# Biology of Immune Senescence

**Rich Miller**
**University of Michigan**
**ICEID, March, 2002**

# 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 $2^o$ 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**

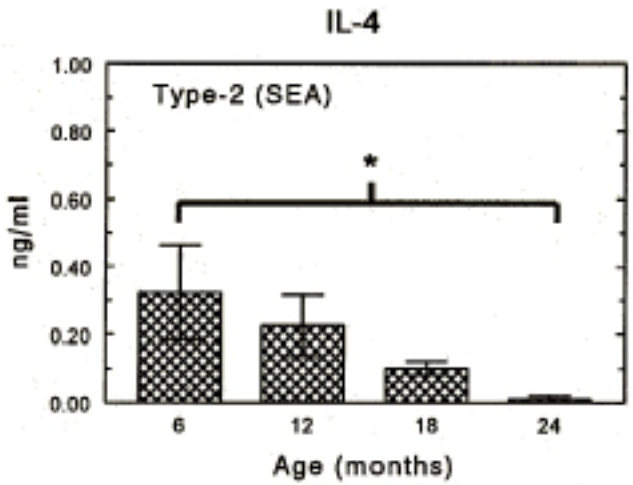
# NK Cells in Human Spleen: Place Your Bets

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

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

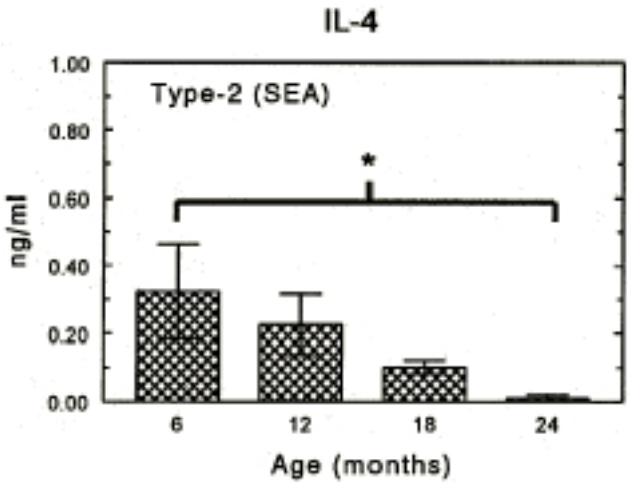
# Type II Cytokines: In Vivo Veritas

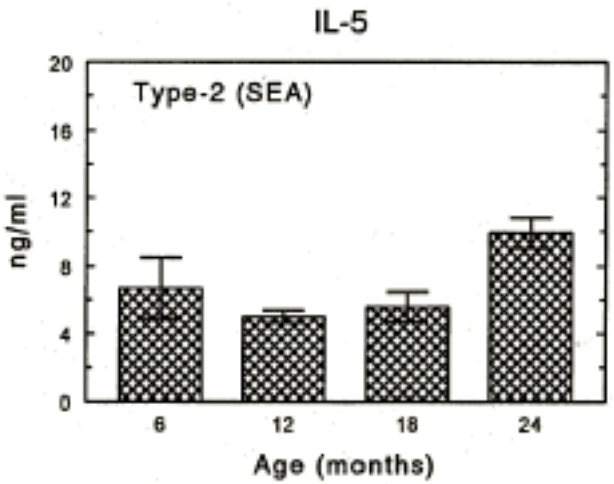
**[Chiu, Chensue et al., 2002]**



# Type II Cytokines: In Vivo Veritas

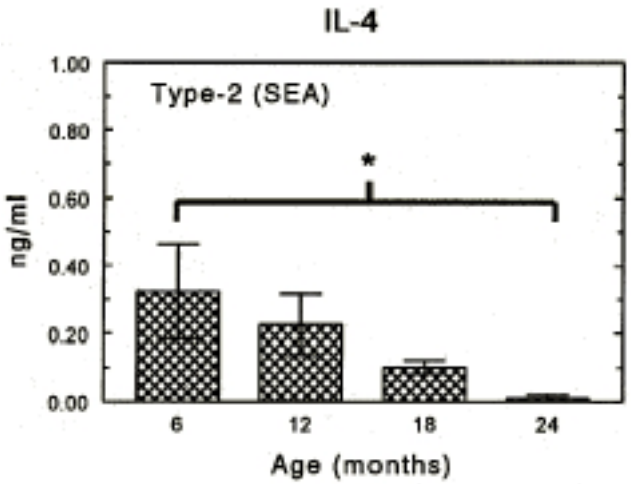
**[Chiu, Chensue et al., 2002]**

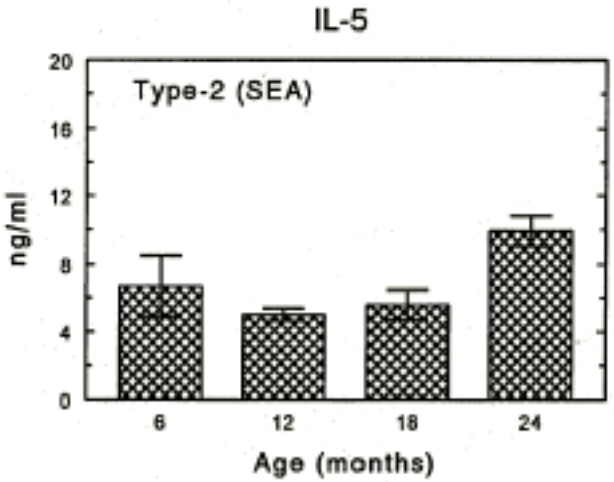


