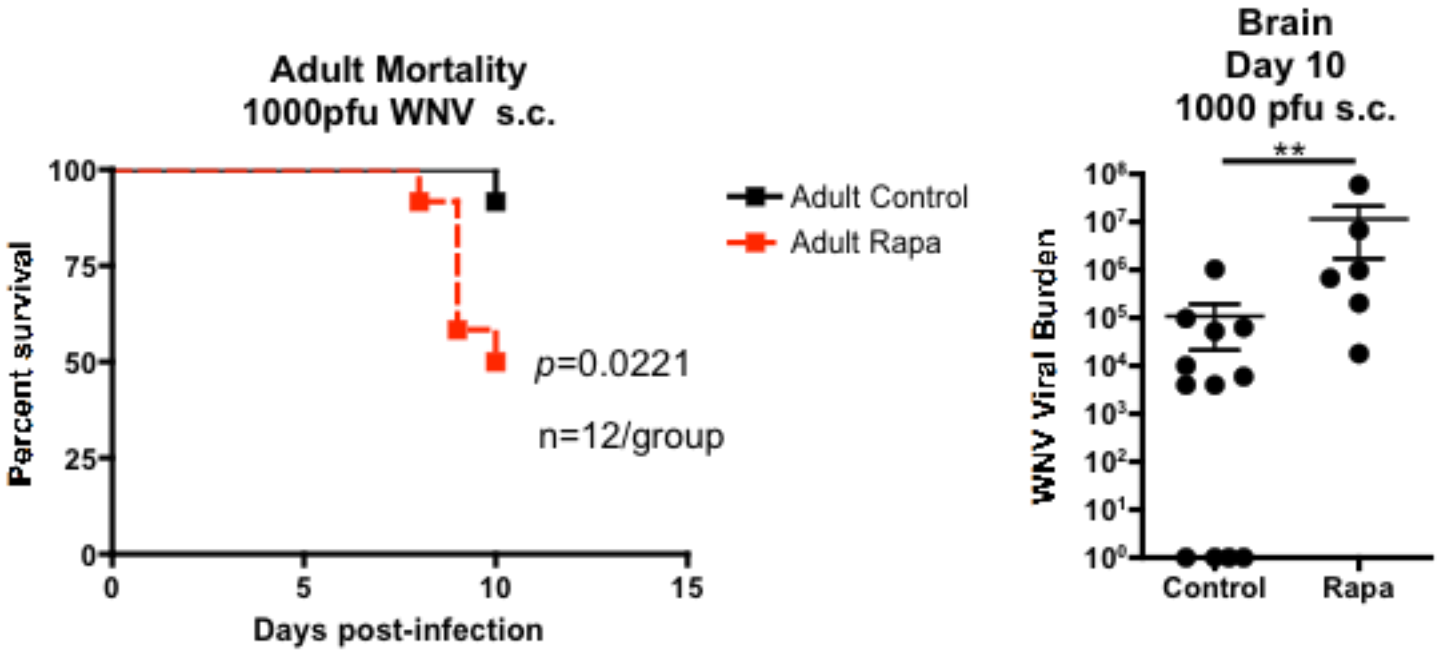








Increased viral titer and mortality in mice treated with rapa during WNV infection



Macrophage vesicle acidification impaired by Rapa.

Goldberg, E. et al., J. Immunol. (2014)

