The aging mouse problem and what we don't know about cancer prevention

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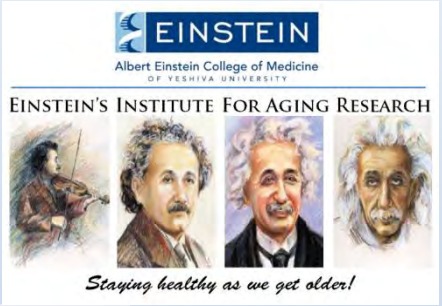
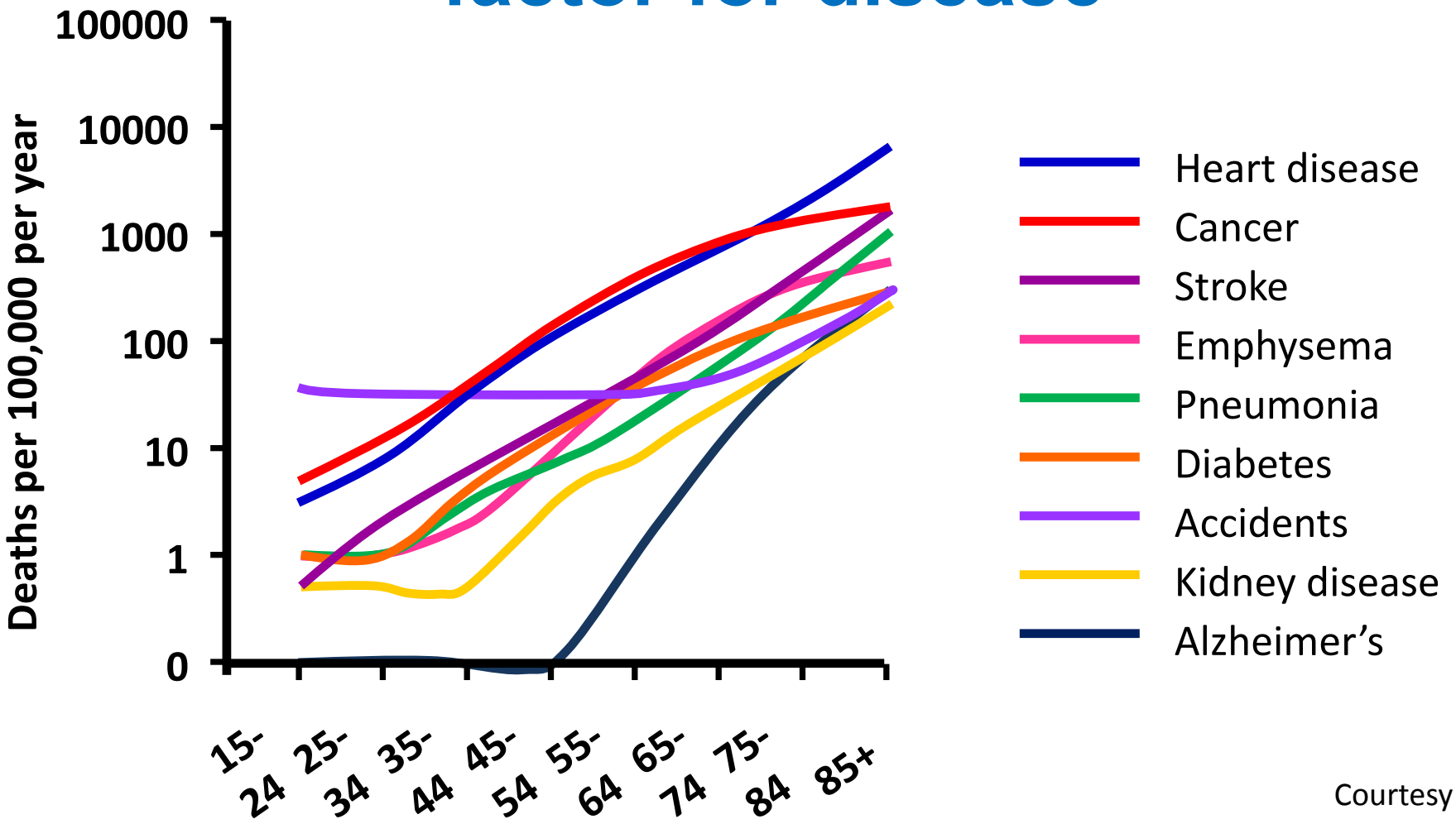


