

Biology of Immune Senescence

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Today's Menu

- **5 minutes on what everyone agrees on**
- **5 minutes on controversies**
- **5 minutes on what we've been doing**

Consensus (95% Confidence)

- **Protective immunity drops with age**
 - Poor priming to new antigens
 - Poor recall of old antigens
 - Poor affinity maturation; poor IgG
- **T cell defects easy to see in vitro or in vivo**
- **B cell defects subtler, and often 2° to T Cells**
- **Accessory cells usually ok**
 - [Except follicular dendritic story]
- **Autoantibodies but not autoimmune disease**

Consensus: T Cells

- **T cell problems: poor IL-2, poor proliferation**
- **Later cytokines (IL-4, IFN): premature consensus**
 - Most say IL-4 up; I would not bet on this
- **T cell subsets**
 - CD4 vs CD8 -- small changes if any
 - Naïve down; memory up
- **Thymic involution**
 - Yes, but can that be all?

Consensus: Heterochronic Transplantation

- **Young cells in old bodies do fine (T,B)**
- **Old cells in young bodies stay not-fine**
- **Young marrow (plus infant thymus) restores immunity in old recipient**
- **Old marrow (plus infant thymus) restores, but only for a while**
- **Humans: reconstitution problems in recipients older than ~10 - 15 years**

Controversies (I): T Cell Microclones

- **Not controversial: present in aged mice and humans**
- **Unresolved questions:**
 - Where do they come from?
 - Why don't they stop proliferating?
 - Is it 1% or 10% or 80%?
 - Do they have functional consequences?

Controversies II: Telomeres

- **Telomeres in blood cells are shorter in old than in young people.**

But:

- **No evidence that clonal senescence occurs in old humans, let alone in T cells from old humans**
- **Naïve cells show age decline, despite longish telomeres**
- **Mice have long telomeres and senesce just fine.**

Controversies III: Antigen Presenting Cells

- **Inflammatory cytokines: in vitro data a ghastly rotten tangled horrible mess**
- **Serum data only slightly better**
 - **Example: IL-6 increases mostly in studies for which it is the primary focus**

Controversies IV: NK Cells

- **Problem: could age change in NK contribute to late life disease?**
- **Mouse: clear loss with age**
- **Human: very small (if any) change**

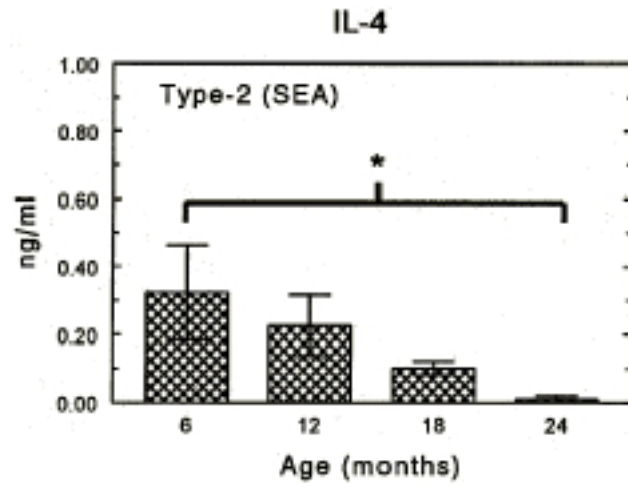
NK Cells in Human Spleen: Place Your Bets

	Spleen	Blood
Mouse	Down	[No change]
Human	??	No change

Controversy V: Do Type II cytokines (IL4, IL5, etc) go up or down with age?

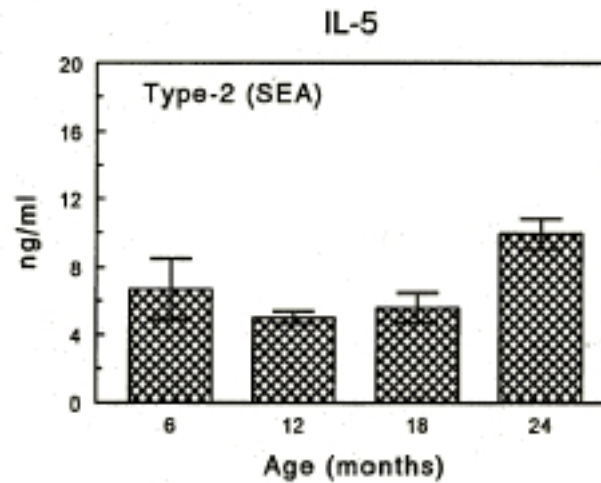
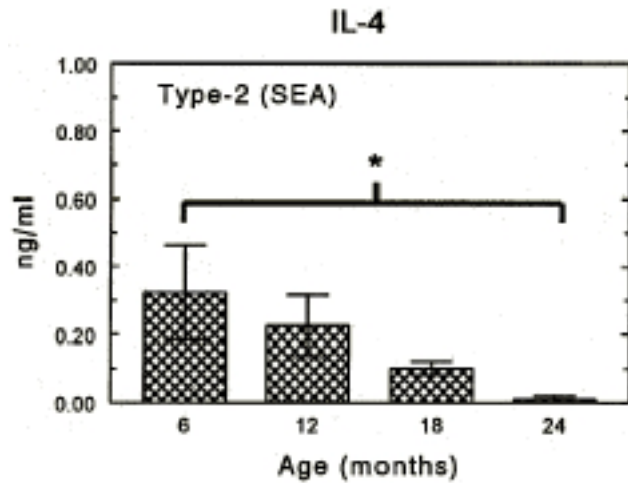
Type II Cytokines: In Vivo Veritas

[Chiu, Chensue et al., 2002]