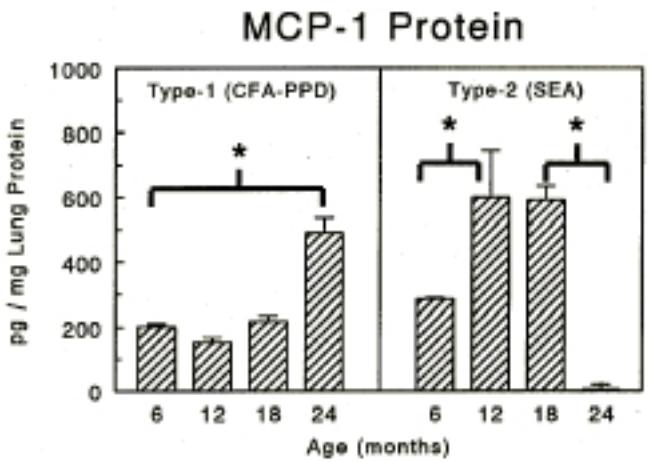



# Type II Cytokines: In Vivo Veritas

**[Chiu, Chensue et al., 2002]**

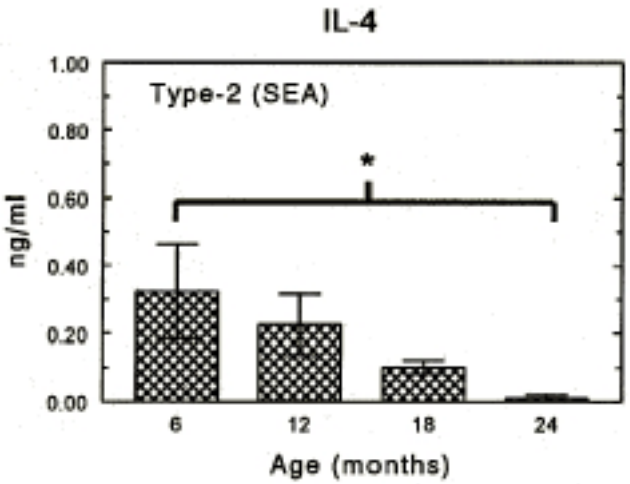


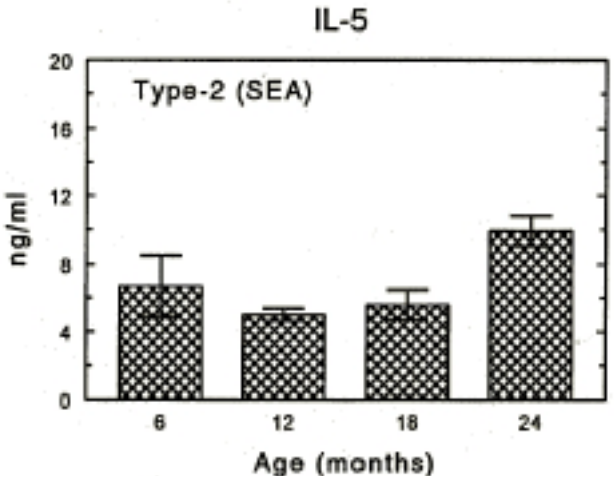



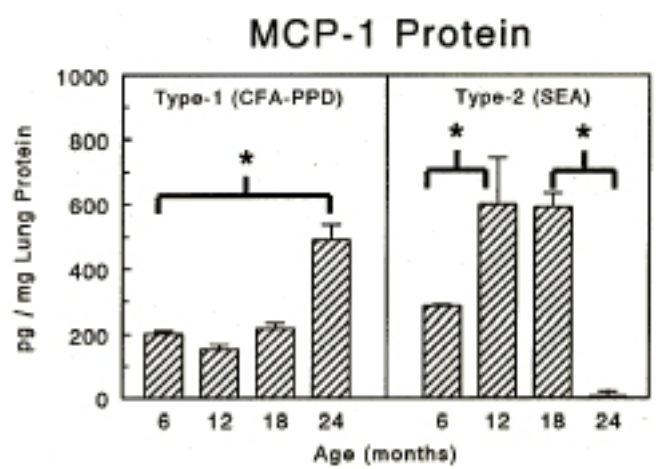



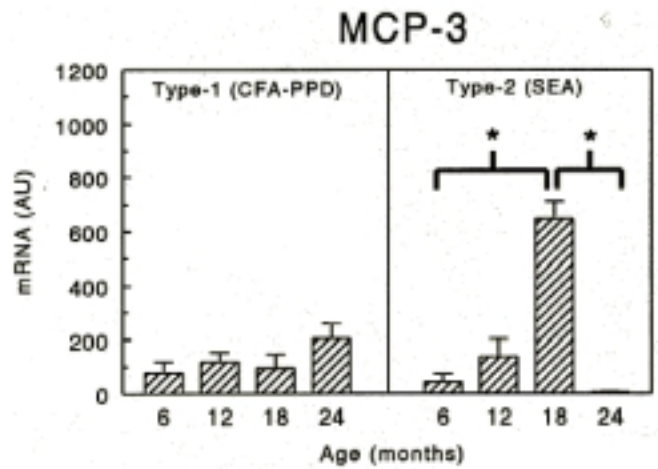
