The Biology of Aging

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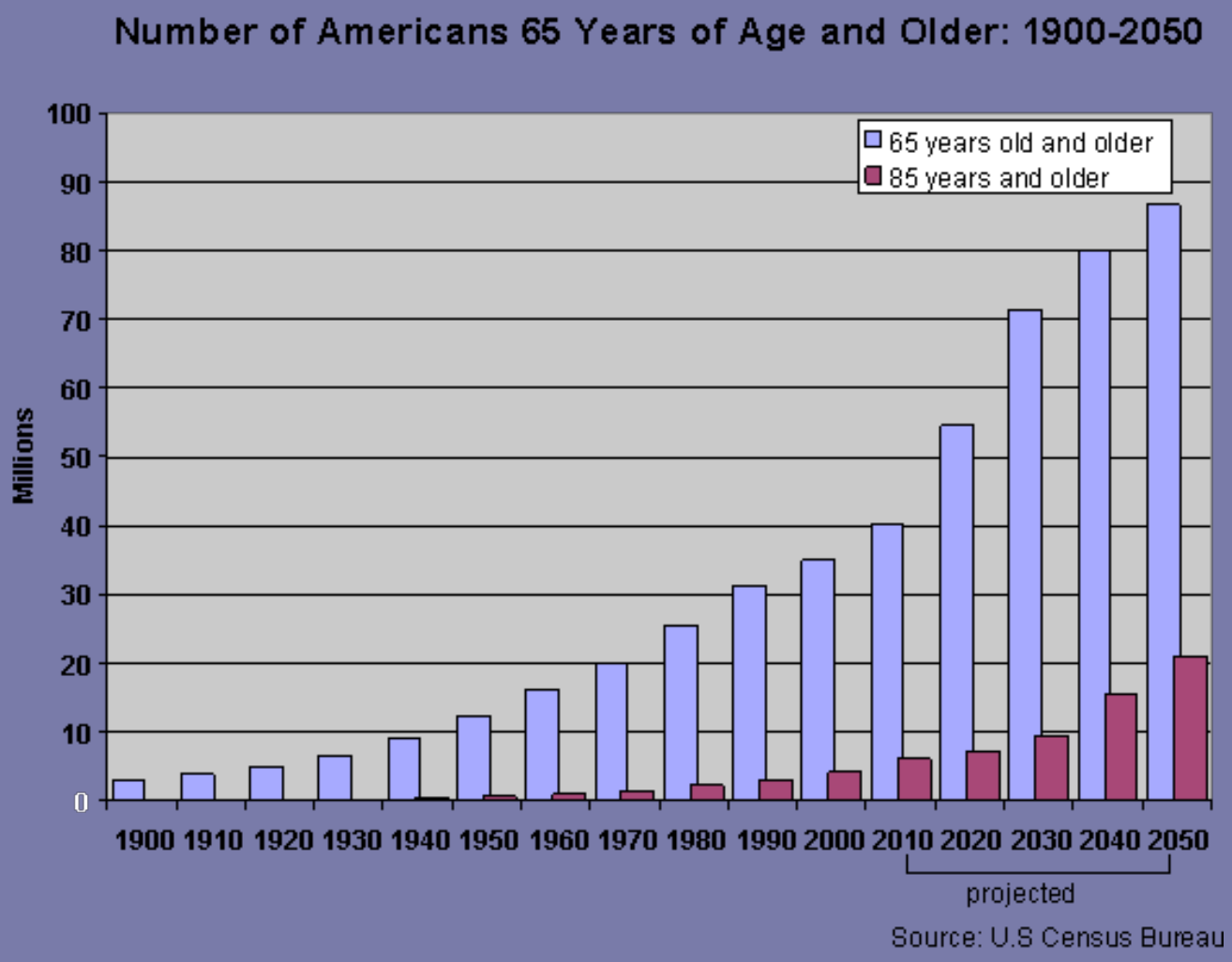
Presentation Overview

- Part 1 (Dena)
  - What is aging? Why study aging?
  - Lessons from centenarians
  - Evolutionary perspective on aging
  - Calorie restriction
- Part 2 (Michael)
  - Long lived mutants
  - Conserved aging pathways
  - Hot topics: aging in the news

What is aging?

- “To grow old or show signs of growing old”
  Webster’s New World Dictionary, 2005.
- “a process of intrinsic, progressive, and generalized physical deterioration that occurs over time beginning at about the age of reproductive maturity”
  Austad, Handbook of the Biology of Aging, 2005.

Why should we study aging?

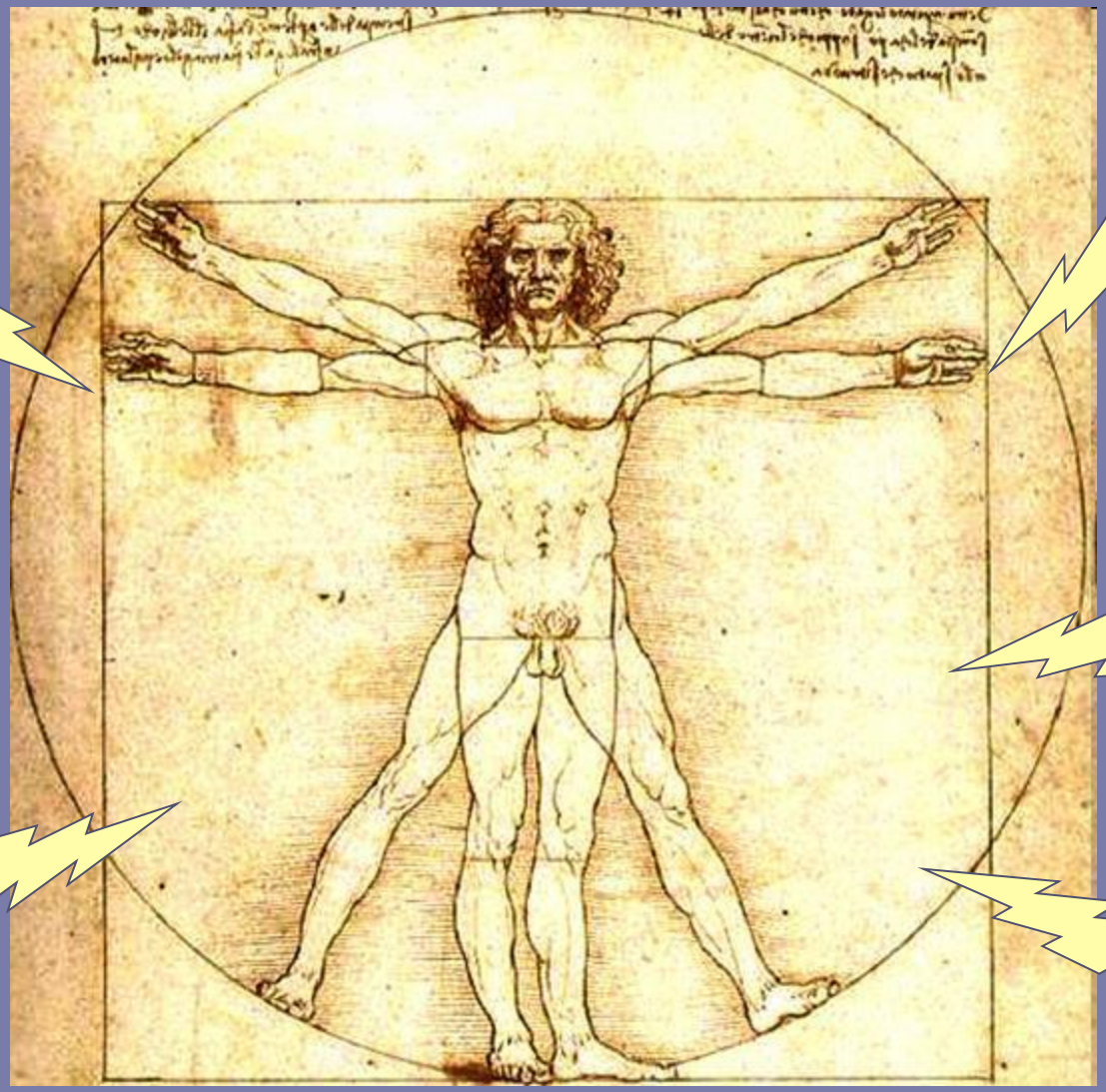


Is this a big deal?

- People over 65 in the US outnumber the entire population of Canada
- The number will more than double by 2050
- Diseases associated with aging will pose a huge social and economic burden

Can we hope to delay all of the diseases of aging and extend healthy lifespan?

What Causes Aging?