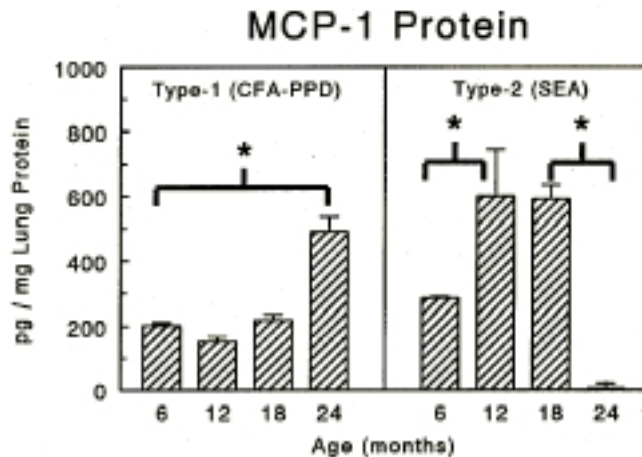
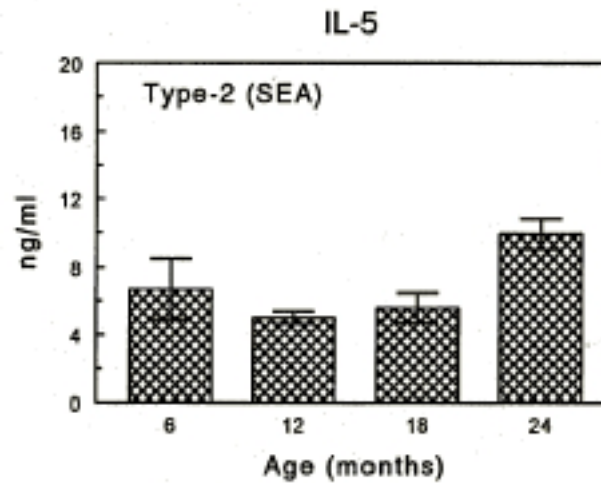
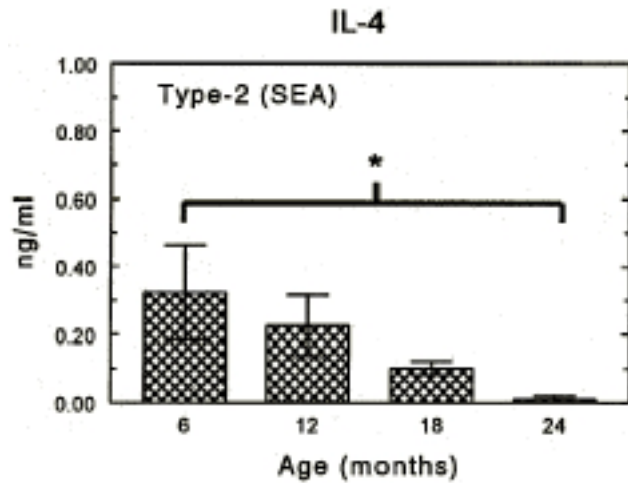
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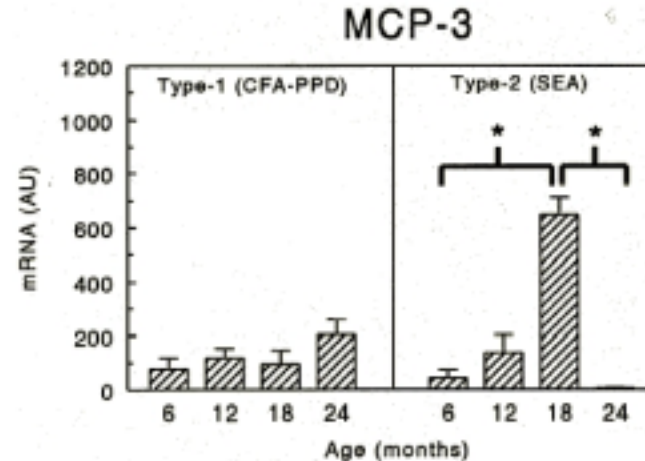
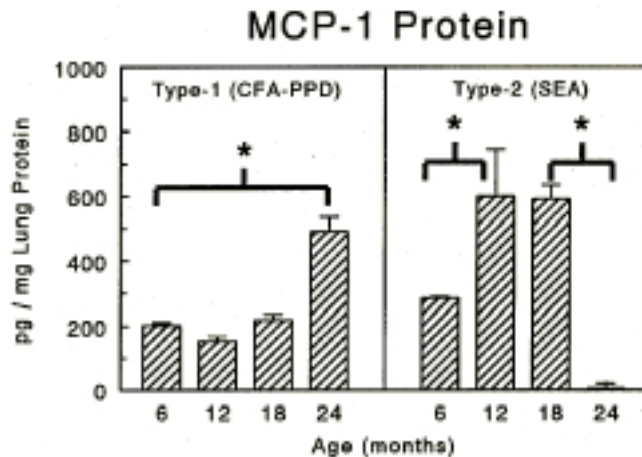
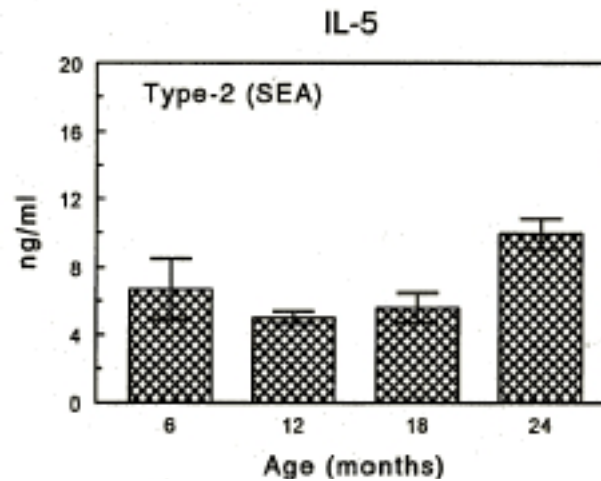