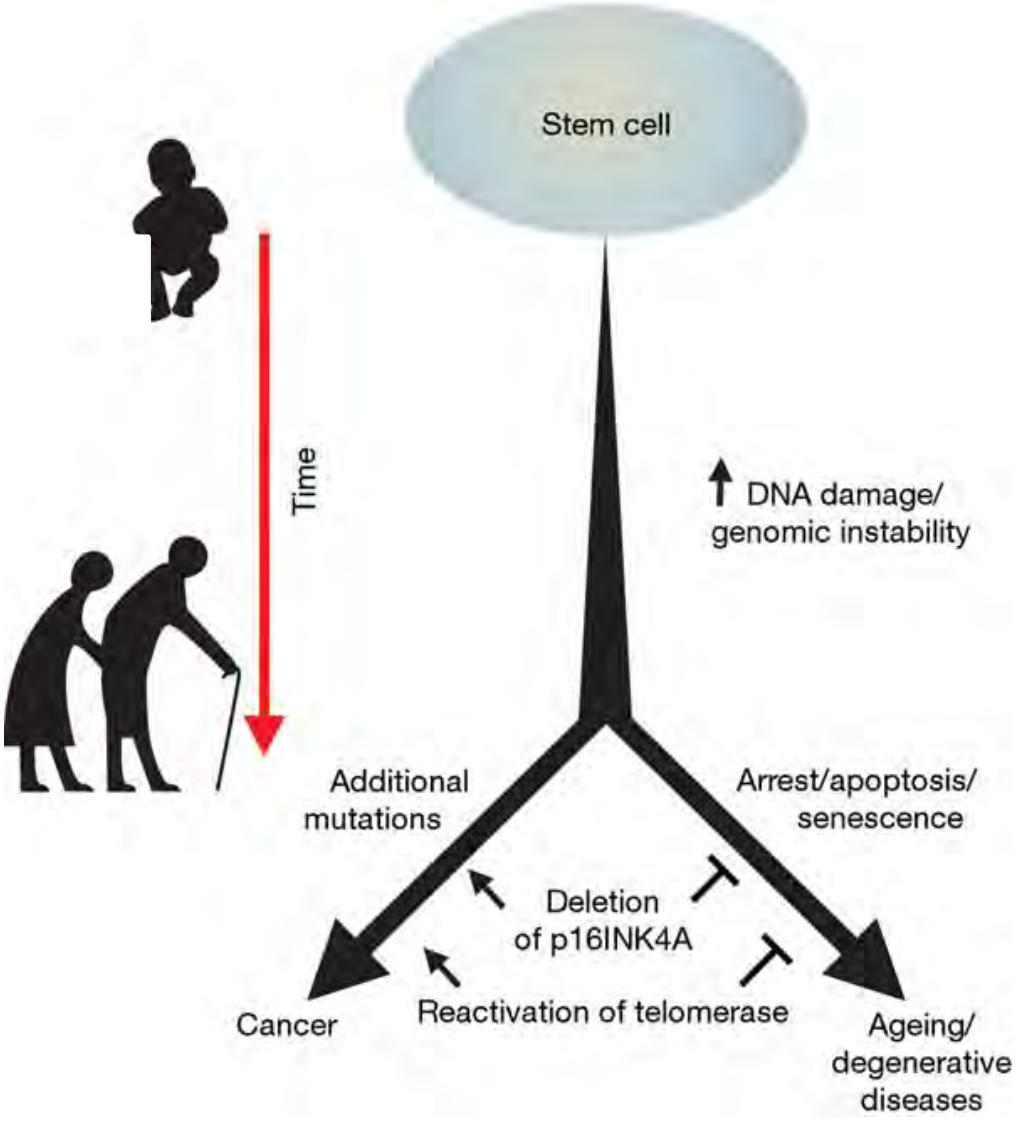
Aging is the major underlying risk factor for disease