# Type II Cytokines: In Vivo Veritas

**[Chiu, Chensue et al., 2002]**



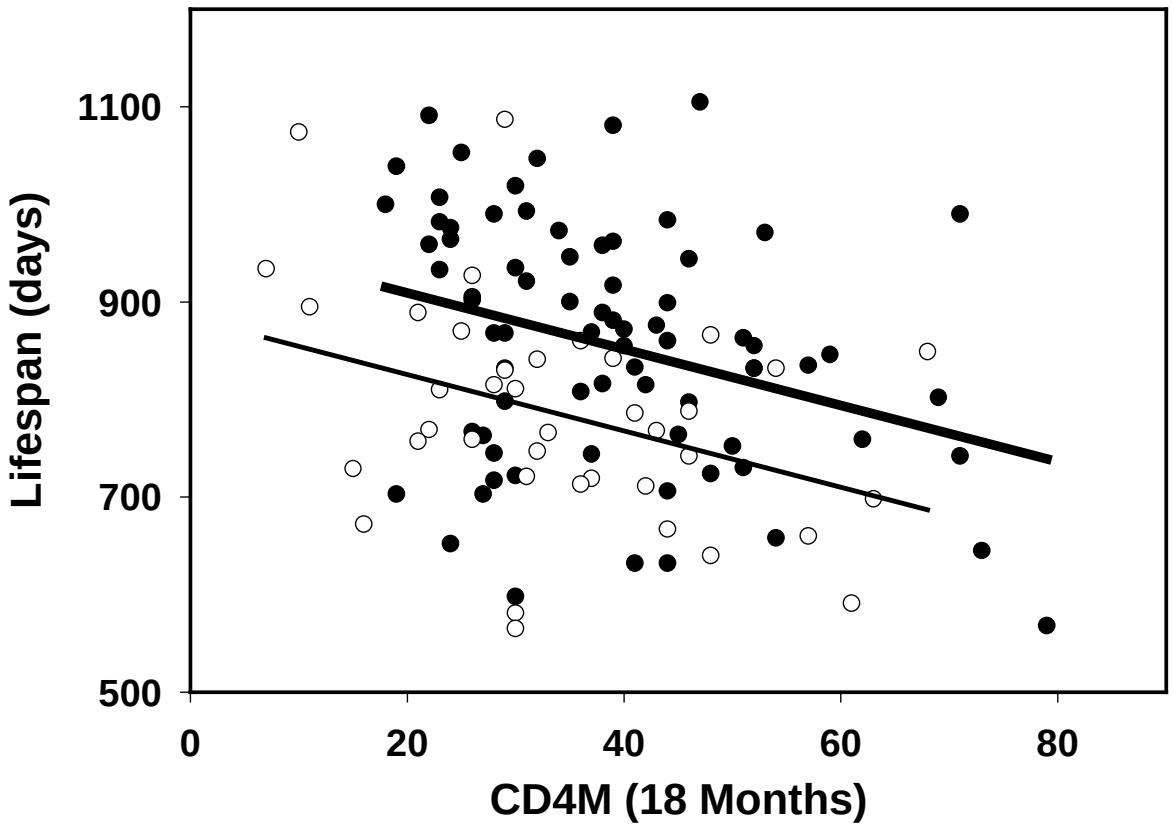



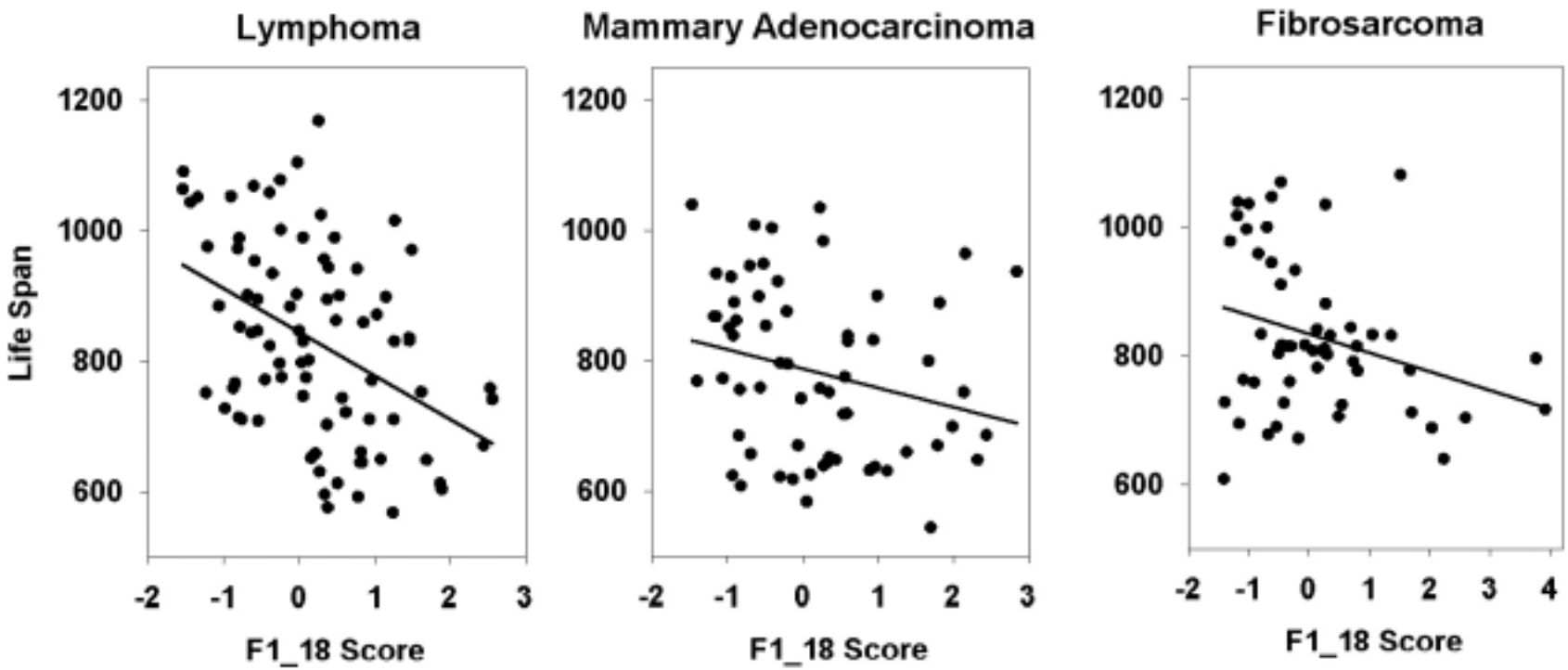
# Local Knowledge: News from Ann Arbor

- **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



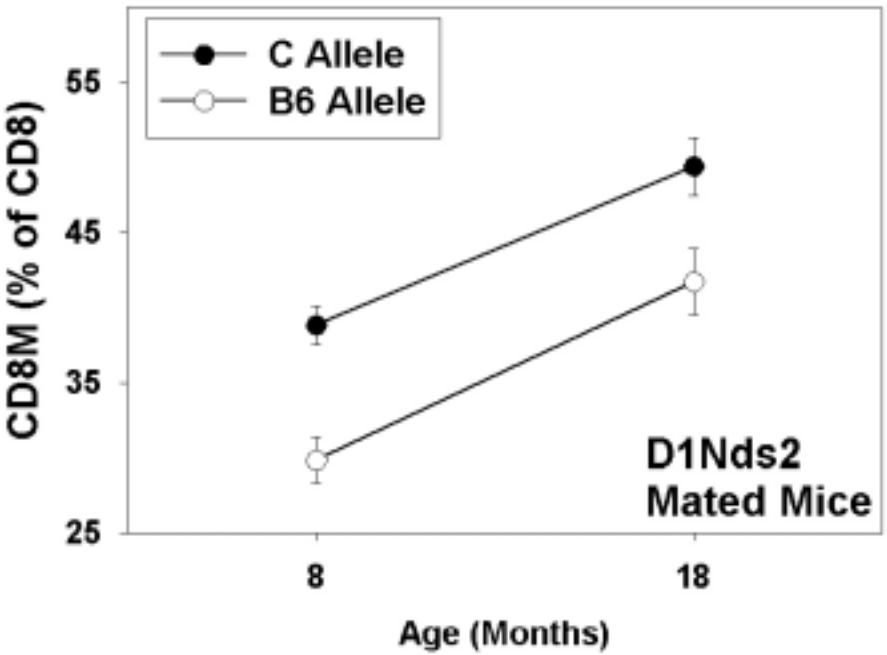
# Immune Score (At 18 Months) Predicts Longevity for Three Major Causes of Death