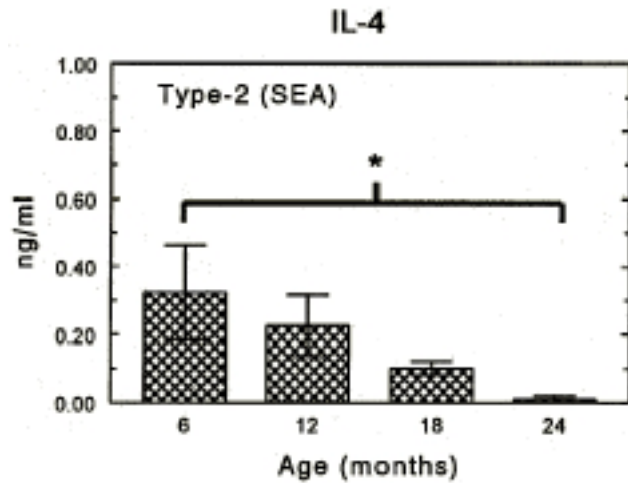
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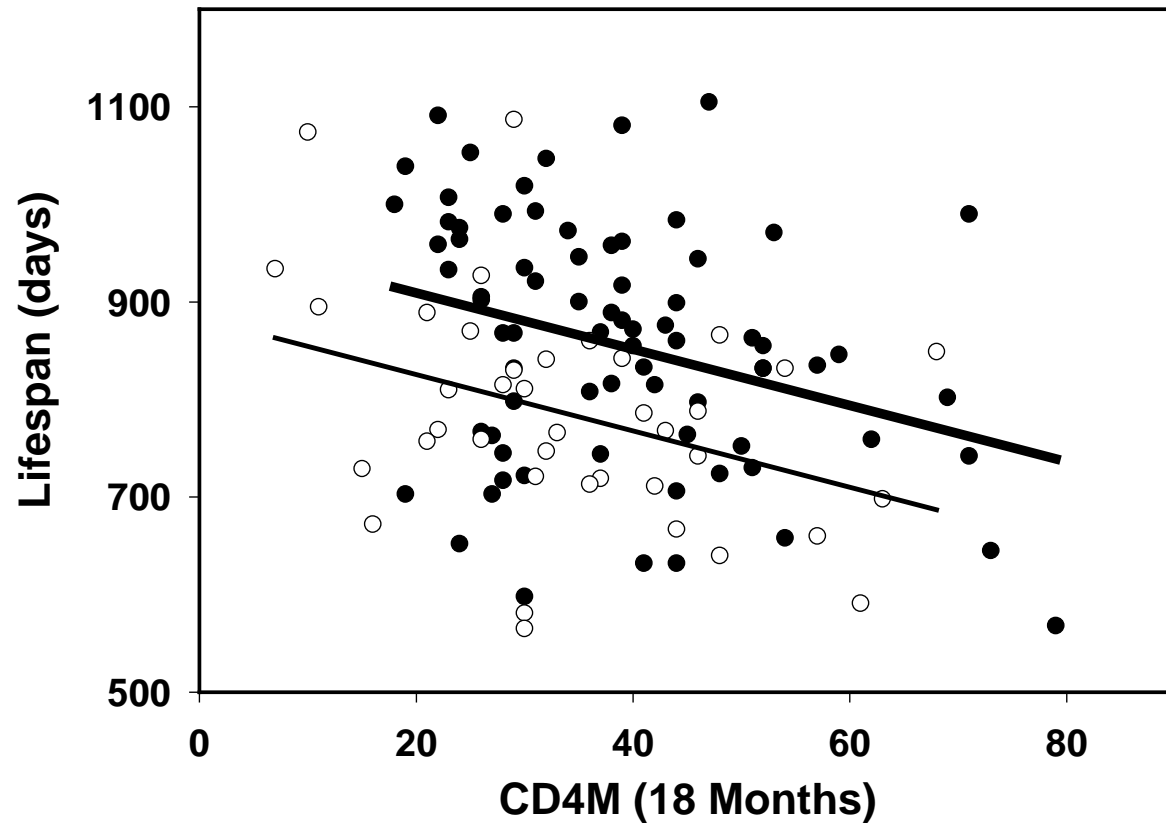
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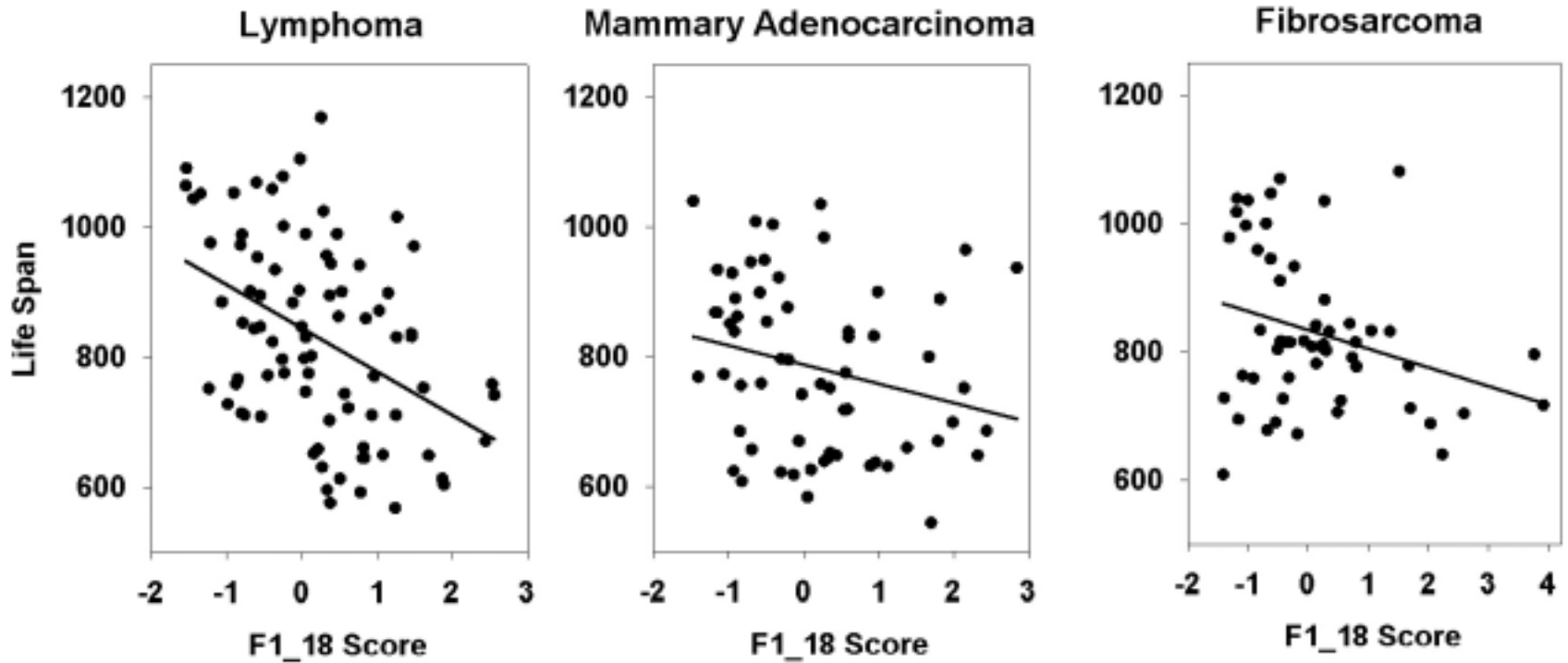
Local Knowledge: News from Ann Arbor