DNA damage

Reactive oxygen species

Loss of telomeres

Wear and tear

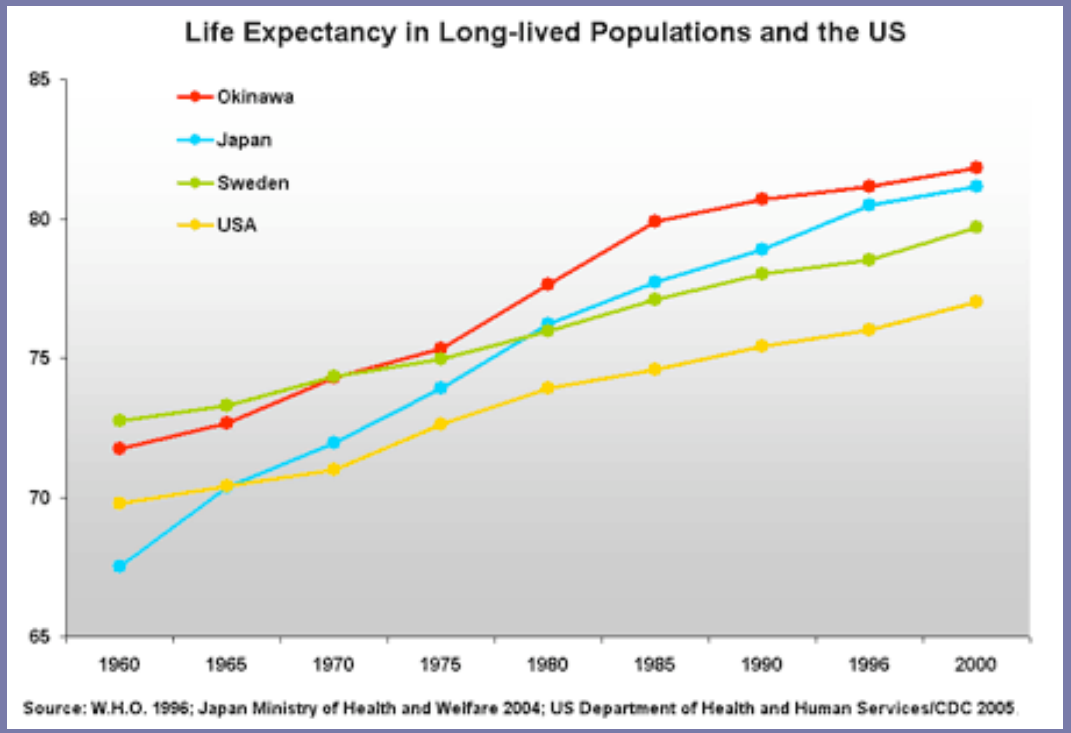
Reduced stem cell function

Longest-lived Human

- Jeanne Louise Calment
- 21 February 1875 – 4 August 1997
- longest confirmed human life span in history
- 122 years and 164 days

Lessons from Centenarians: Okinawans

- 50 centenarians per 100,000
  - US: 10-20 per 100,00
- Genetics and environment



Lessons from Centenarians: Ashkenazi Jews

- Large genetic component
  - Likely to be passed from generation to generation
- Correlated with high HDL and low LDL

Observation from all centenarians

"Our work suggests that most centenarians have been remarkably healthy and experienced a rapid terminal decline late in life, resulting in a compression of morbidity to their final years"
(Bernstein et al., J Gerontol Biol Sci. 2004; Willcox DC et al. Am J Geriatr Psychiatr. 2007).

Can we confer these benefits to more people?

Evolutionary perspectives on aging:
The traditional view

No selection!

Selection!

When would delayed aging be an evolutionary advantage?

Famine:
not a good time for offspring!

delay reproduction

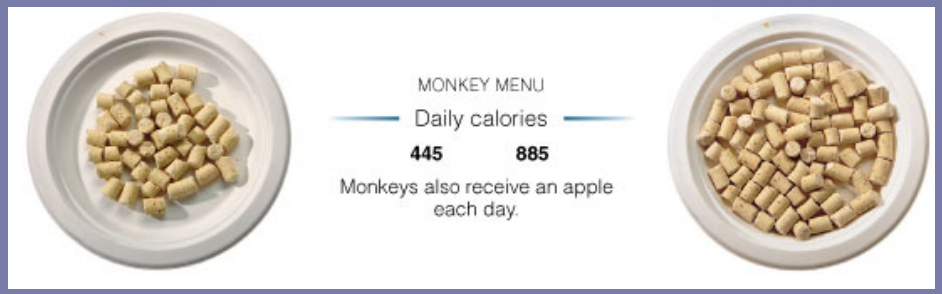
postpone aging

No more famine!

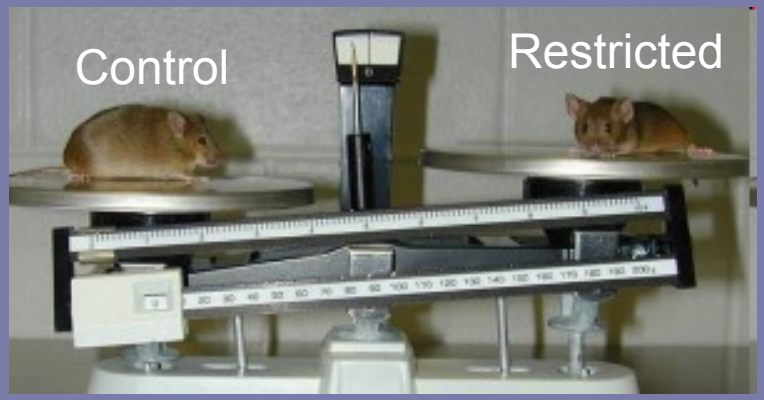
Selection!

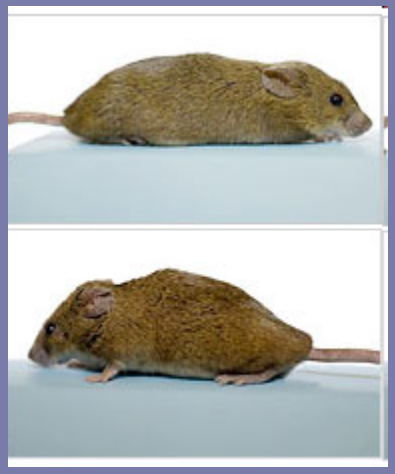
Calorie Restriction

- Reduction in calories without malnutrition
  - May mimic natural periods of nutrient scarcity
- In the lab, calories are reduced 10-30%