Experimental Design

C57BL/6J

Adult (12 weeks old)
Old (18 months old)
Old CR – since 2 months of age

± Rapa, n=8/group

Rapamycin 75μg/kg

Days: -2 0 7 8 40 45 50

Primary CD8 T cell response

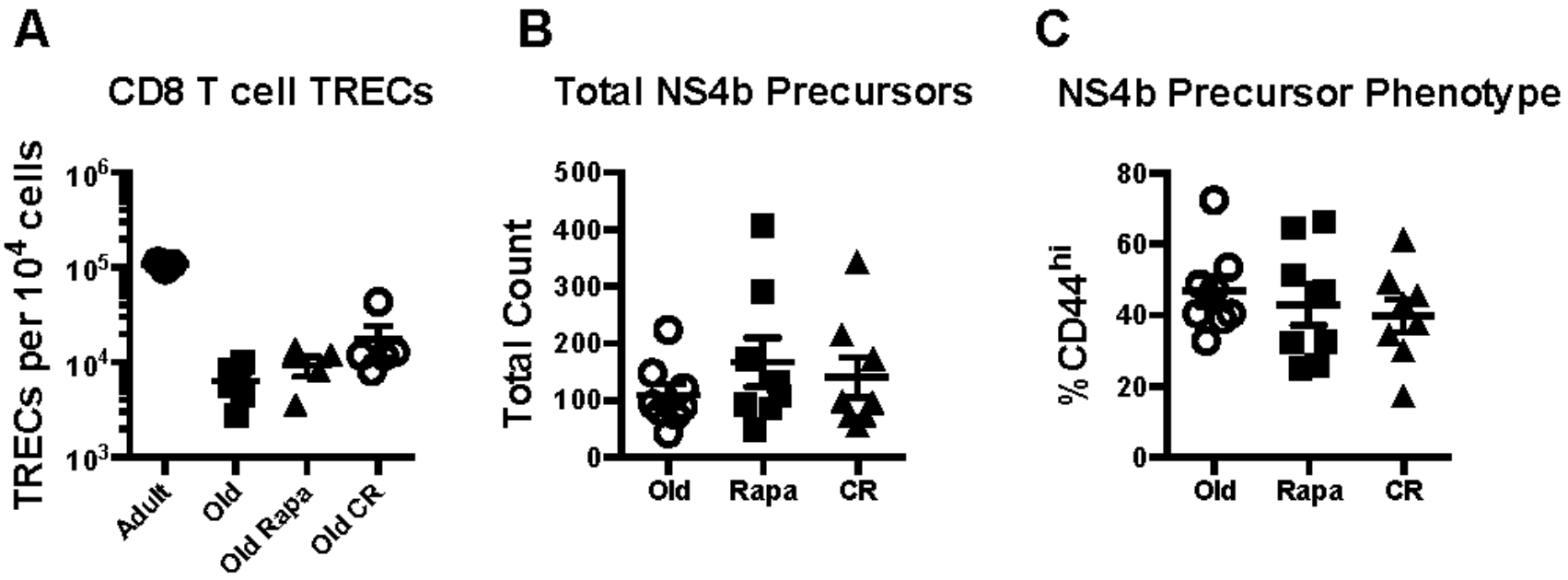
Memory Bleed

Memory CD8 T cell response

Lm-OVA infection
10^3 cfu/mouse

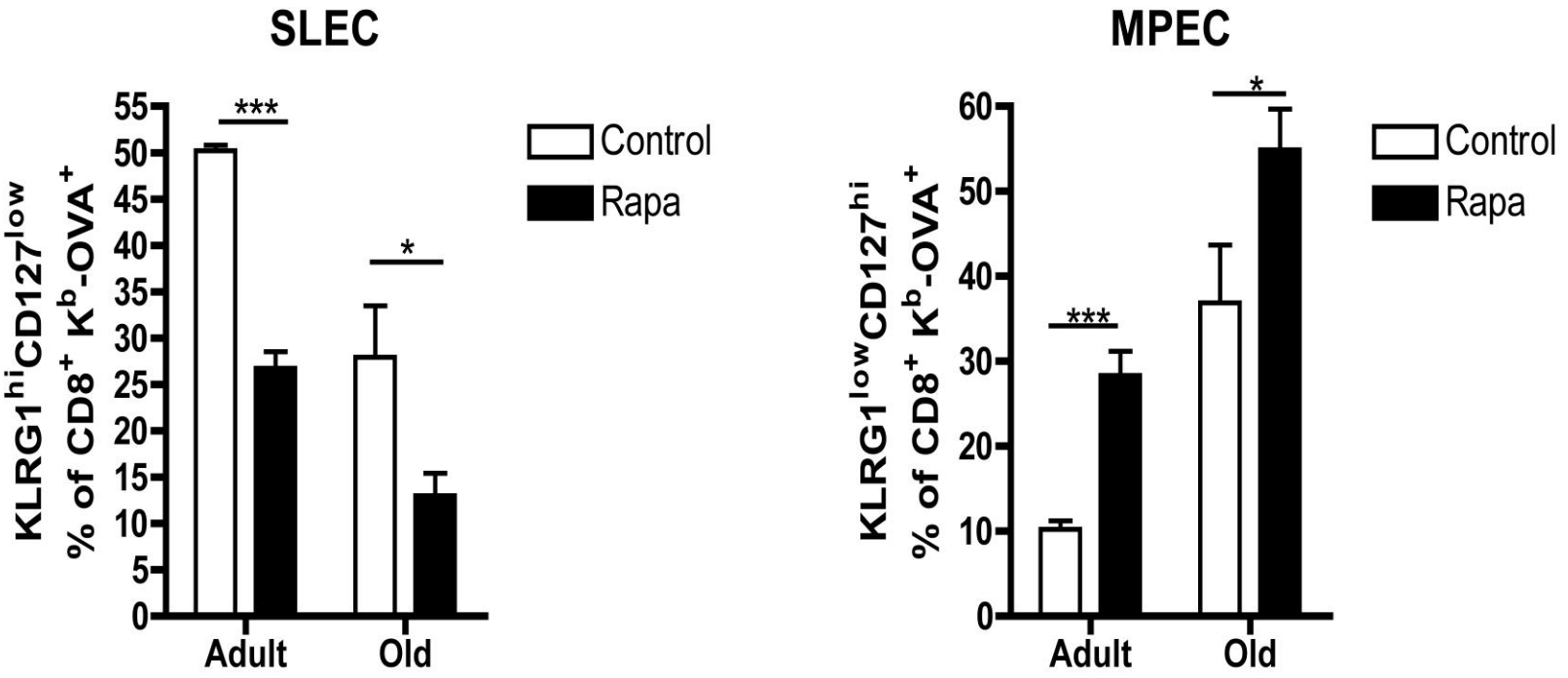
Lm-OVA challenge
10^5 cfu/mouse

Rapa and CR impact on peripheral T cell subsets



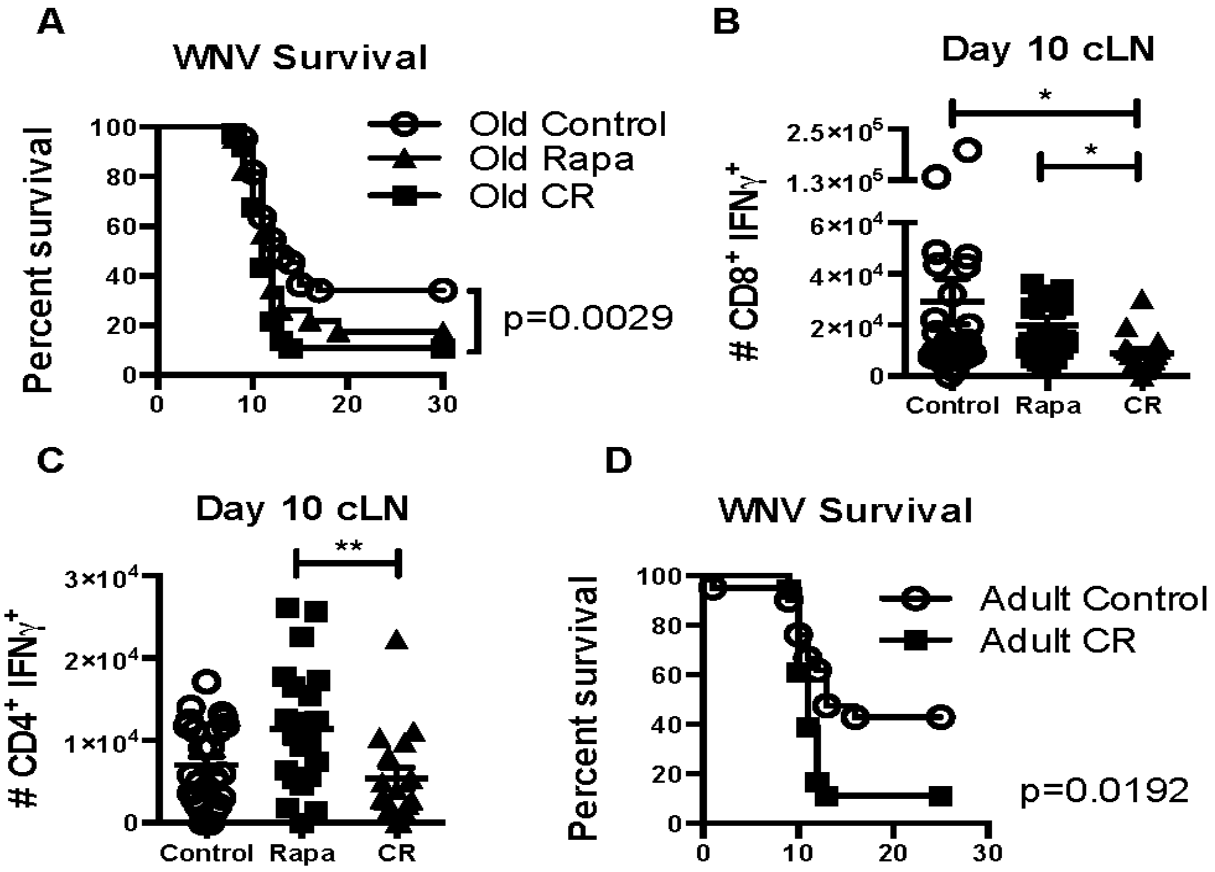
NEITHER RAPA nor CR HAVE ANY EFFECT ON PERIPHERAL NAÏVE T CELL COMPARTMENT (as judged by cell #, sj-TRECs or numbers or phenotype of of Ag-specific precursors