- **Gerontology: Immune biomarkers of aging**
- **Genetics: Genes for immune aging**
- **Mutant mice with slow immune aging**
- **Biochemistry: Why T cells don't respond**

Memory CD4 Cells Predict Future Longevity in Middle-Aged Mice



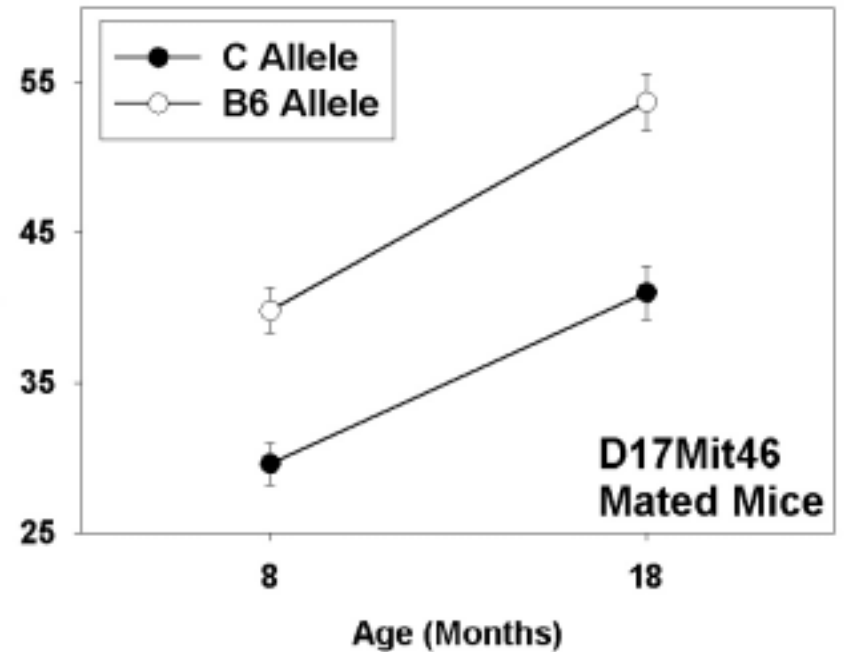
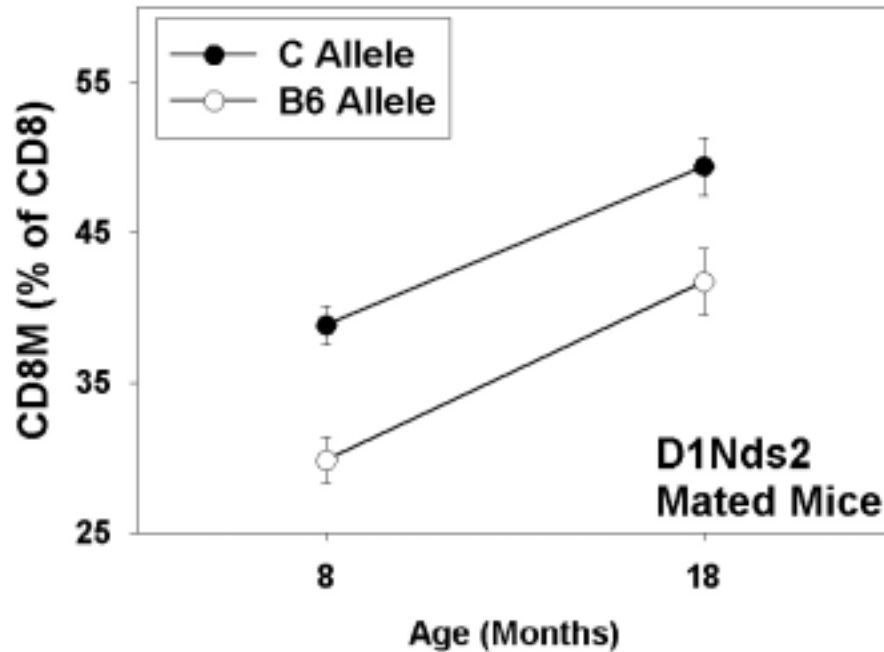
Immune Score (At 18 Months) Predicts Longevity for Three Major Causes of Death