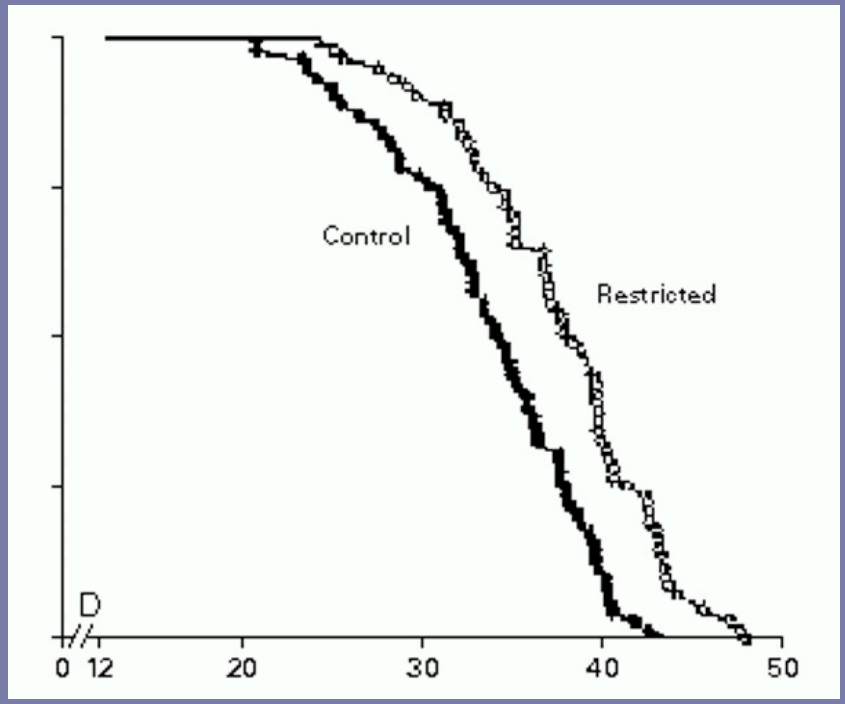


Calorie restriction extends lifespan in rodents



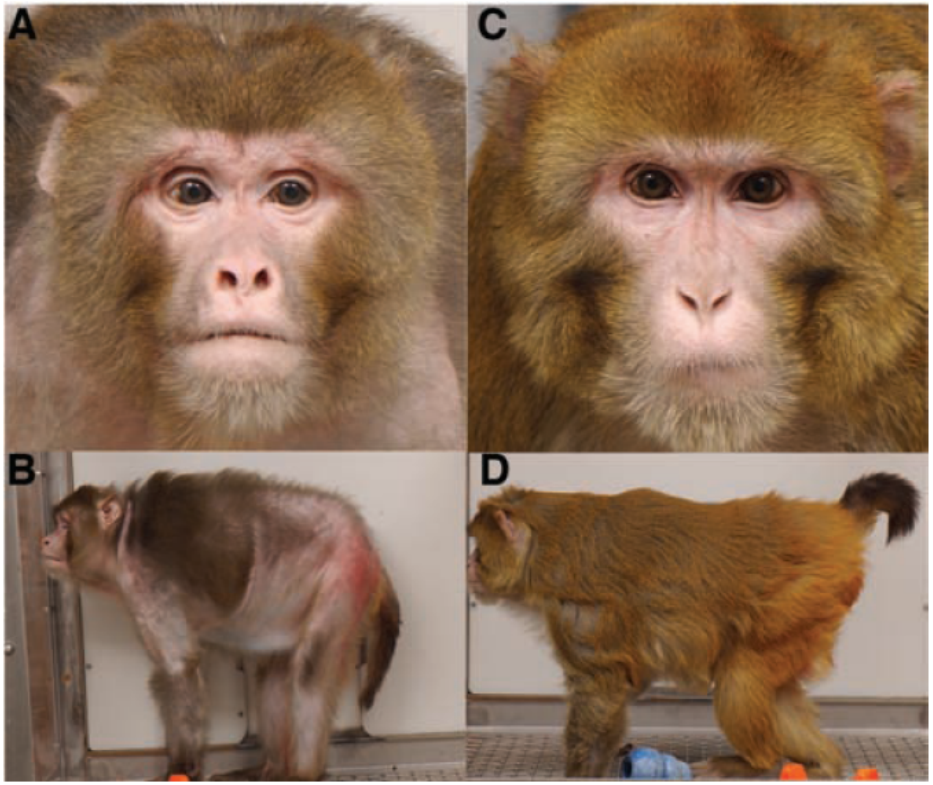


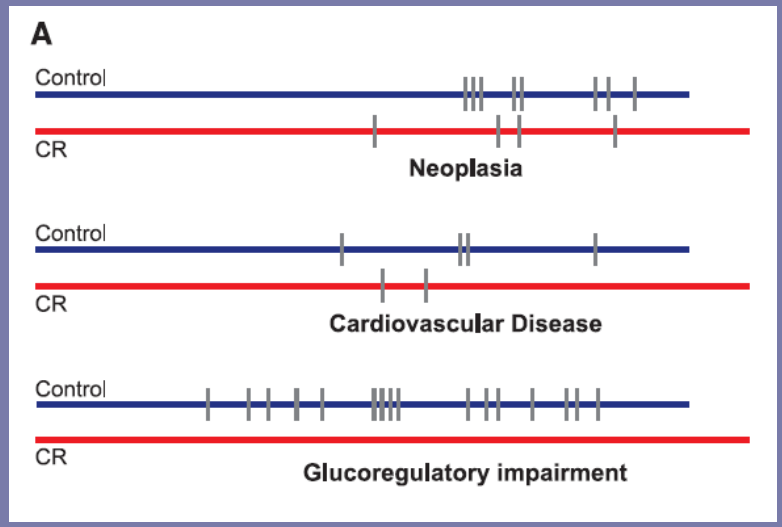
Age: 28 months

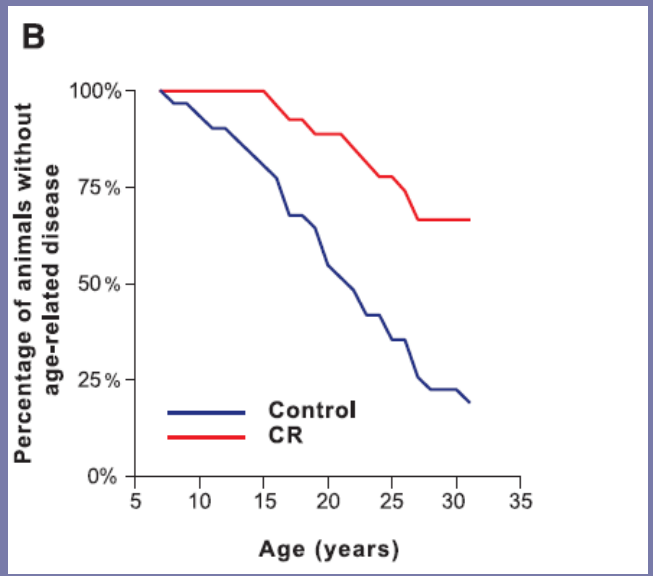


Calorie Restricion in Primates

Normal diet Calorie restriction







Could Calorie Restriction Work in Humans?

- CALERIE Study
  Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy
- Funded by National Institutes of Aging
- 3 Sites (Including Tufts), ~150 people
- 25% reduction in calories, 2 years
- Study ongoing

Summary of Part 1

- Biological aging is a decline in function over time, beginning after the reproductive years
- Symptoms of aging have many causes
- Aging can be controlled by complex genetics and by diet

Questions for Part 2

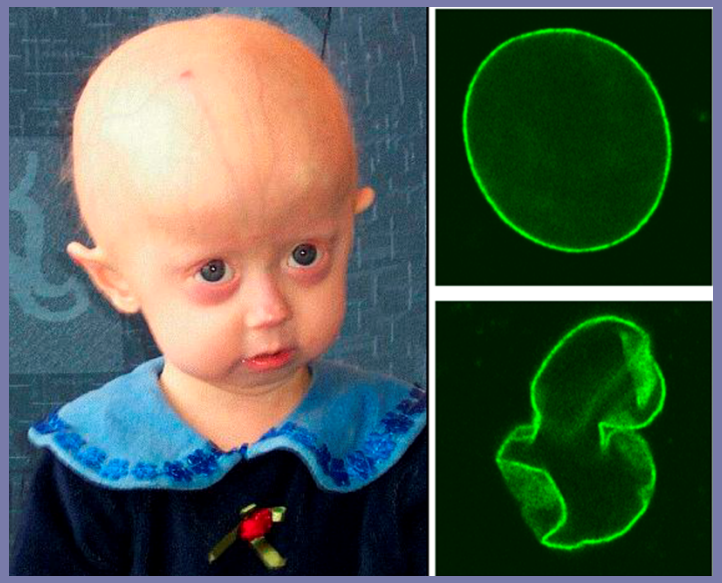
- Are there individual genes that control aging and lifespan?
- Is aging controlled the same way in all species?
- Can we harness the genetic pathways that control aging and create drugs to extend lifespan?

Outline for Part 2

- Genes that control aging
  - Mutations that mimic accelerated aging
  - Mutations that extend lifespan
- Conserved aging pathways
- Hot topics: drugs that extend lifespan

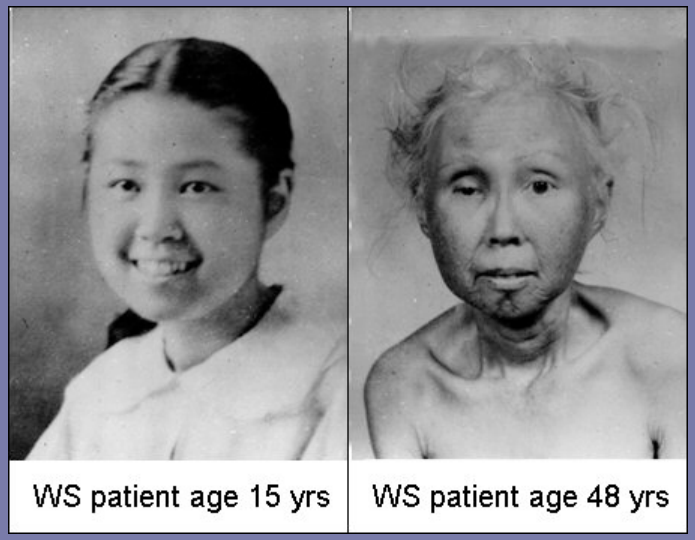
Hutchinson-Guilford Progeria

- 1 in 4 million affected
- Caused by mutation that affect structure of the nucleus
- Many classic “aging” symptoms
  - alopecia , wrinkles, atherosclerosis, CVD
- But: no “wear and tear” diseases like cataracts or arthritis



Werner Syndrome

- Disease onset in teens; very rare
- Caused by mutation in DNA processing enzyme
- Unstable chromosomes
- Many signs of aging
  - Grey hair, cataracts, CVD, diabetes
- No senility