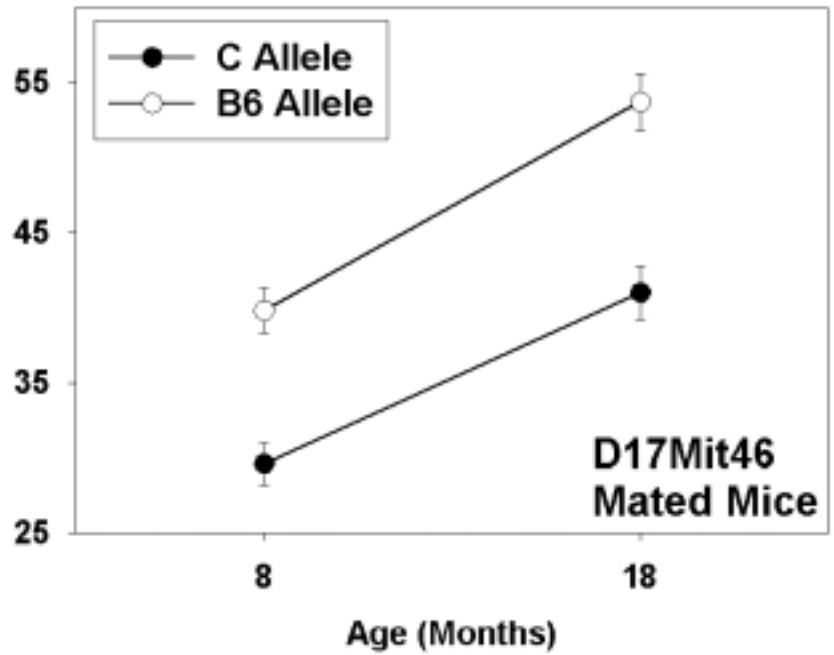


# Local Knowledge: News from Ann Arbor

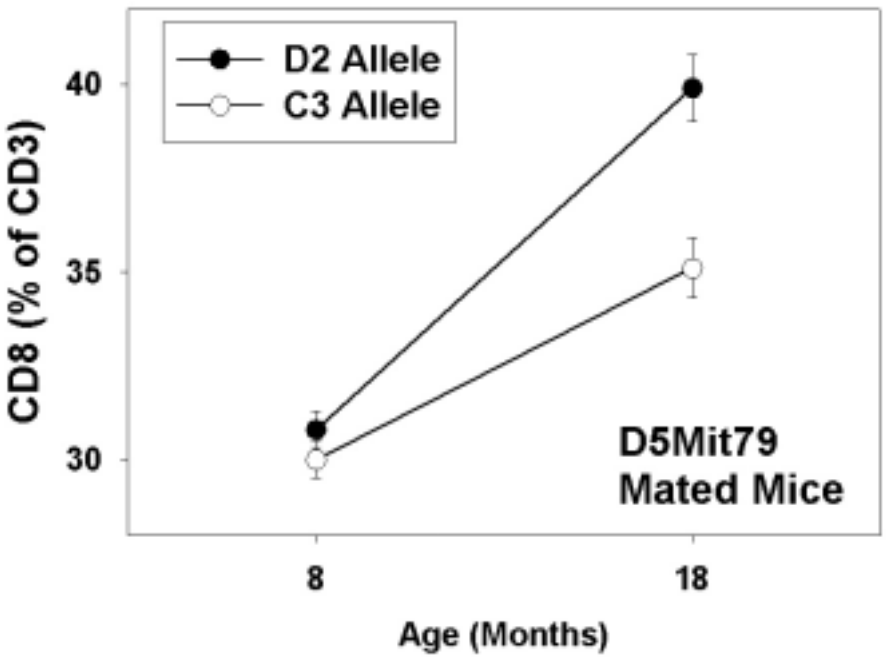
- **Gerontology: Immune biomarkers of aging**
- **Genetics: Genes for immune aging**
- **Mutant mice with slow immune aging**
- **Biochemistry: Why T cells don’t respond**

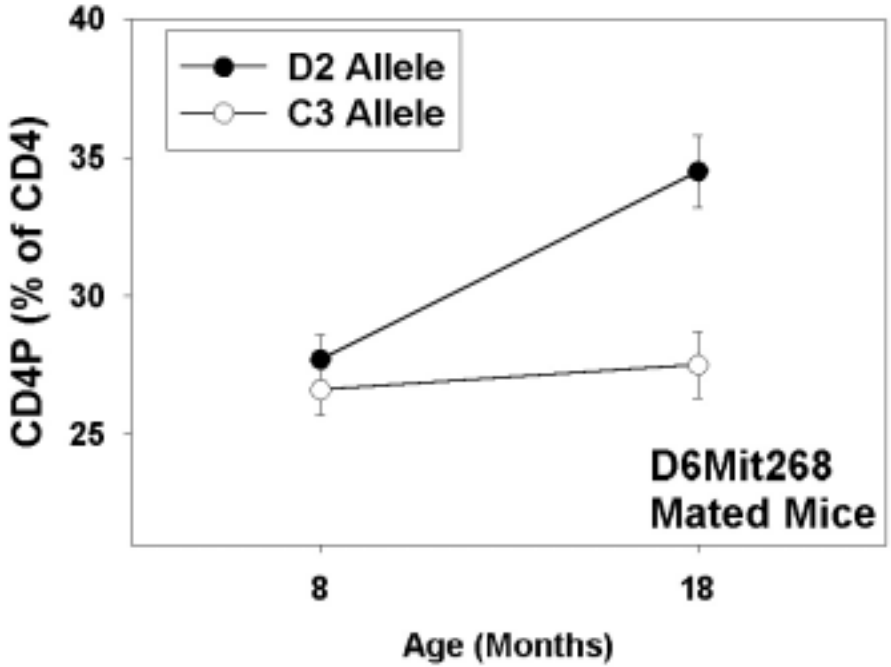
# Genes With Stable Effects on Age-Sensitive T Subsets