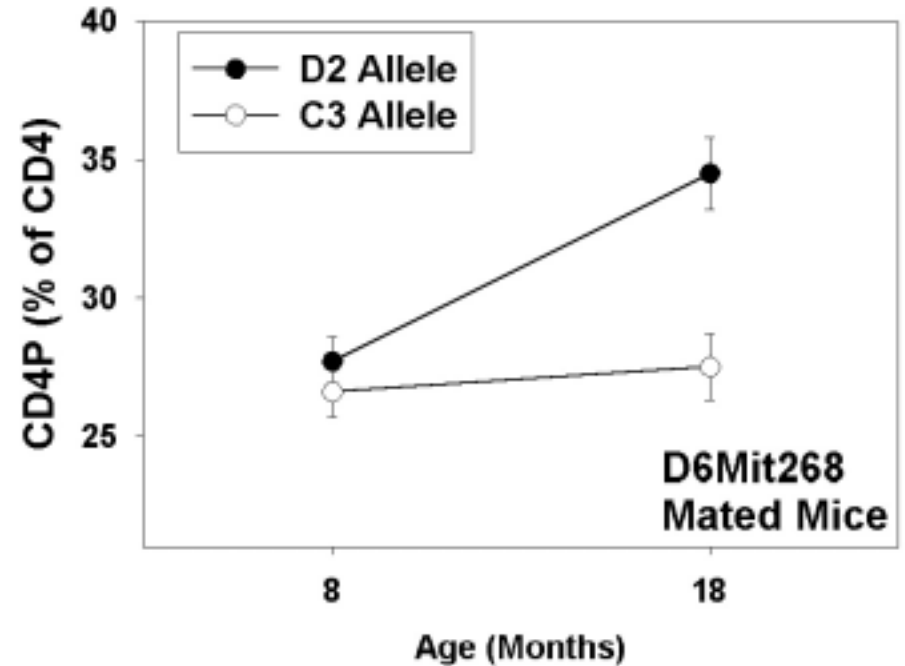
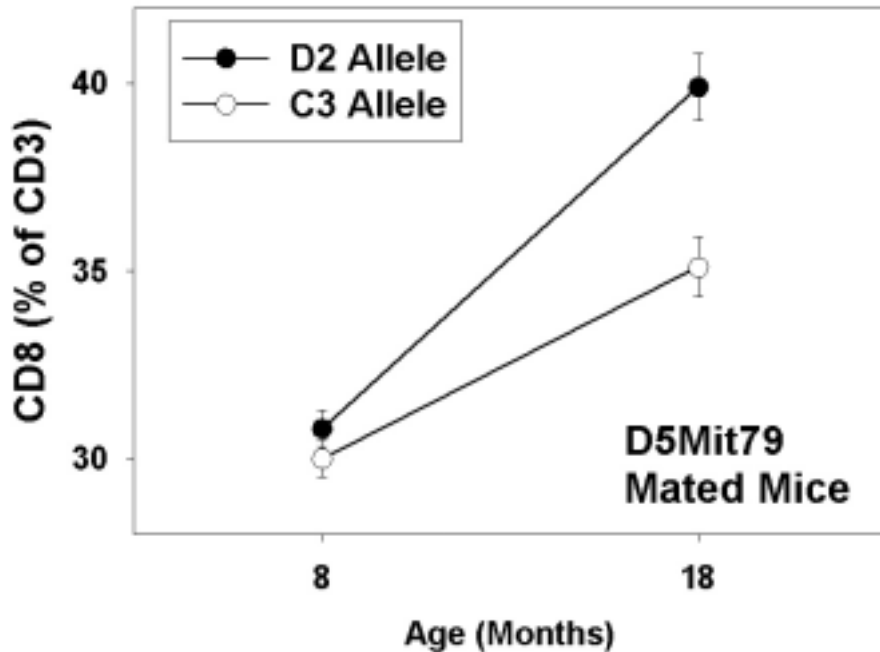
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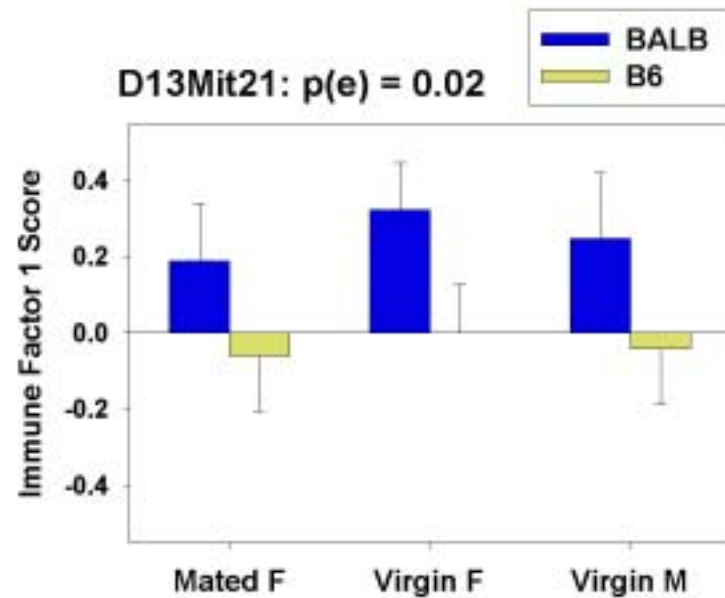
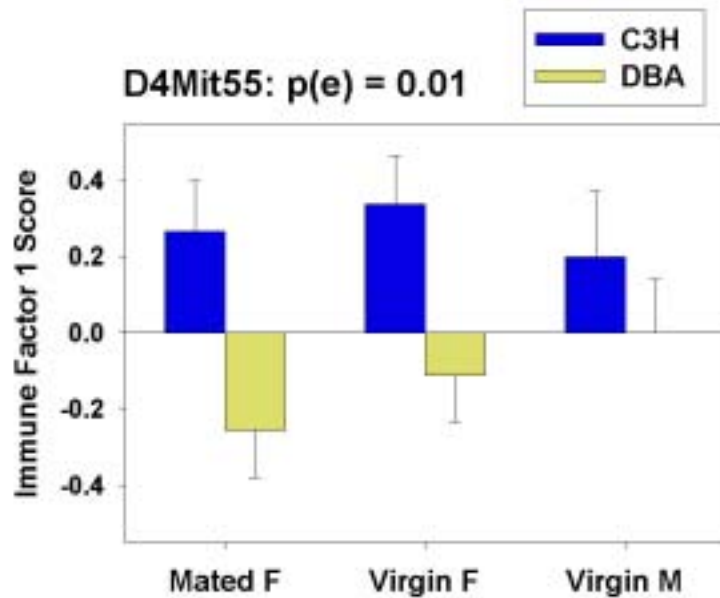
Genes With Stable Effects on Age-Sensitive T Subsets