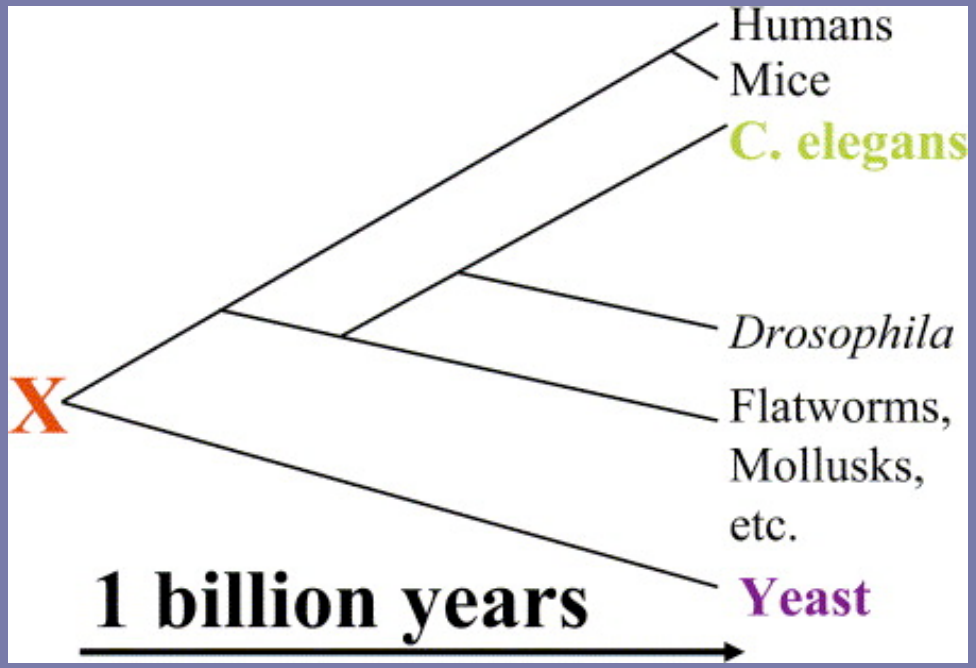
WS patient age 15 yrs | WS patient age 48 yrs

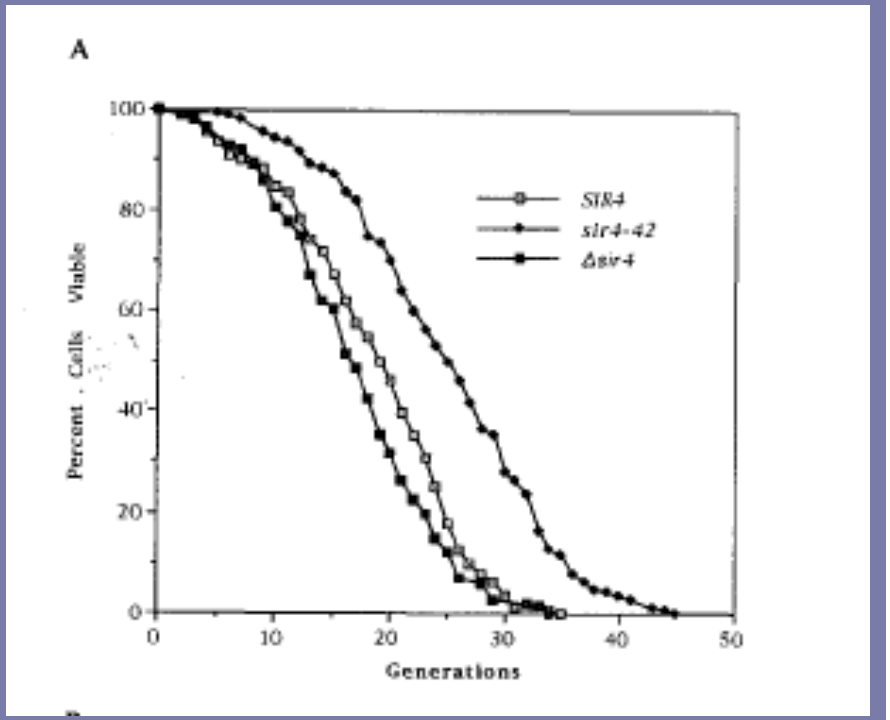
Progeria Sumary

- Very rare syndromes
- Mimic some, but not all, phenotypes of aging
- Give some clues about causes of aging

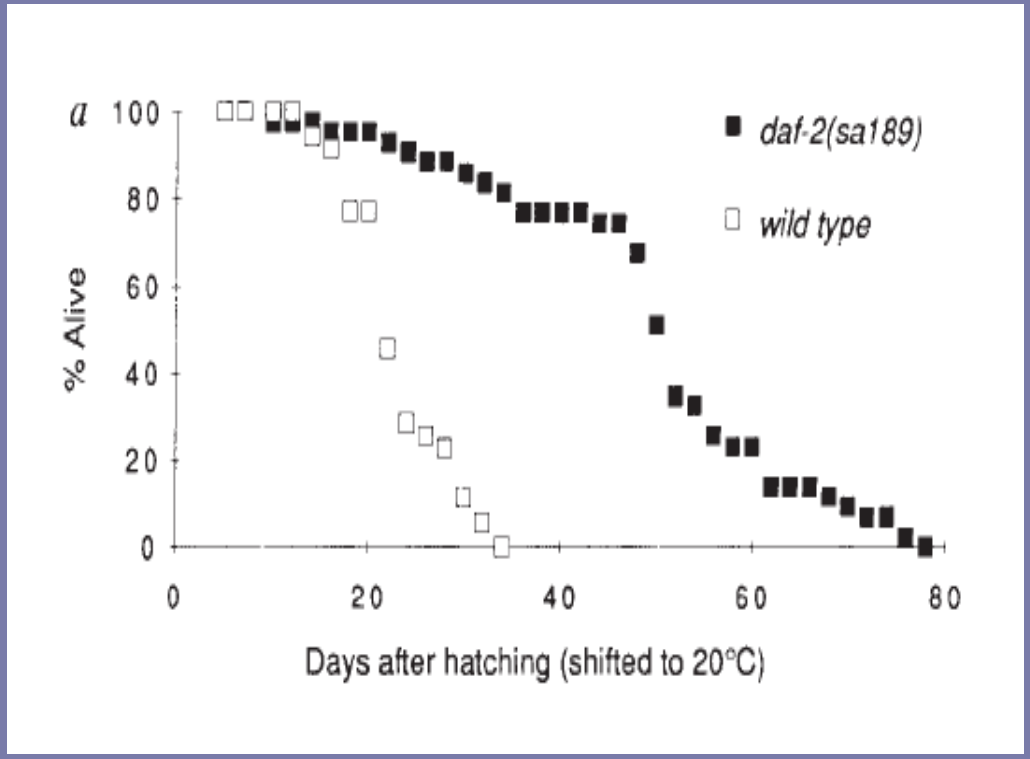
What about mutations that delay aging and extend life?

Mutations can extend the lifespan of yeast (*S. cervisae*)