Rapamycin decreases SLEC differentiation and increases MPEC differentiation



D7, Listeria-OVA infection

Rapa and CR impact on immune defense



* $p<0.05$
** $p<0.01$

Conclusions

- Both low-dose rapamycin and CR treatment inhibit CD8 T cell effector differentiation
- Rapa treatment during T cell priming did not alter CD8 T cell survival into memory phase or the memory response (not shown)
- CR and Rapa show deleterious effects in both adult and old mice upon defense against infection. Potential beneficial effects on CD8 T cell memory formation likely come at the cost of effector differentiation
- Rapamycin may not be a suitable candidate for extending healthspan. Better rapalogues and/or alternative discrete treatments may need to be designed to achieve healthspan extension.

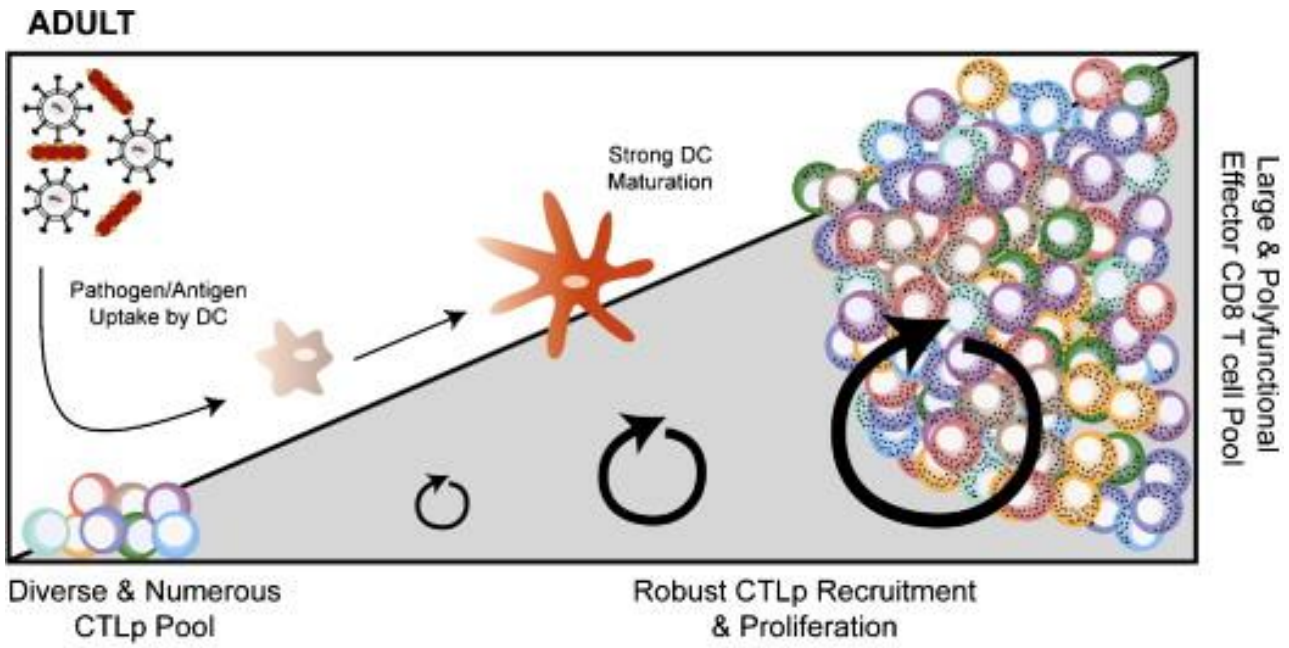
How we think about aging [immune (T cell)]?