Genes With Delayed Effects on Age-Sensitive T Subsets

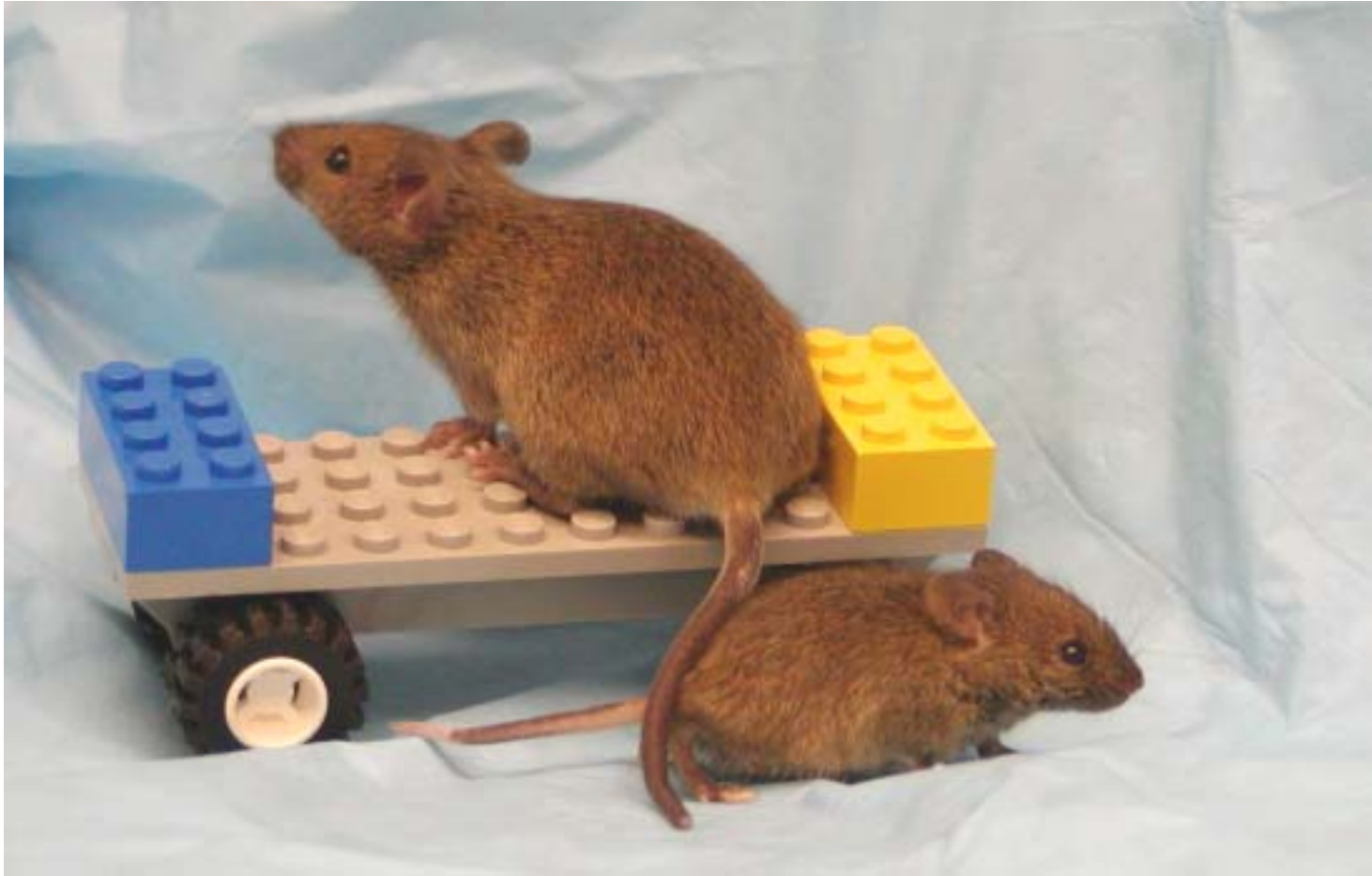


Two QTL That Regulate Immune Factor 1 in 18 Month Old Mice

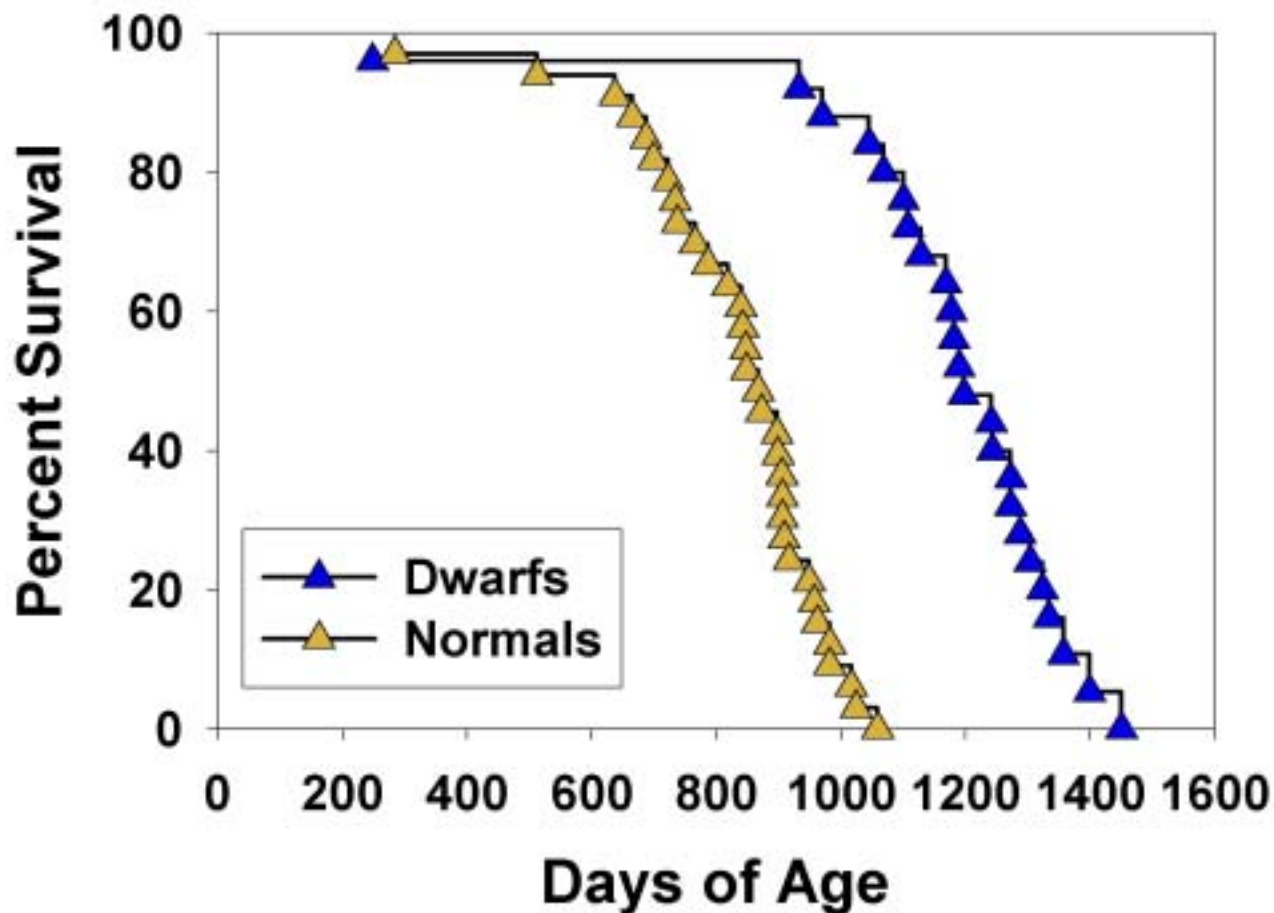