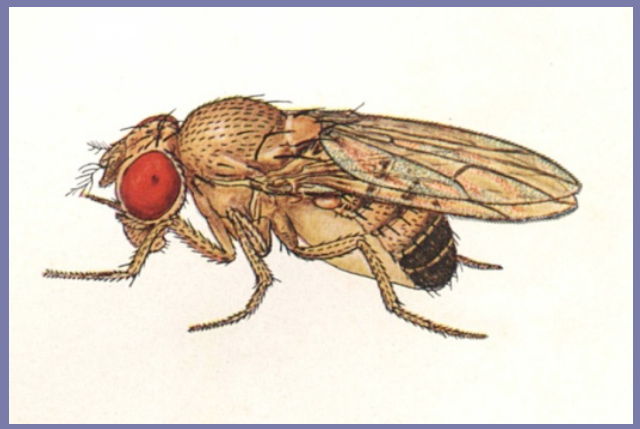


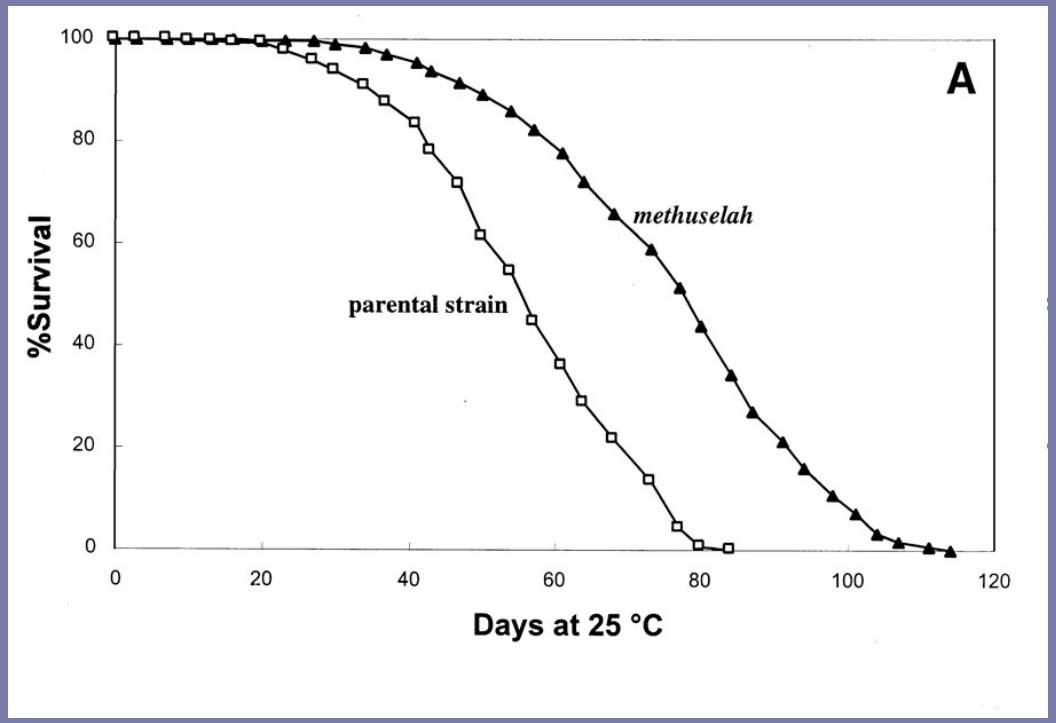


A single gene that regulates lifespan in an animal: *C. elegans*, 1993

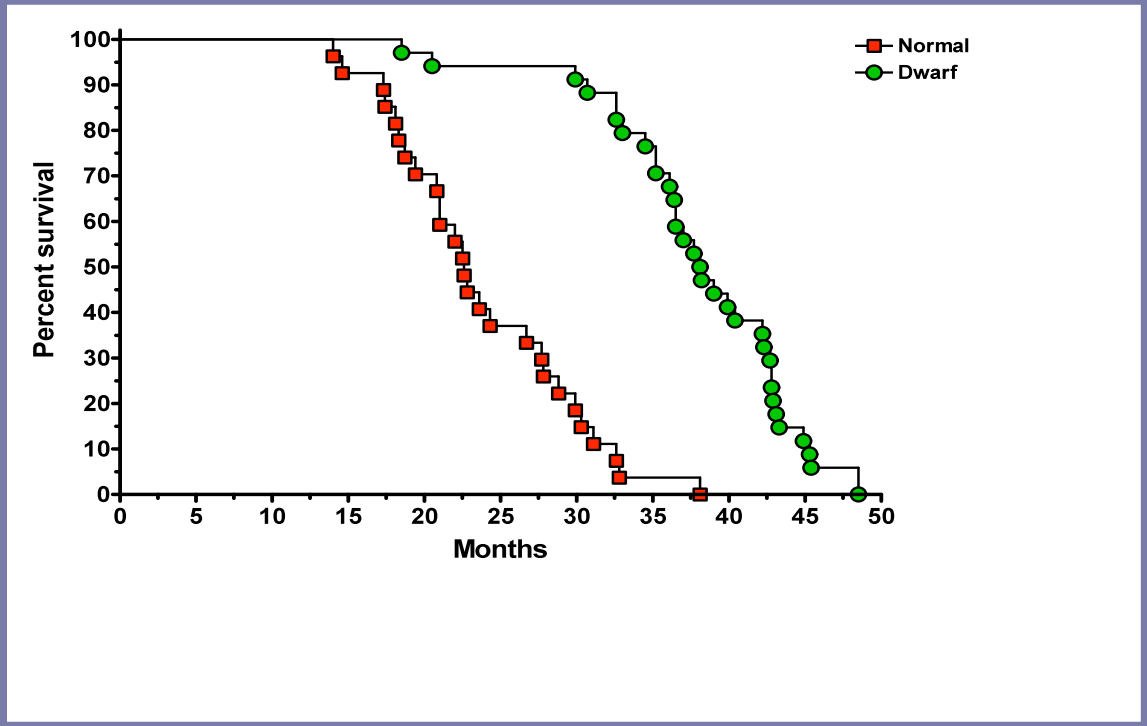


A gene that regulates lifespan in *D. melanogaster*: 1998

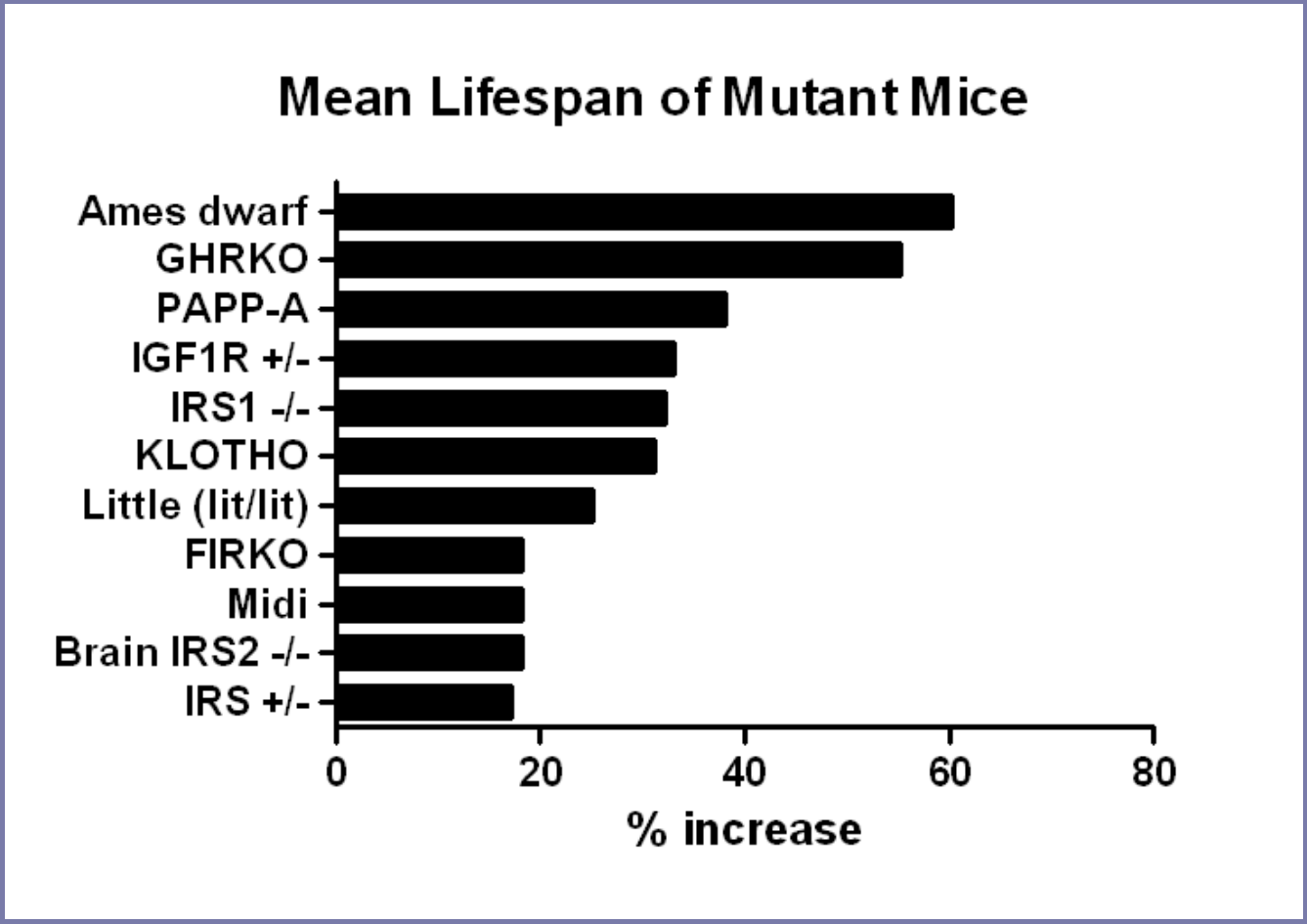




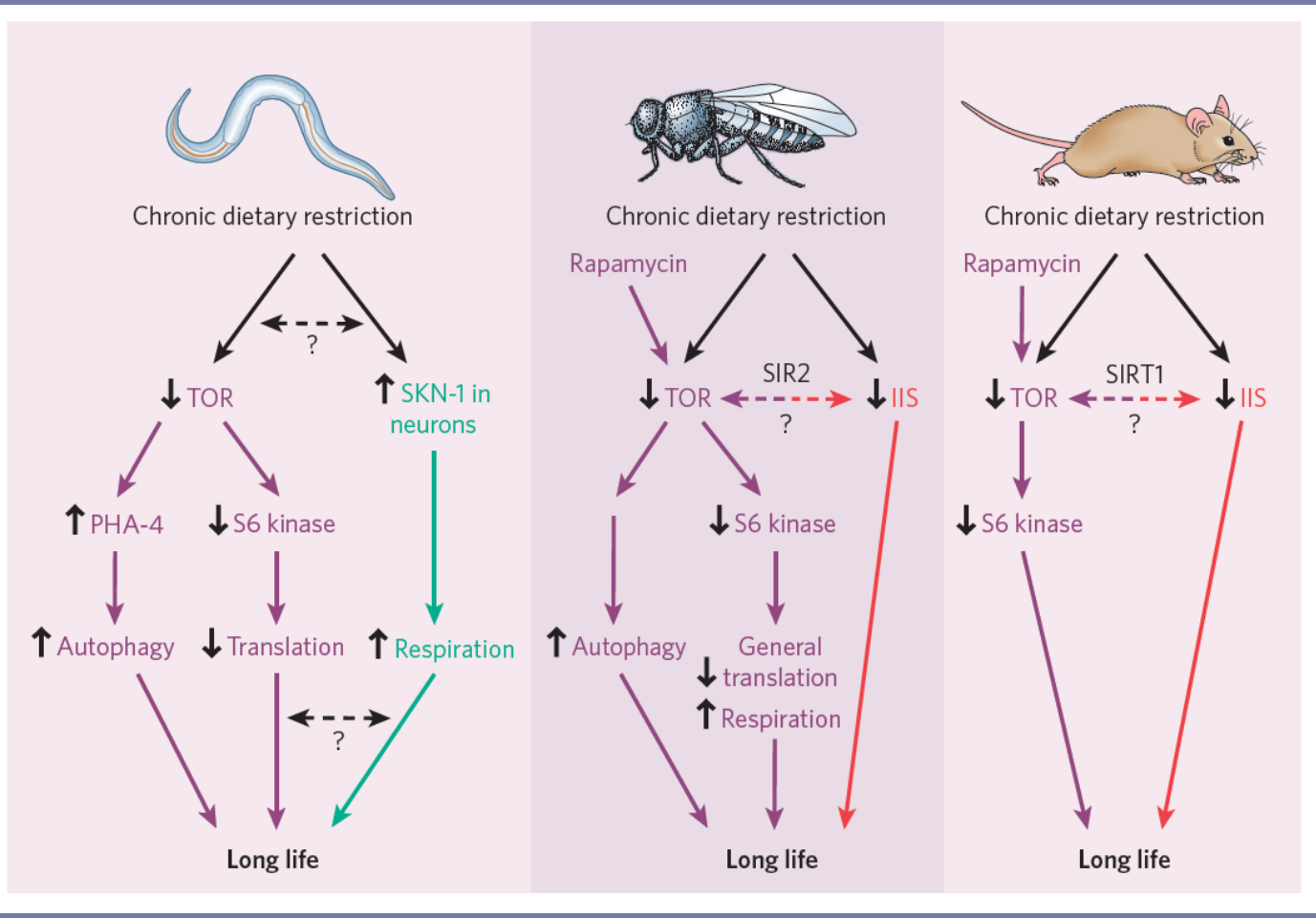
A single mutation extends lifespan in mouse: 1996



Many mutations that extend mouse lifespan are now known



Pathways that regulate lifespan are evolutionarily conserved