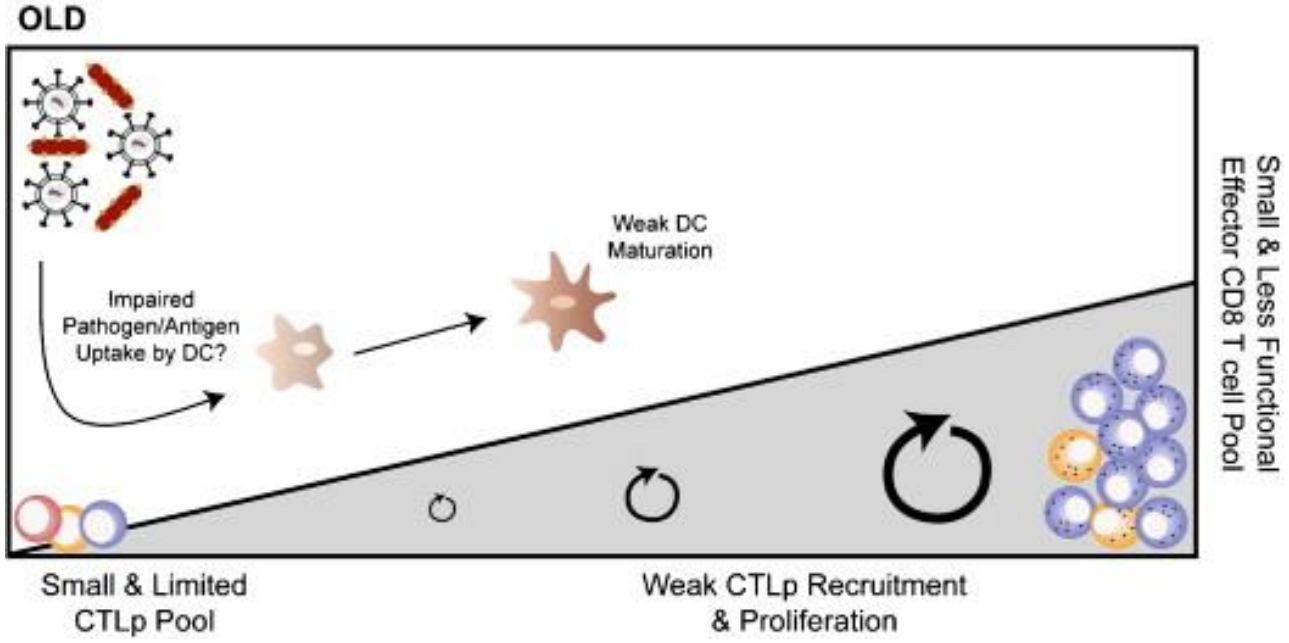
A. Molecules, cells, processes (subcellular or cellular) numerically reduced, slower, inefficient (quantitative changes, but over time can give rise to qualitative changes too)

B. Molecules, cells, processes (subcellular or cellular) damaged due to age-related alterations (qualitative changes; but can give rise to quantitative changes as well).

C. Conceptual change(s) in rules that govern (immune system) maintenance and function.

Is #C correct and if yes, who are the rule breakers?





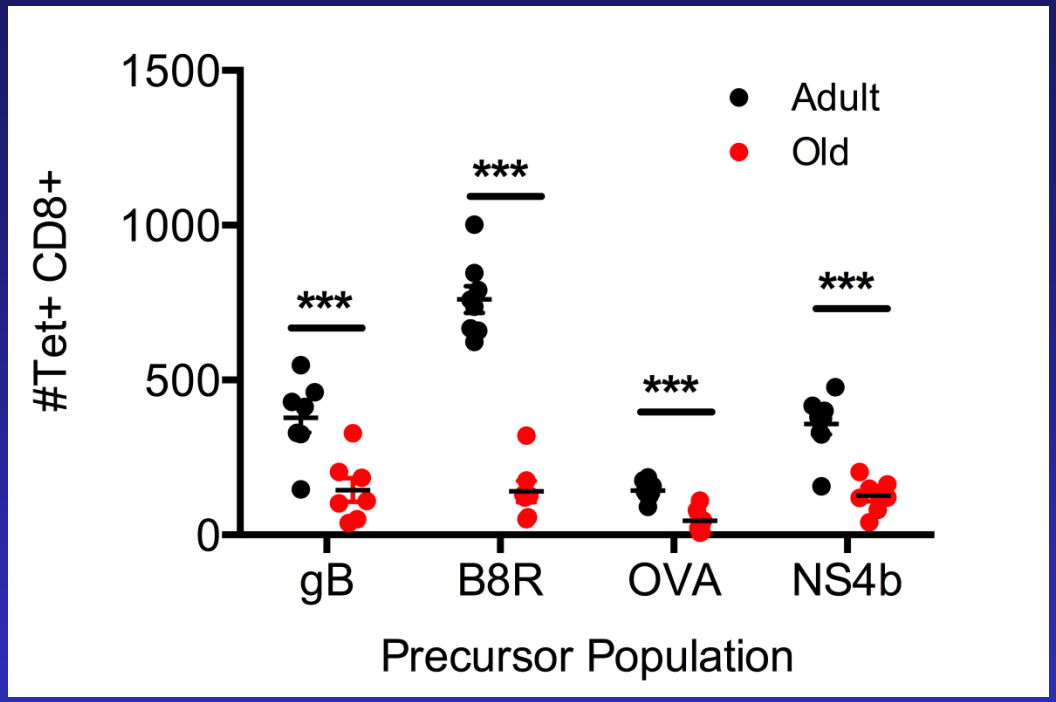
Fewer CD8+ Effector cells

Make less IFNγ, TNFα, killing molecules

Fewer cells are multifunctional (e.g. make 2 or 3 effector molecules)