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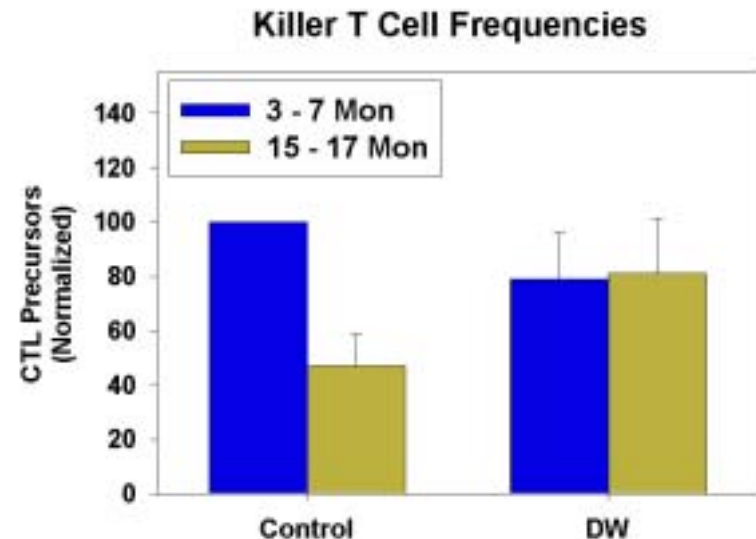
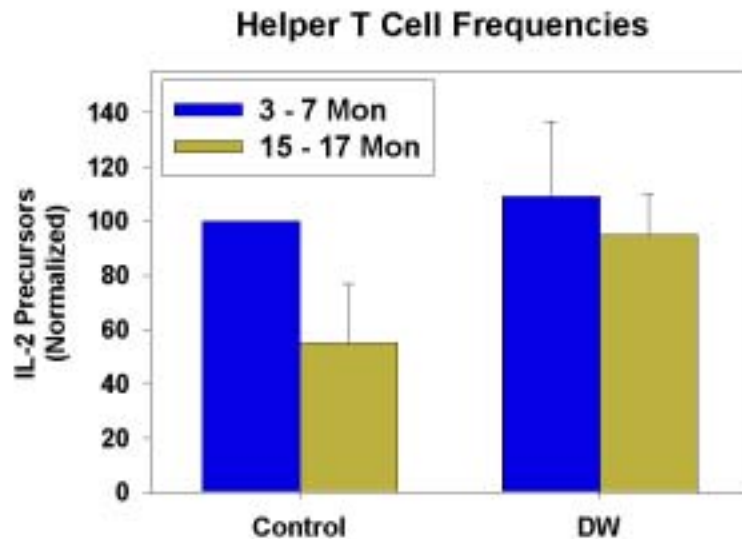
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Snell Dwarf Mice Live 40% Longer Than Their Normal Size Sibs