Summary: Genes and Aging

- Single gene mutations can extend lifespan
- Amazingly, aging pathways are conserved across 1 billion years of evolution
- Aging genes and calorie restriction affect the same biological pathways
  - Is there a single regulatory pathway for lifespan?

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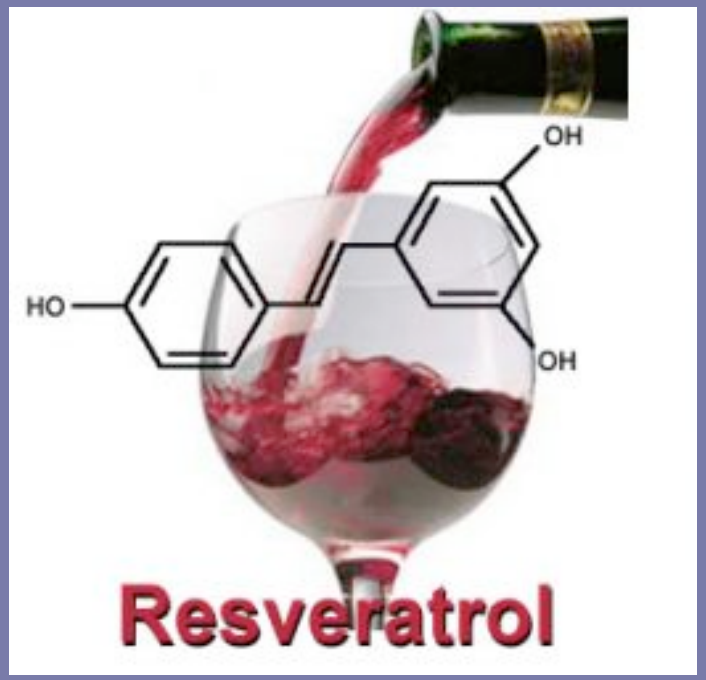
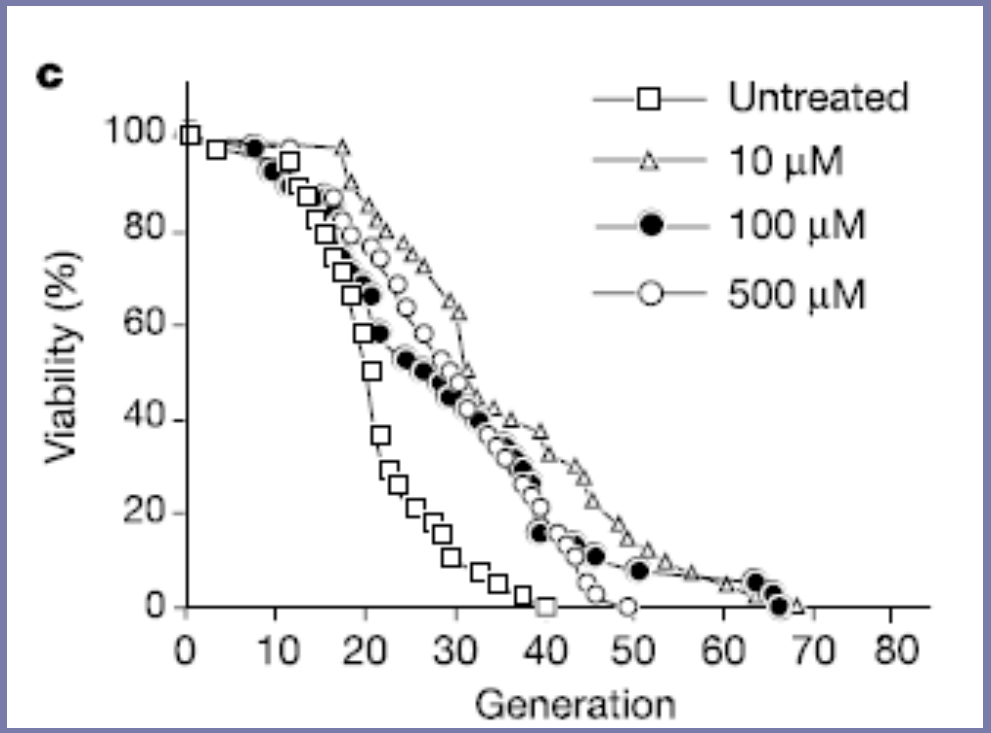
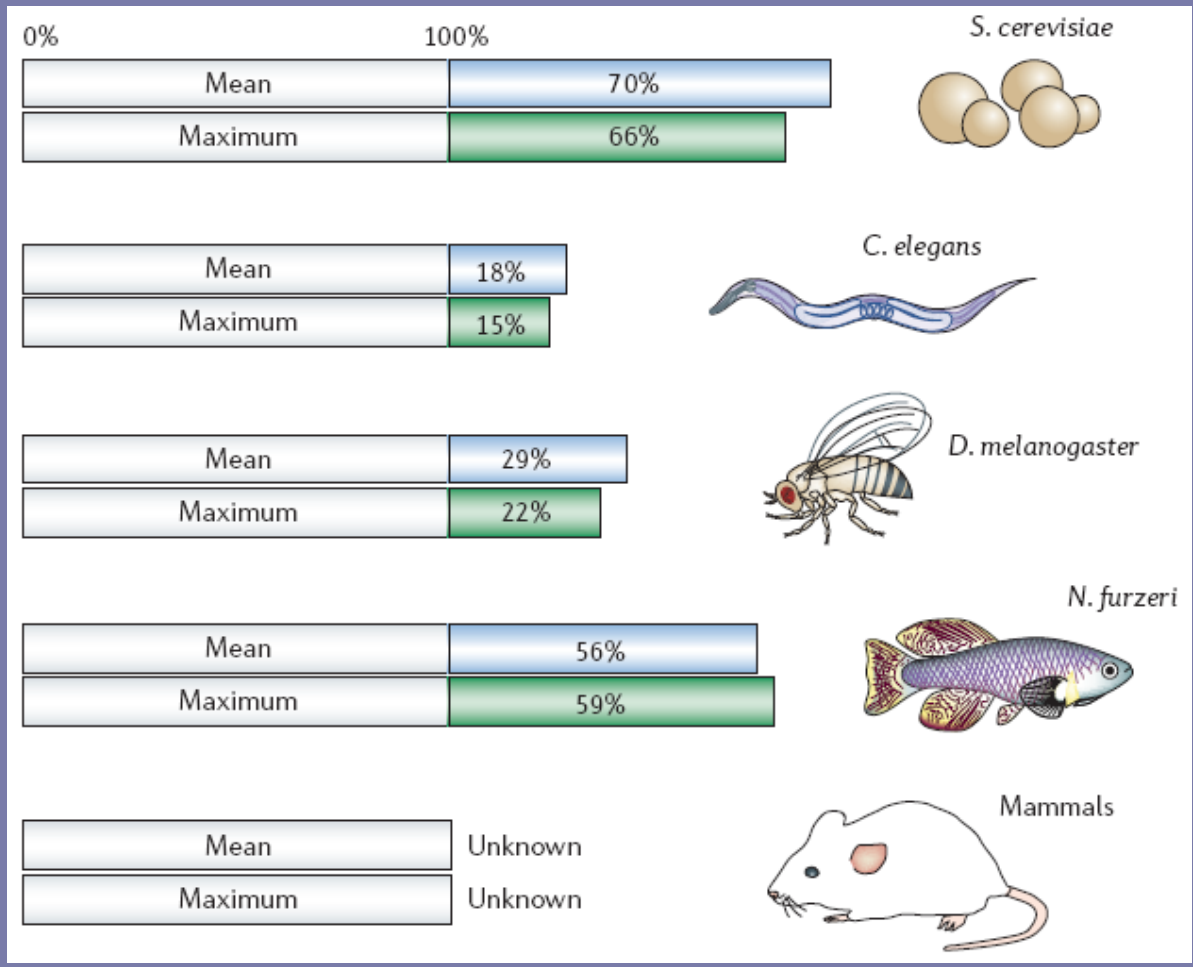
Can we make drugs that delay aging?