Nikolich-Zugich J, et al. 2012. *Seminars in Immuol*

Loss of CD8 T cell precursors with age



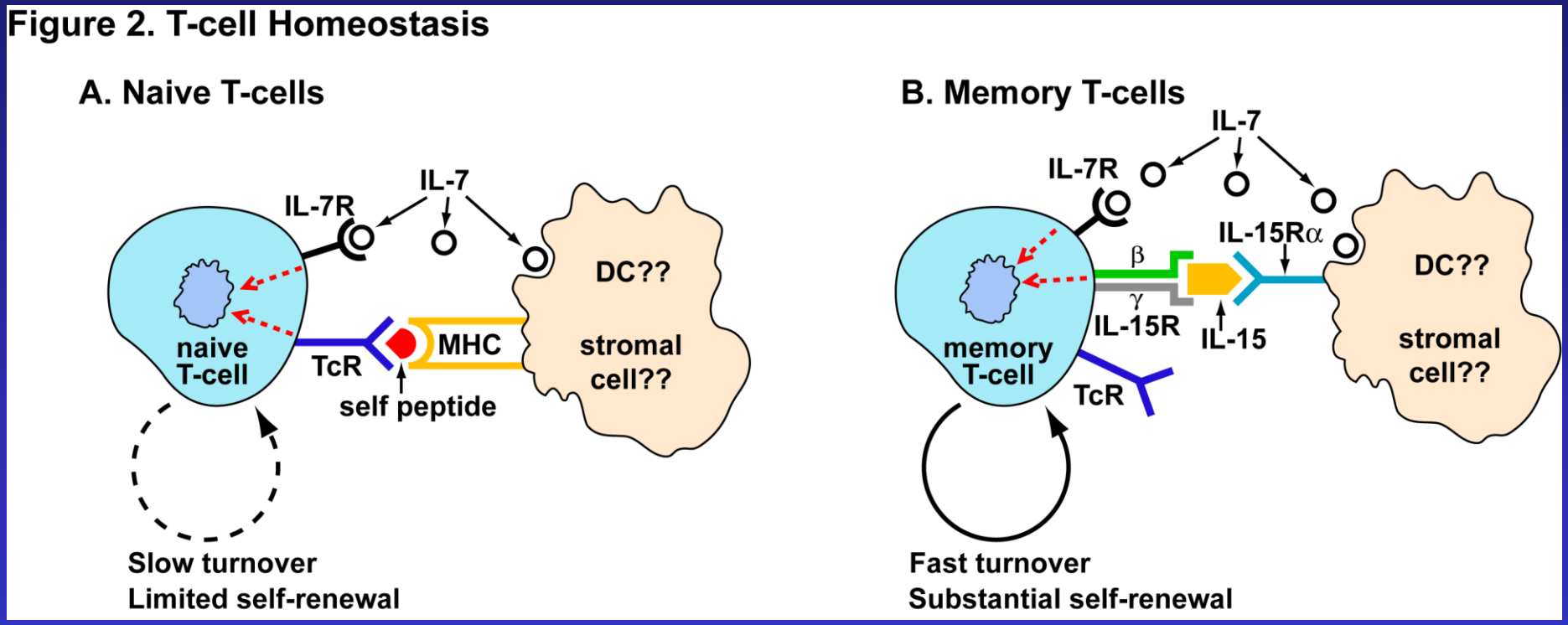
Tetramer Enrichment
Adult and Old B6

***p<0.001

	Adult Avg. #	Old Avg. #	%Loss with age
gB	379	145	62%
B8R	760	140	82%
OVA	143	45	68%
NS4b	358	126	65%

Renkema KR and Li G, et al. *In preparation*

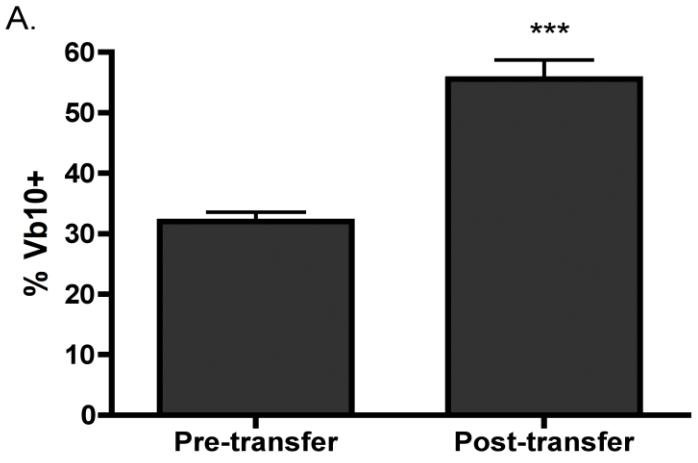
T-cell homeostasis: the ability to maintain optimal balance

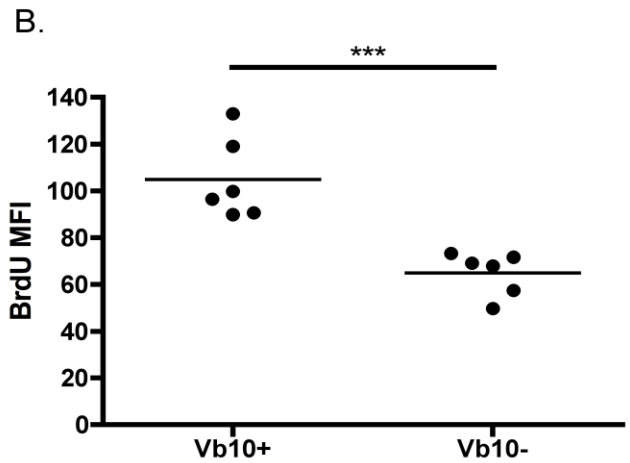


But this fails at some point for naïve T cells during aging…

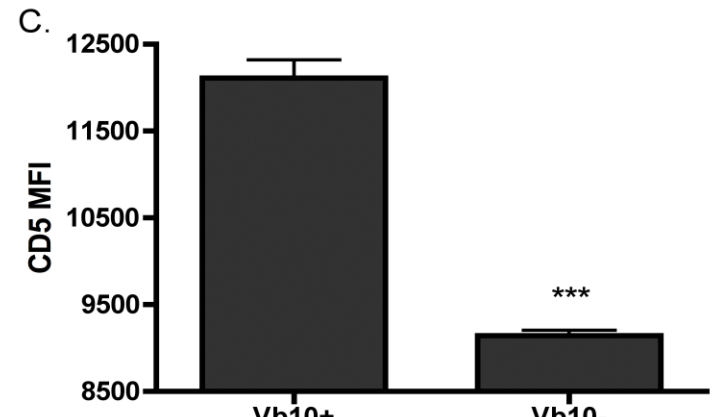
Selection of naïve T cell precursors in old mice

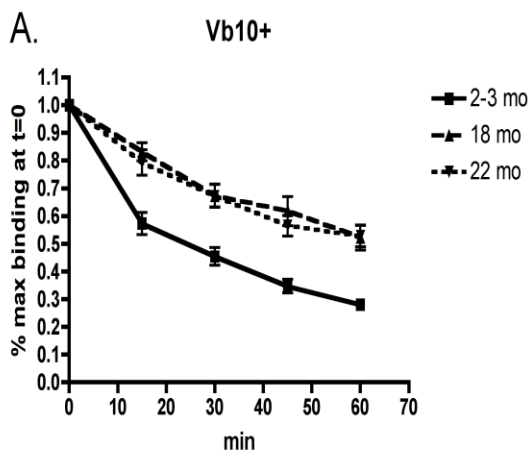
HSV-1 specific CD8 response in B6 mice is focused almost entirely on gB and is dominantly made of TCRVb10+ cells; dominance increases in aging.