Courtesy of NIH

The biologic hallmarks of aging

Increased prevalence of cancer with aging is more than “it just takes time”



Aging is changing our cells and the cellular environment

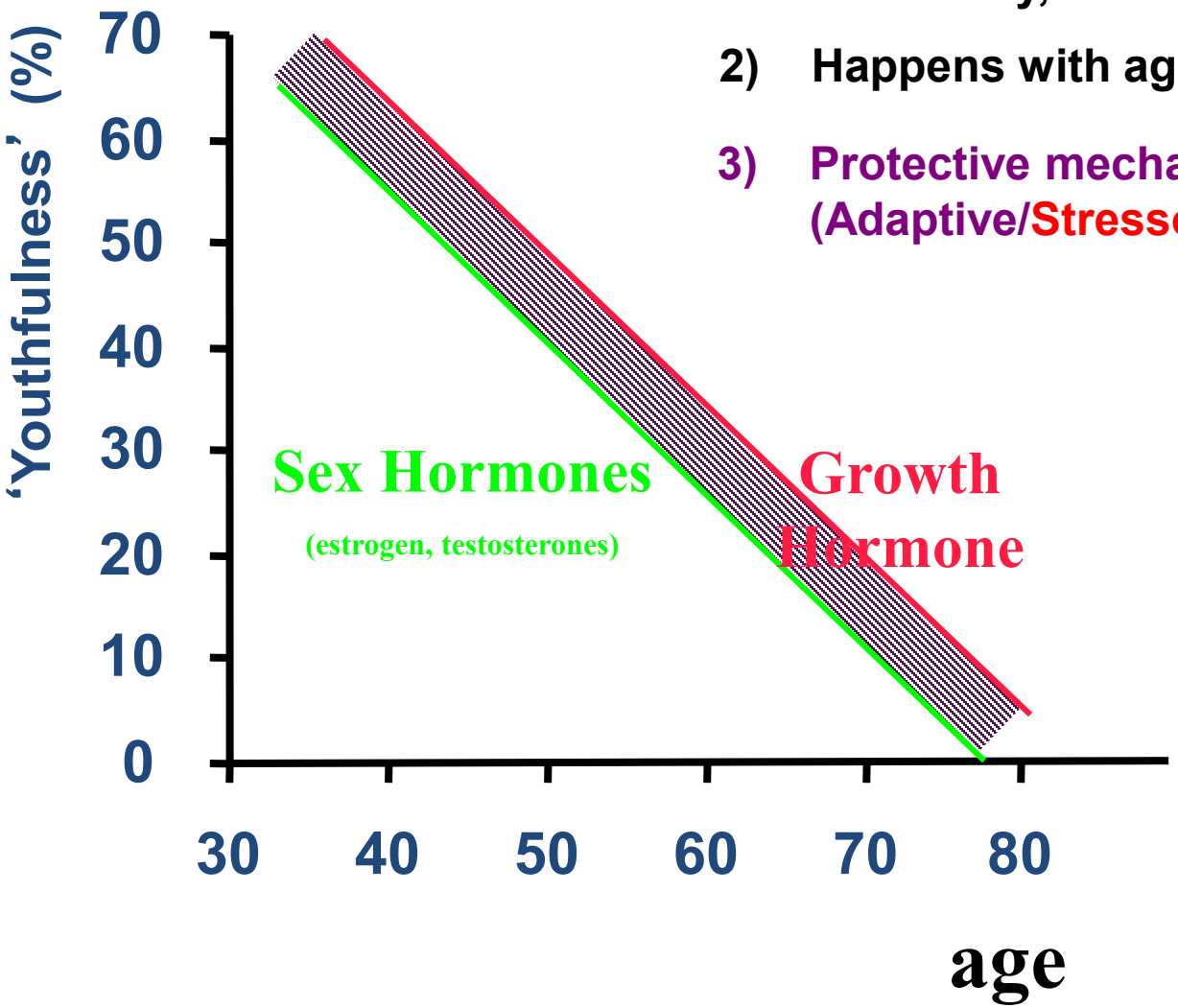
Diseases and responses to treatments or prevention strategies should not be assumed to work the same way in young and old

Drivers of Aging: A Conceptual Overview

1) Causes of aging (primary and secondary, wear and tear etc.).