Resveratrol treatment extends lifespan in yeast

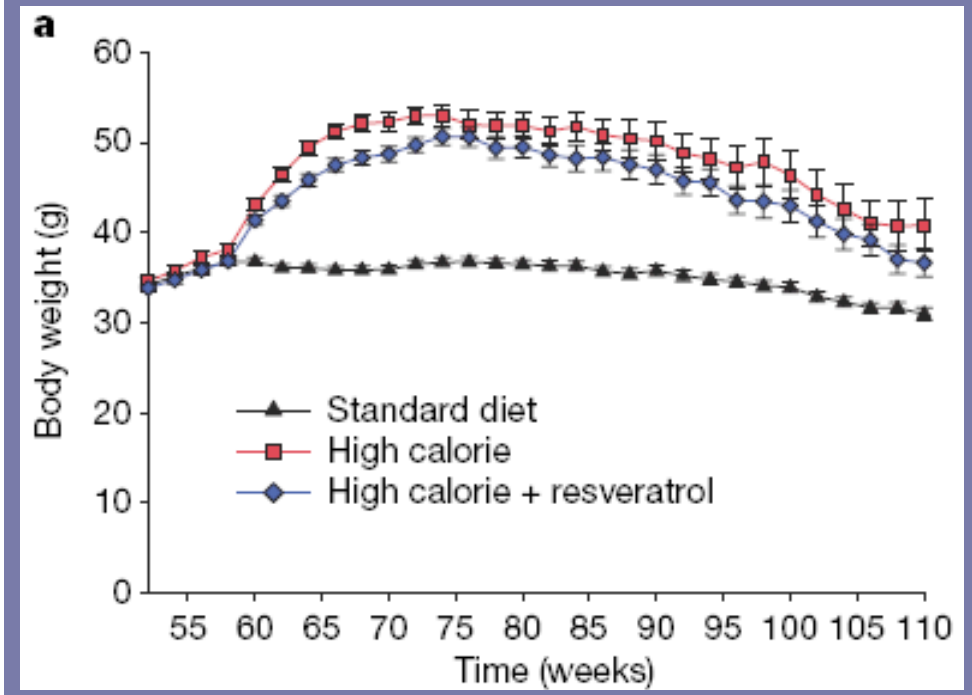


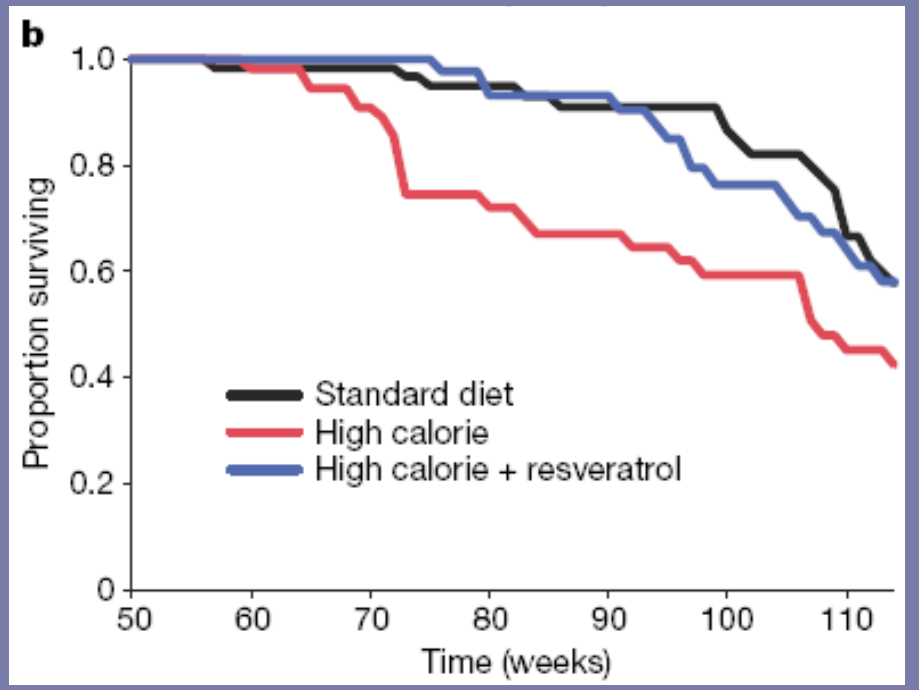


Resveratrol treatment extends lifespan in other organisms



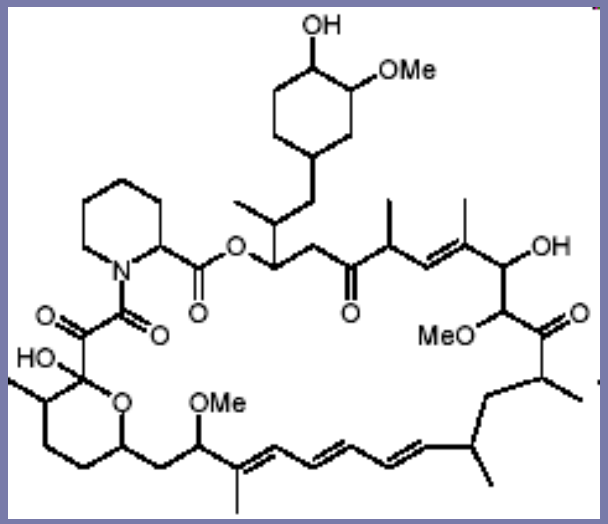
Resveratrol improves health and survival in mice fed a “high fat” diet