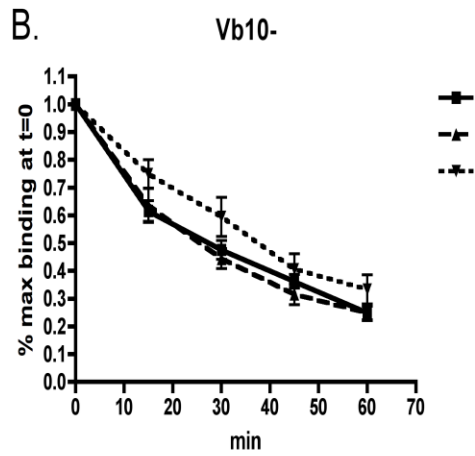




Rudd B.D. et al, PNAS 2011; Renkema K.R. et al. J. Immunol, 2014







Conceptual change(s) in rules that govern immune system maintenance and function.

Naïve CD8+ T cells are strongly selected with aging for the best competitors for trophic maintenance signals (self peptide:MHC ().

Naïve CD4+ T cells do something similar but with different flavors (Deshpande, N.R. et al, eLife, 2015). Both maintenance patterns are consistent with data on deterioration of maintenance areas in lymph nodes.

Neither CD8+ (Renkema et al, 2014) nor CD4+ (Deshpande et al., submitted) naïve old T cells are functionally very robust immune responders (fewer divisions, less differentiation).

Rule breaker #1: “Staying alive, staying alive…”; only the best competitors for weakened maintenance will survive, but may not be the best responders to infection.

CHIKV - Brief Background

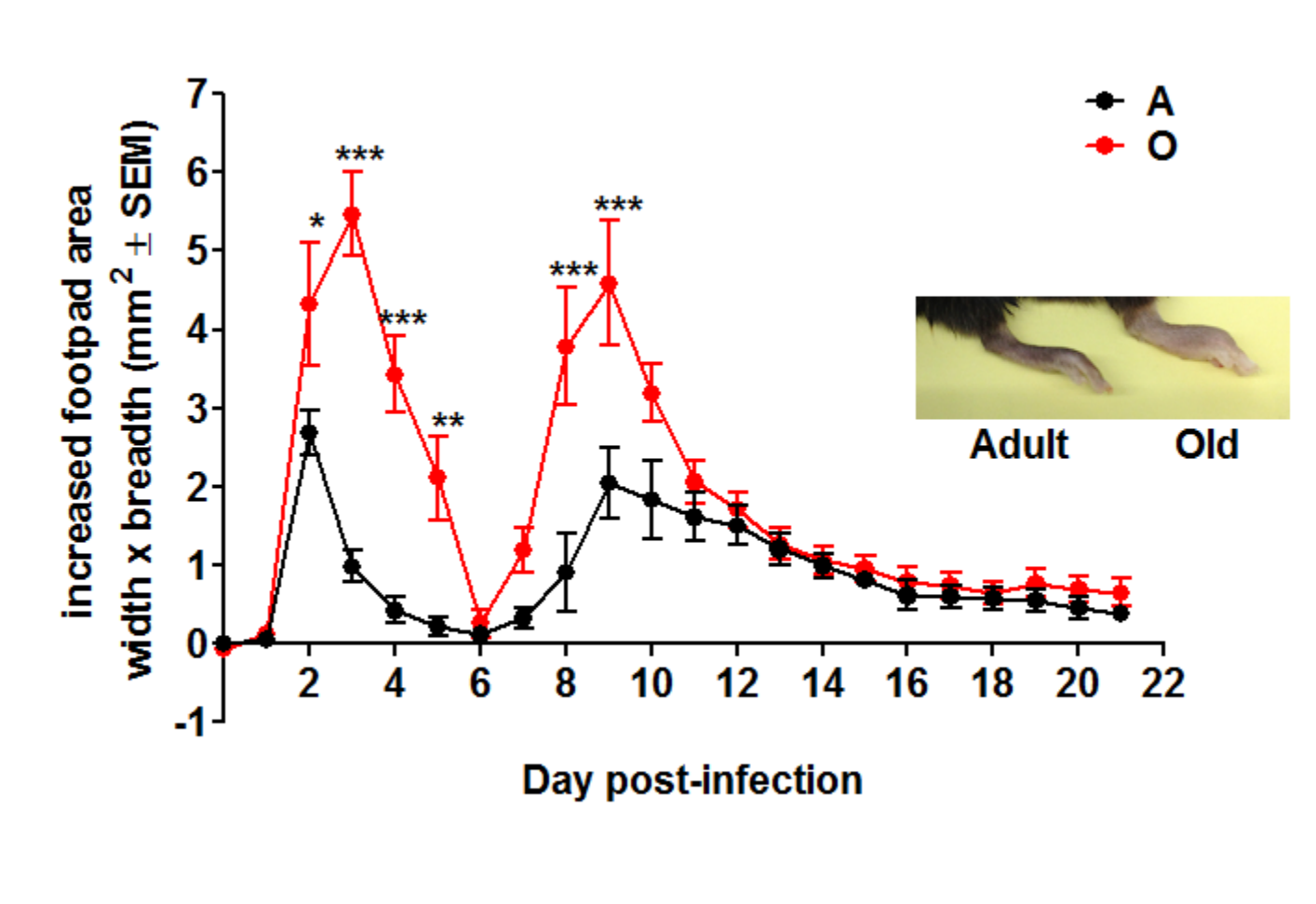
- Isolated in Tanzania, 1953; + ssRNA mosquito-borne alphavirus
- Fever, rash, extreme fatigue + joint pain/swelling that discriminates it from Dengue; no vaccine or antivirals.
- Spread from the Indian Ocean countries to Europe & the Americas
- Outbreaks in tropical areas include 10^5 -10^6 persons, direct transmission person-mosquito-person; viremia up to 10^{12} /ml.
- **Up to 90% of all infected develop chronic disease and 30-45% still exhibit debilitating arthritis 18mo post infection**
- **Older adults show increased severity and longer duration of symptoms, and >95% of all deaths (mortality ~0.1%)**