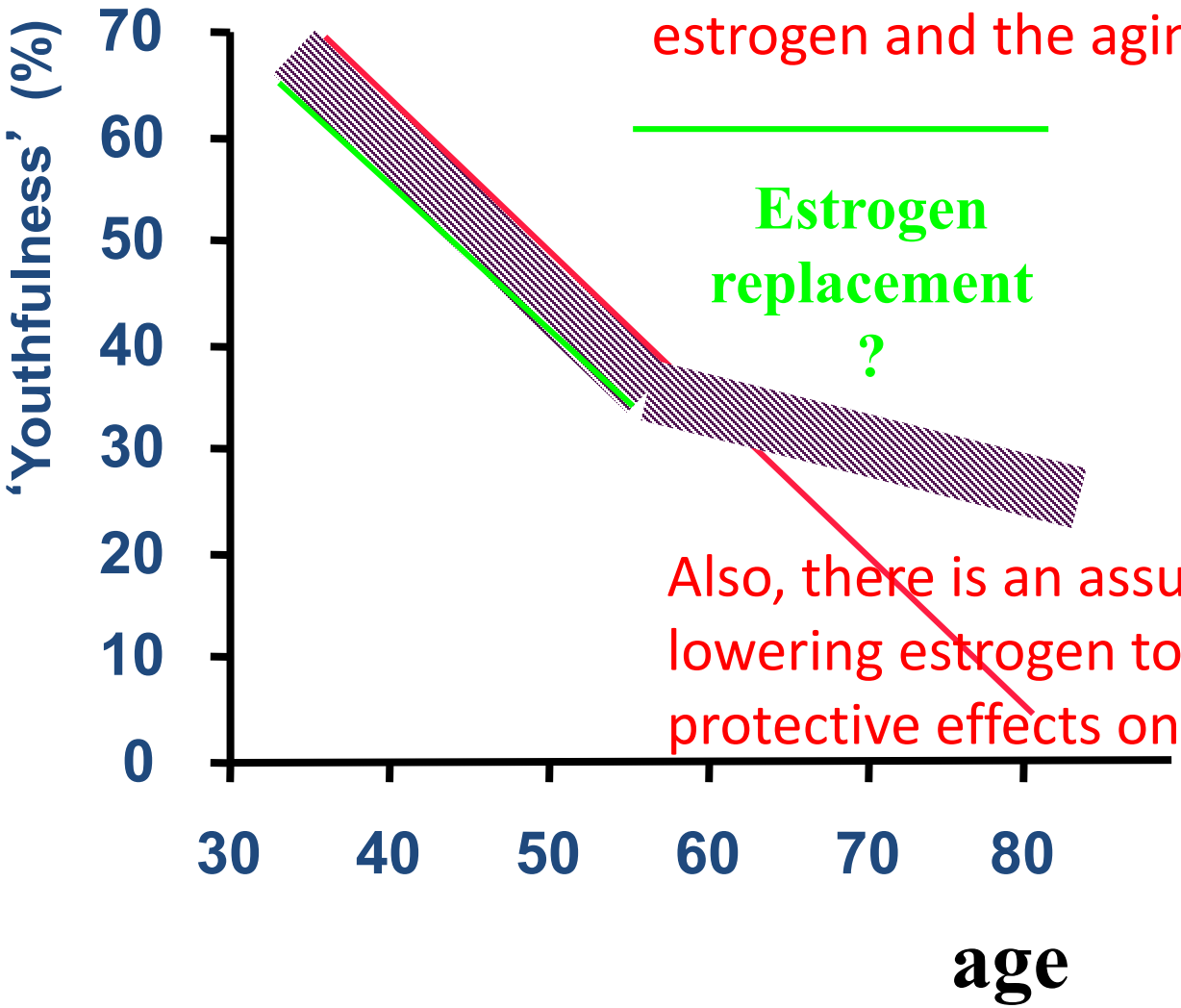
2) Happens with aging but have no role!