Preservation of T Cell Function in Aging Snell Dwarf (dw/dw) Mice



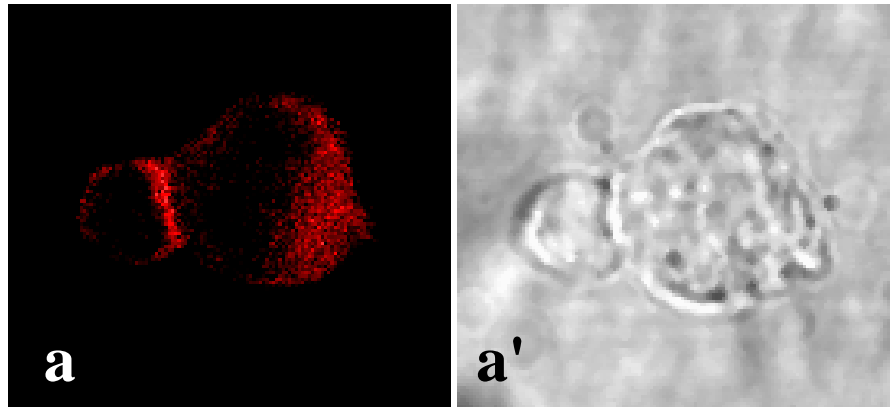
[Flurkey, Miller, Harrison]

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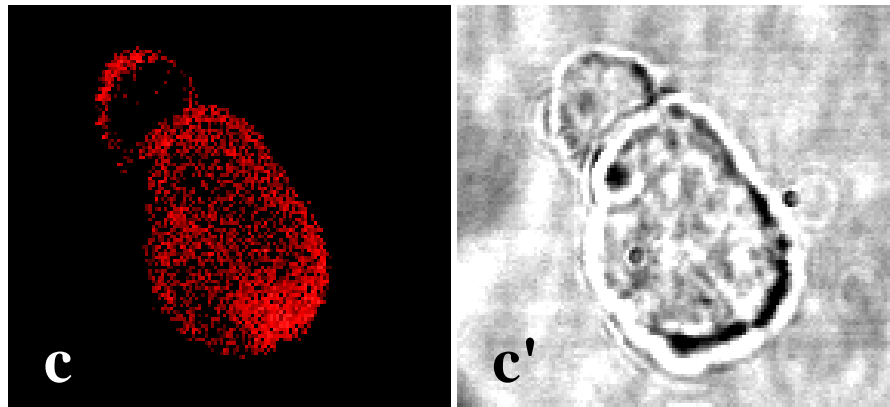
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Some, but not all, T Cells form synapses with antigen-presenting cells

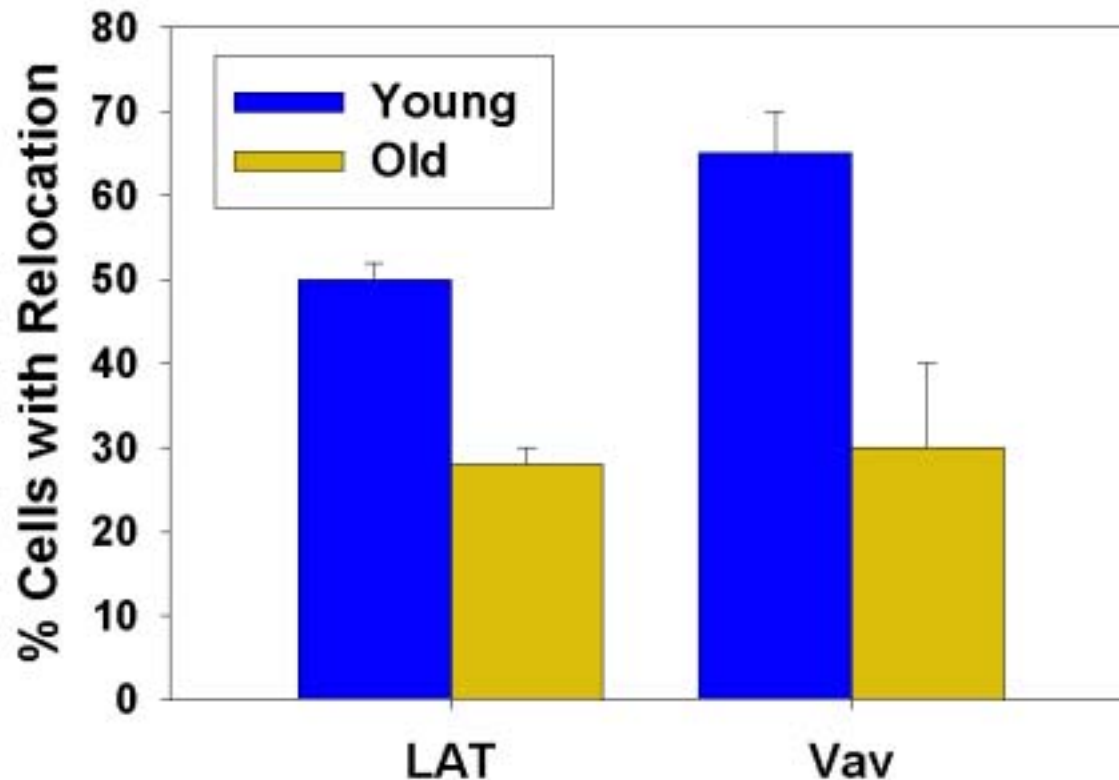
Responder cell:



Non responder:



The Proportion of T Cells Able to Form Synapses Drops With Aging



T Cell Activation: Recent Updates

- The defect in T cell activation involves a very early step (prior to recognition of antigen)
- The defect involves altered affiliation of T cell receptor molecules to cytoskeleton
- The defect can be overcome by alterations of bulky T cell surface proteins

Garcia and Miller, unpublished

Credits

- **Genetics: David Burke, Andrzej Galecki, Anne Jackson**
- **Dwarf mice: Kevin Flurkey, David Harrison**
- **T cell activation: Gonzalo Garcia, Ami Tamir, Mike Eisenbraun**

- **Money: National Institute on Aging**
 - **Also Ann Arbor DVA Medical Center**