Distribution of CHIKV: a closer look at the Americas

- Americas: 1.3 million cases to date (4/24/2015)
- United States: 2,500 cases

Source: Pan American Health Organization

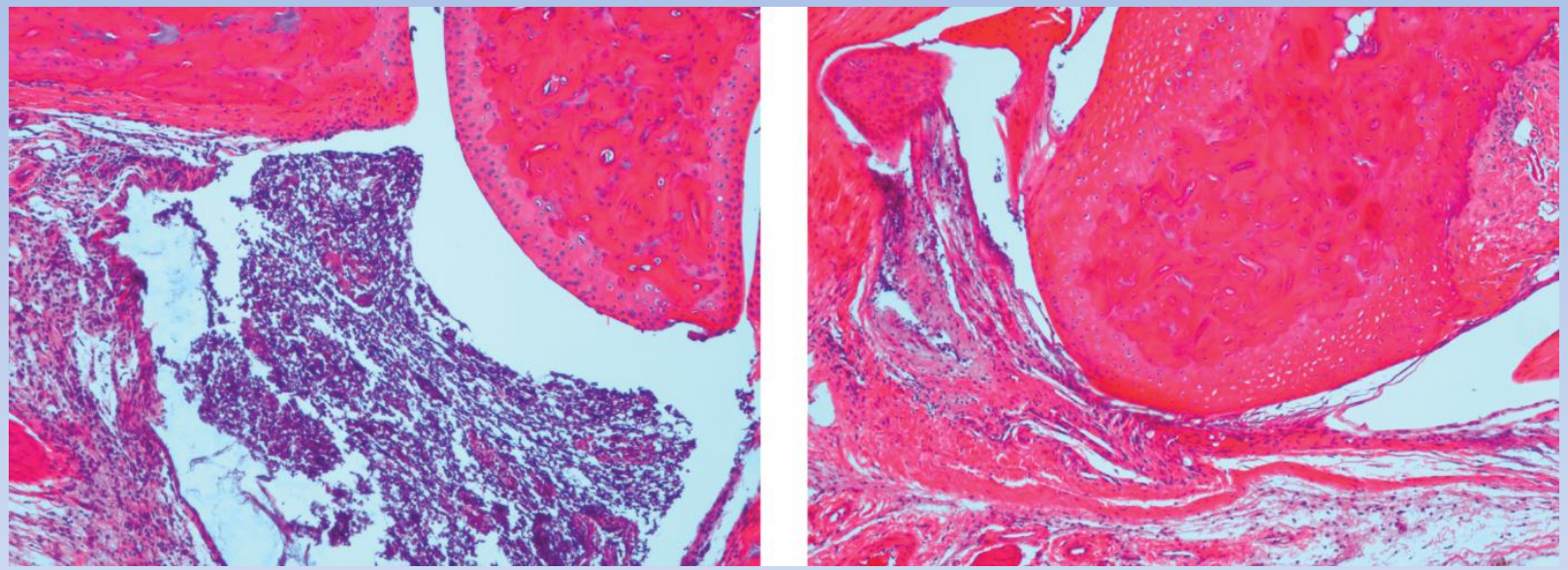
Old mice display increased foot swelling over the acute period of infection



Old mice poorly control the virus – 2-3 log higher viral titers in feet on d 3 & 9; 2-log higher viral RNA copy load on d60.