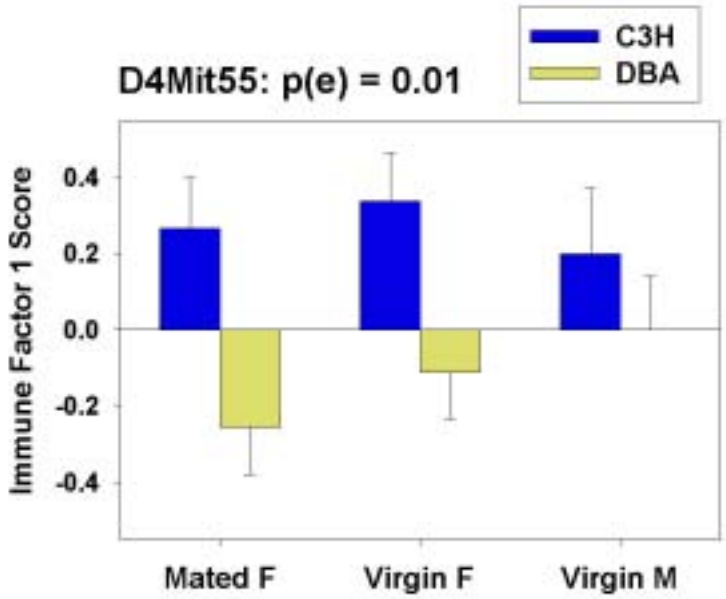



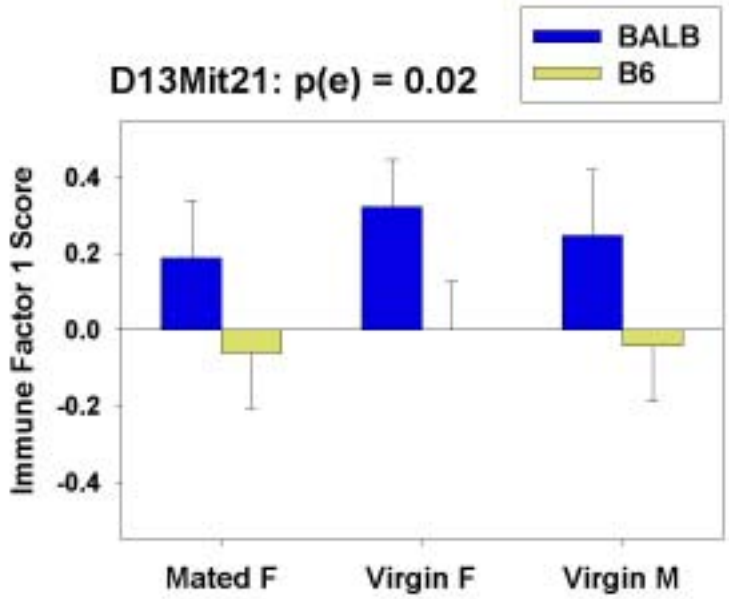
# Genes With Delayed Effects on Age-Sensitive T Subsets