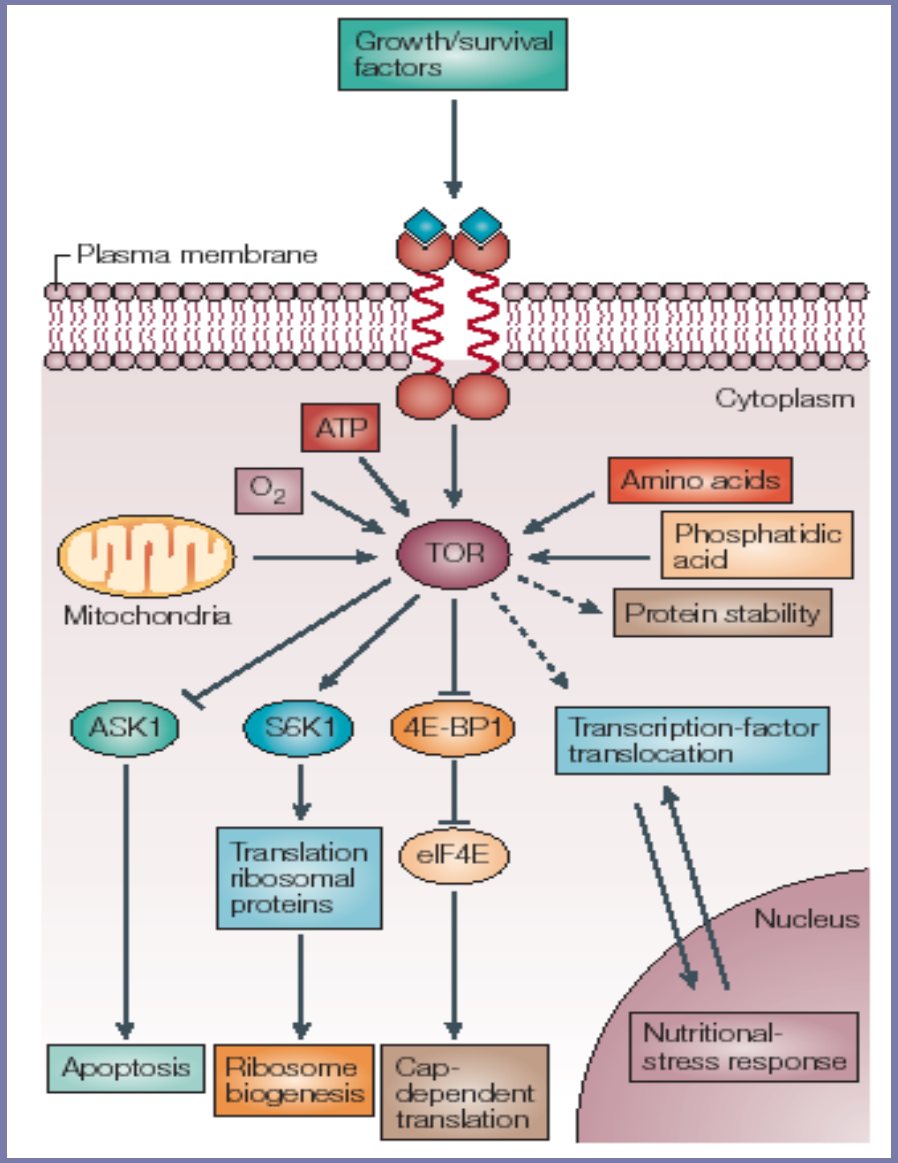


Rapamycin

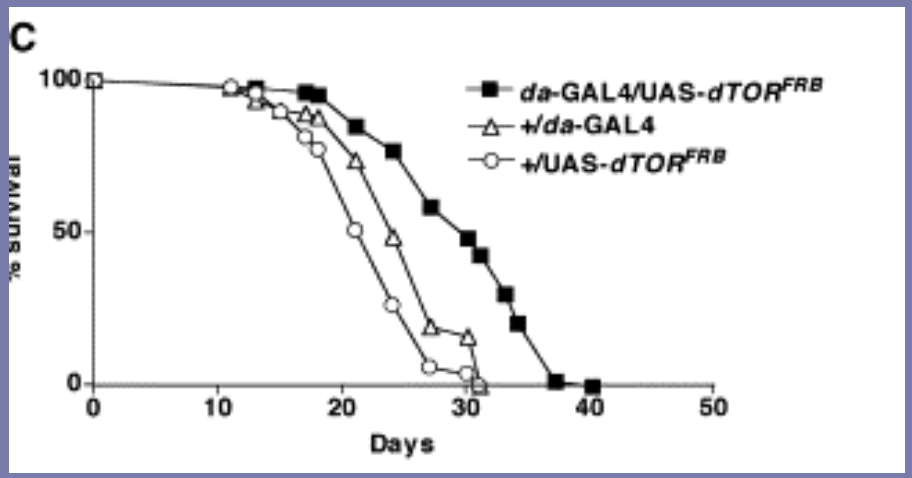
- Drug discovered in the soil on Easter island (Rapa Nui)
- Current clinical use: immunosuppression and chemotherapy



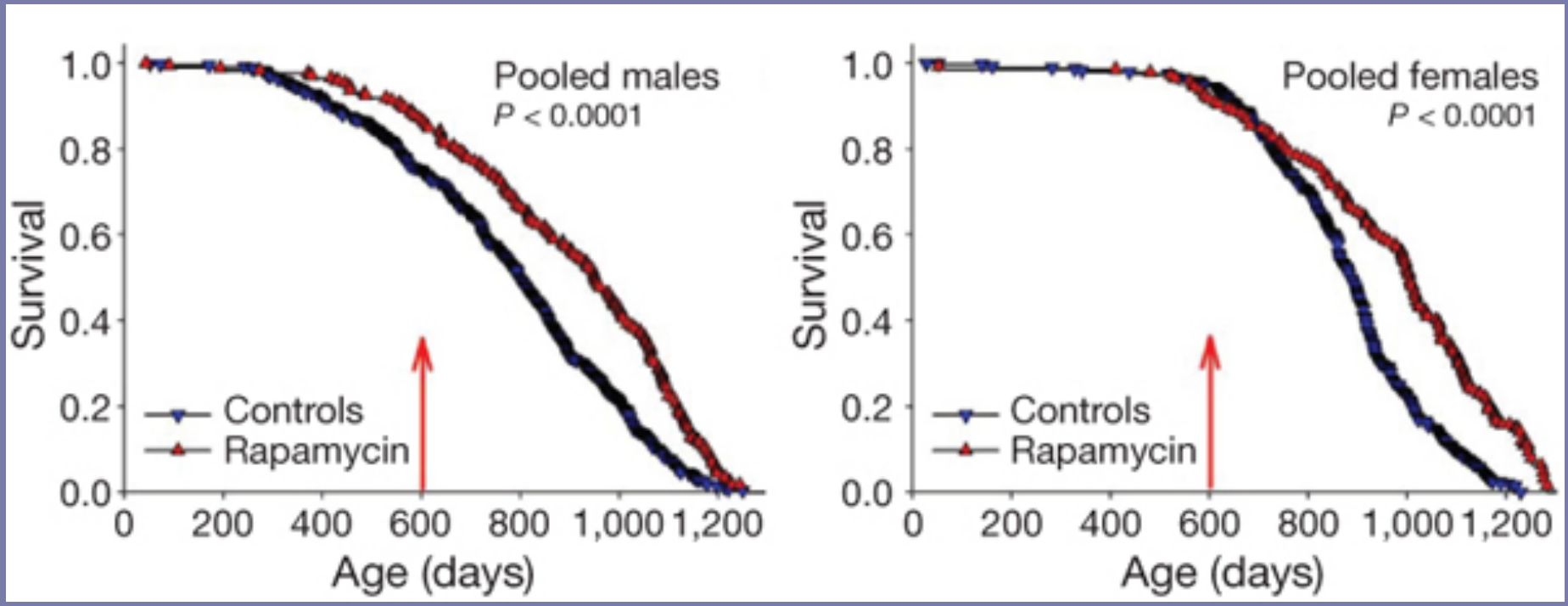
How is Rapamycin linked to aging?



Tor mutations extend lifespan

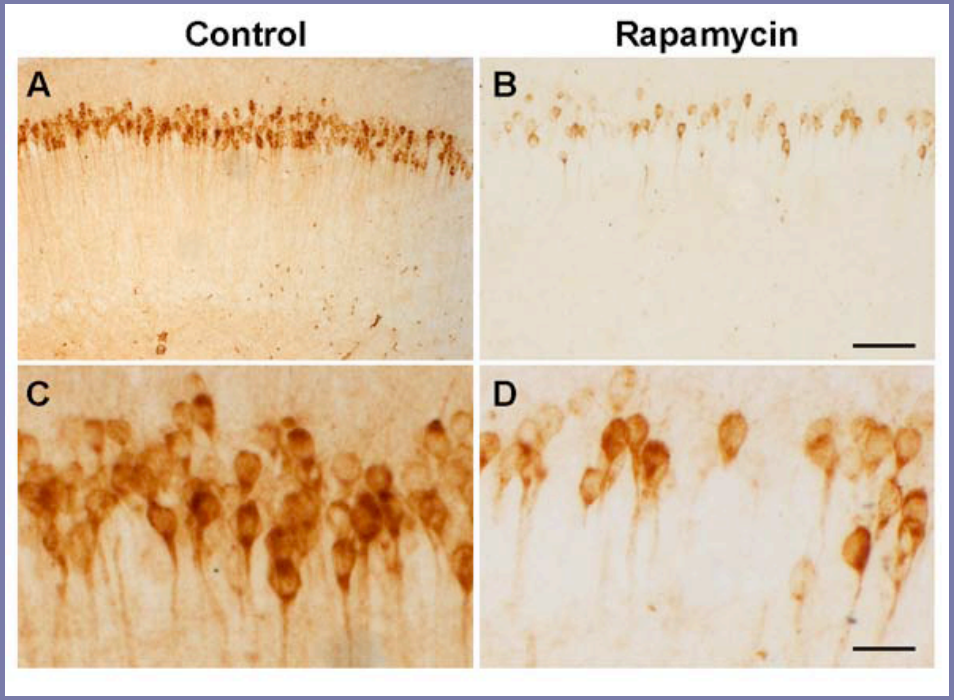


Rapamycin treatment extends lifespan in middle-aged mice



Rapamycin treatment improves Alzheimer's disease in mice

Plaques in the brain



Mice also show improved cognitive performance!

Interventions Testing Program

- Systematic evaluation of compounds that might extend life in mice
- Test compounds suggested by the scientific community
- Multiple sites
- Genetically diverse mice
- Compounds currently being tested:
  - Green tea extract, curcumin, aspirin, and 12-15 others

National Institute on Aging

Summary

- Aging is controlled by genes
- Mutations can accelerate or delay aging
- Pathways that control aging are conserved across 1 billion years of evolution
- Drugs that target these pathways may someday be used to treat diseases of aging and extend life

Thank you!