Lymphocytes poorly infiltrate the joints in old mice

Day 7 post-infection



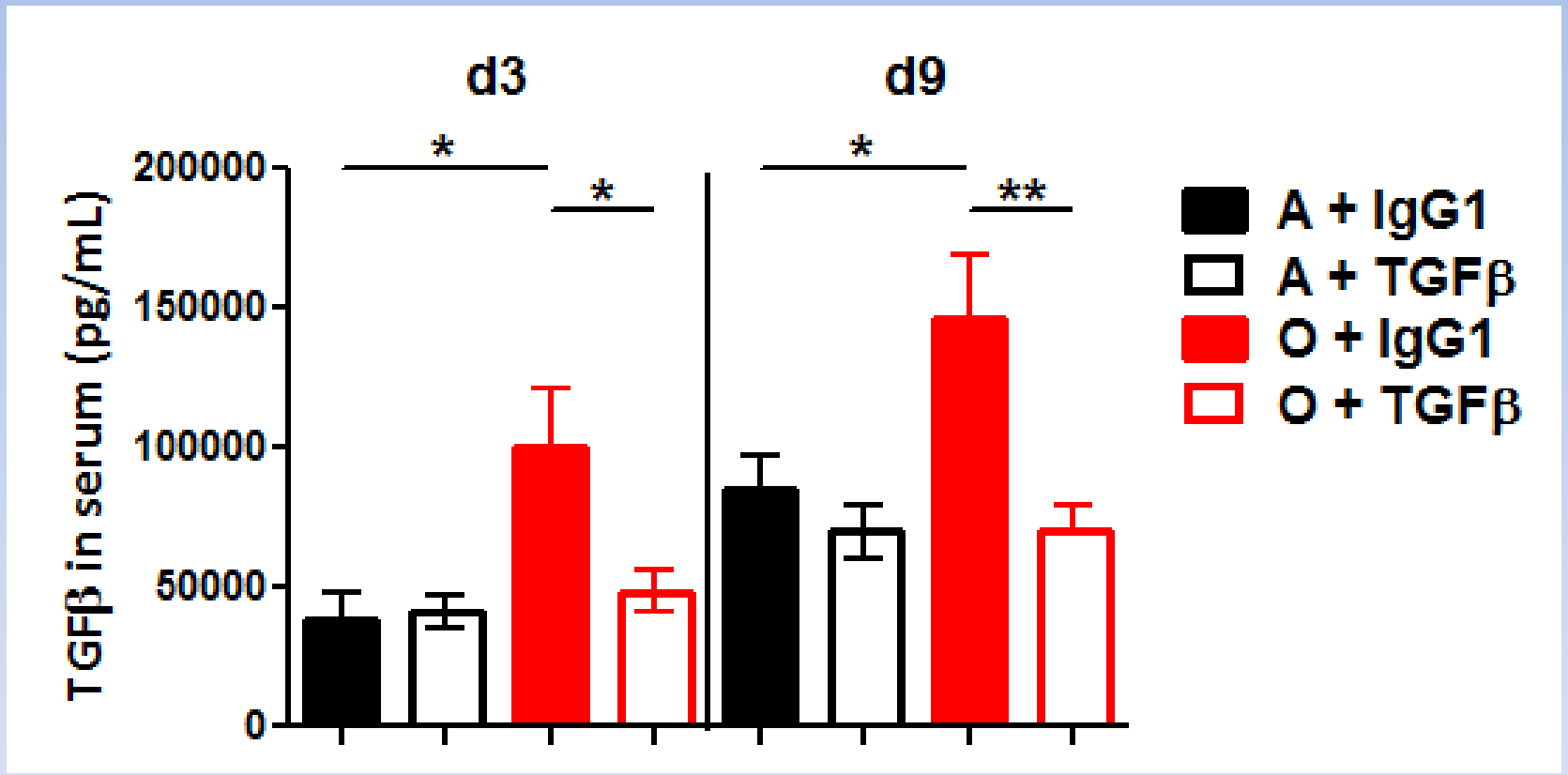
Adult **Old**

- Old mice show significantly reduced CD4 T cell antiviral response and neutralizing antibody response both early and late post infection.
- Old humans show similar antibody defects.

Rule Breaker:

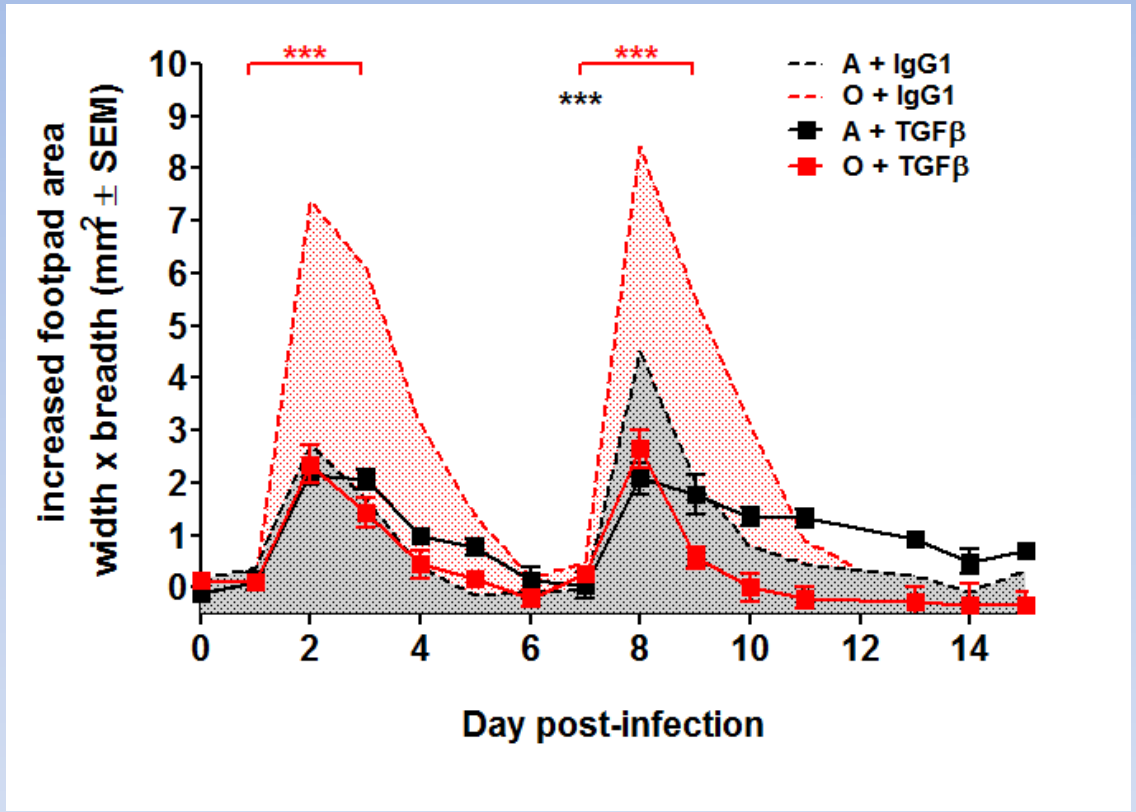
TGFβ

TGFβ is overproduced in old CHIKV-infected mice, can be neutralized in vivo



Humans exposed to CHIKV also show huge spike in TGFβ

TGFβ blockade abrogates excessive pathology in CHIKV-infected old mice



Also reduces excess chronic arthritis in old mice and restores neutralizing Ab production to adult levels

Summary of Rule Breakers (so far……)

- **Rules are broken with aging of the immune system:**

1. Evidence for homeostasis rule breakers : T cell pool maintenance subjected to late Darwinian selection for survival, but not necessarily optimal function.

2. Evidence for acute infection rule breakers: TGFβ dysregulation delays CHIKV clearance (at least in part by misdirecting adaptive T and B cell responses) and promotes chronic CHIKV disease.

3. Evidence for persistent microbiome/virome rule breakers: Cytomegalovirus changes the T cell repertoire mobilized in response to a different acute infection.