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

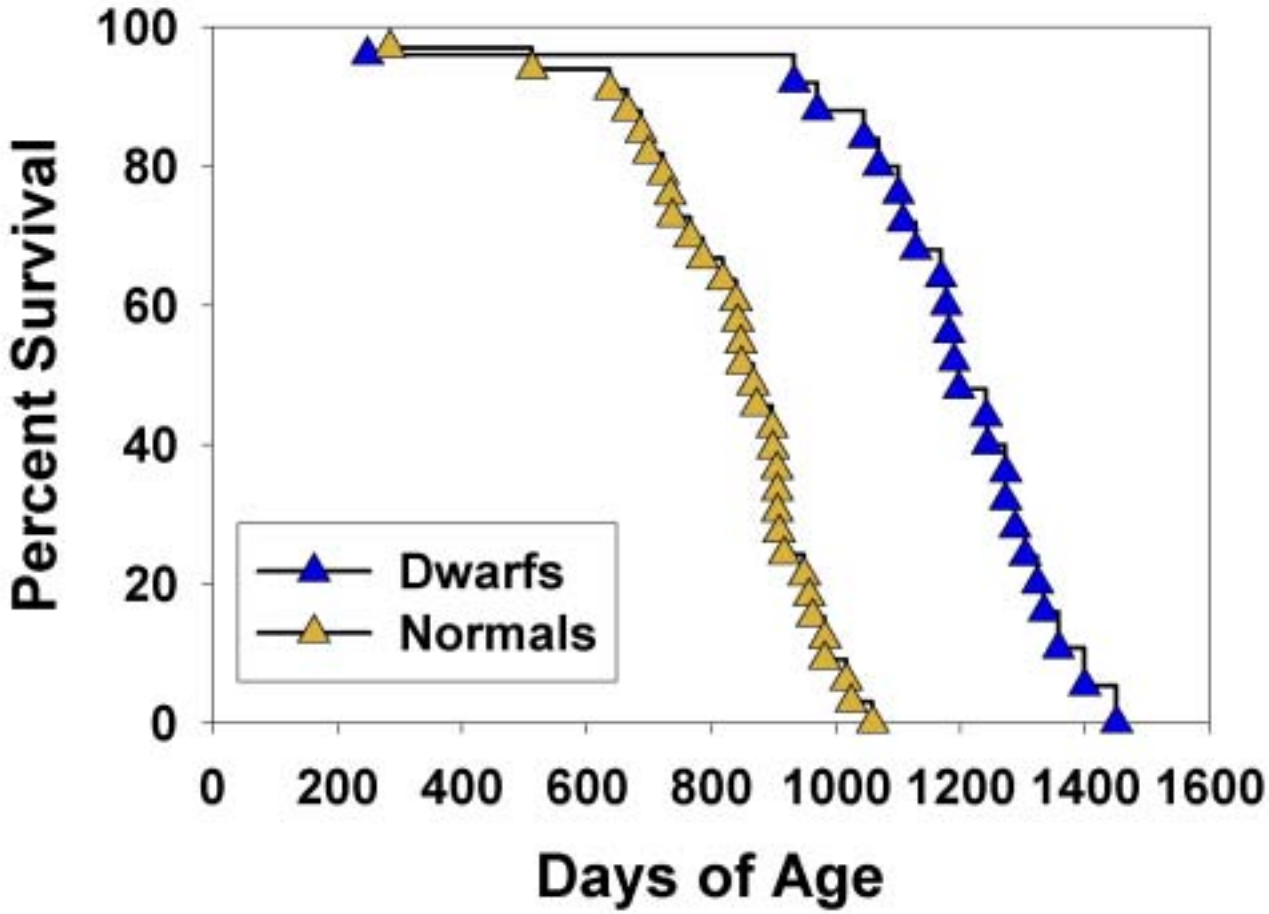


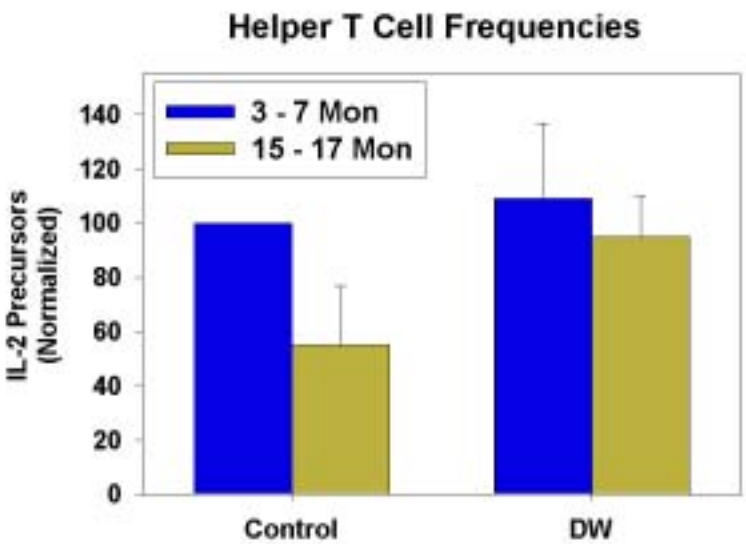
# Local Knowledge: News from Ann Arbor

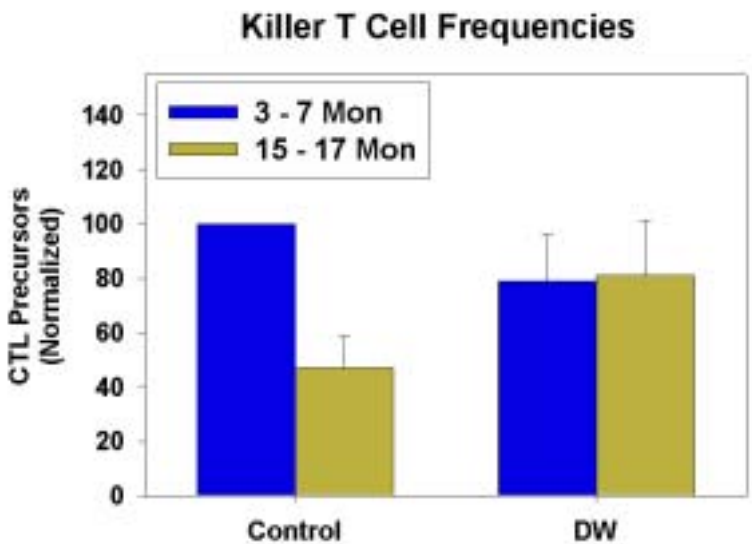
- **Gerontology: Immune biomarkers of aging**
- **Genetics: Genes for immune aging**
- **Mutant mice with slow immune aging**
- **Biochemistry: Why T cells don’t respond**

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



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



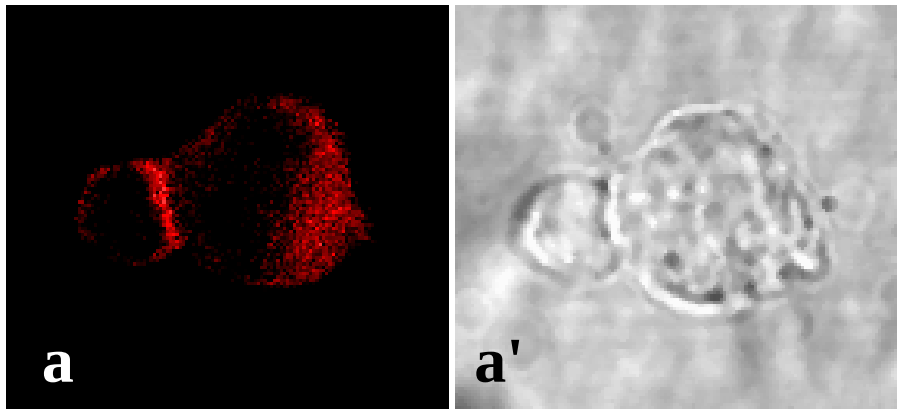

[Flurkey, Miller, Harrison]

# Local Knowledge: News from Ann Arbor

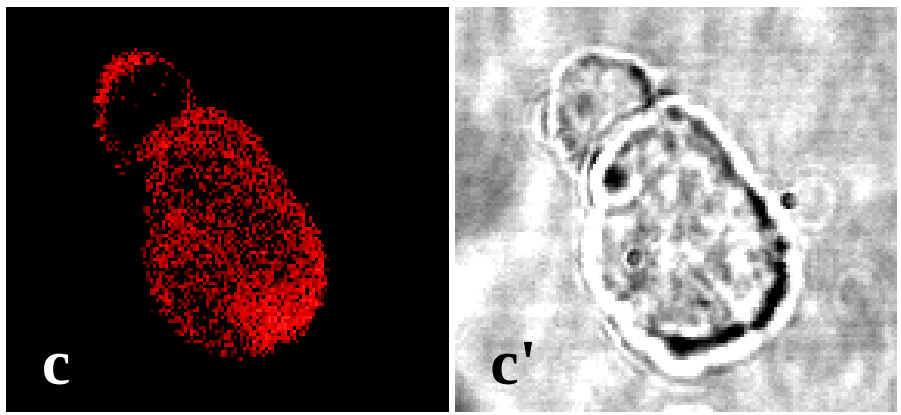
- **Gerontology: Immune biomarkers of aging**
- **Genetics: Genes for immune aging**
- **Mutant mice with slow immune aging**
- **Biochemistry: Why T cells don’t respond**

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

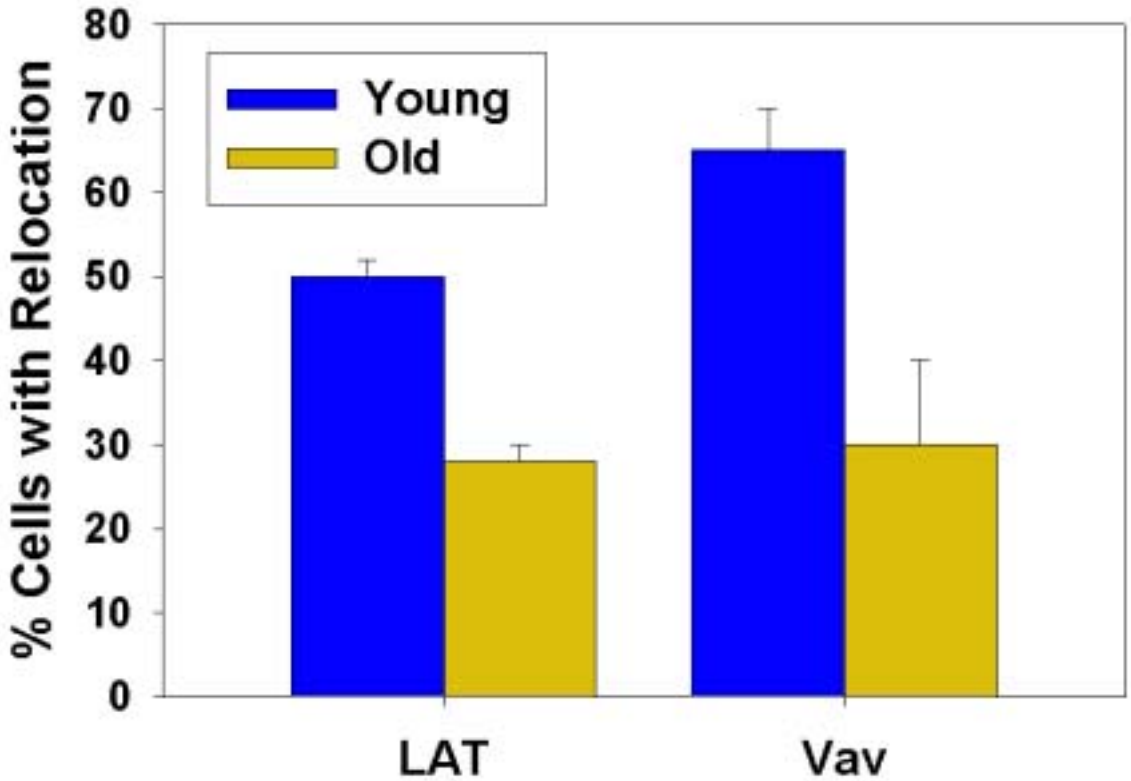
Responder cell:




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**