3) Protective mechanism of aging (Adaptive/Stressor/modifiers)



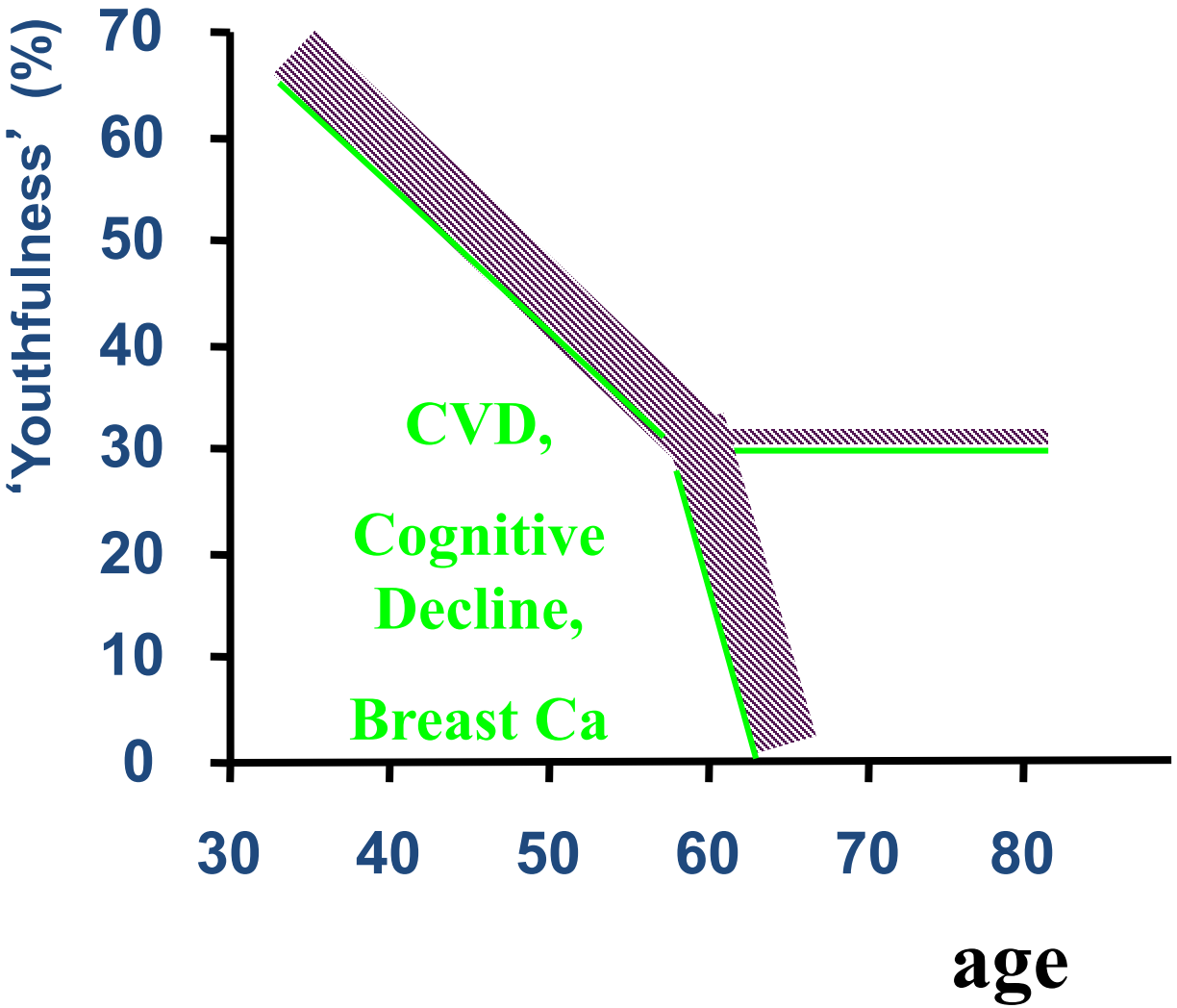
Can we delay or even reverse aging by replacing young factors?

There is a new interaction between estrogen and the aging environment!

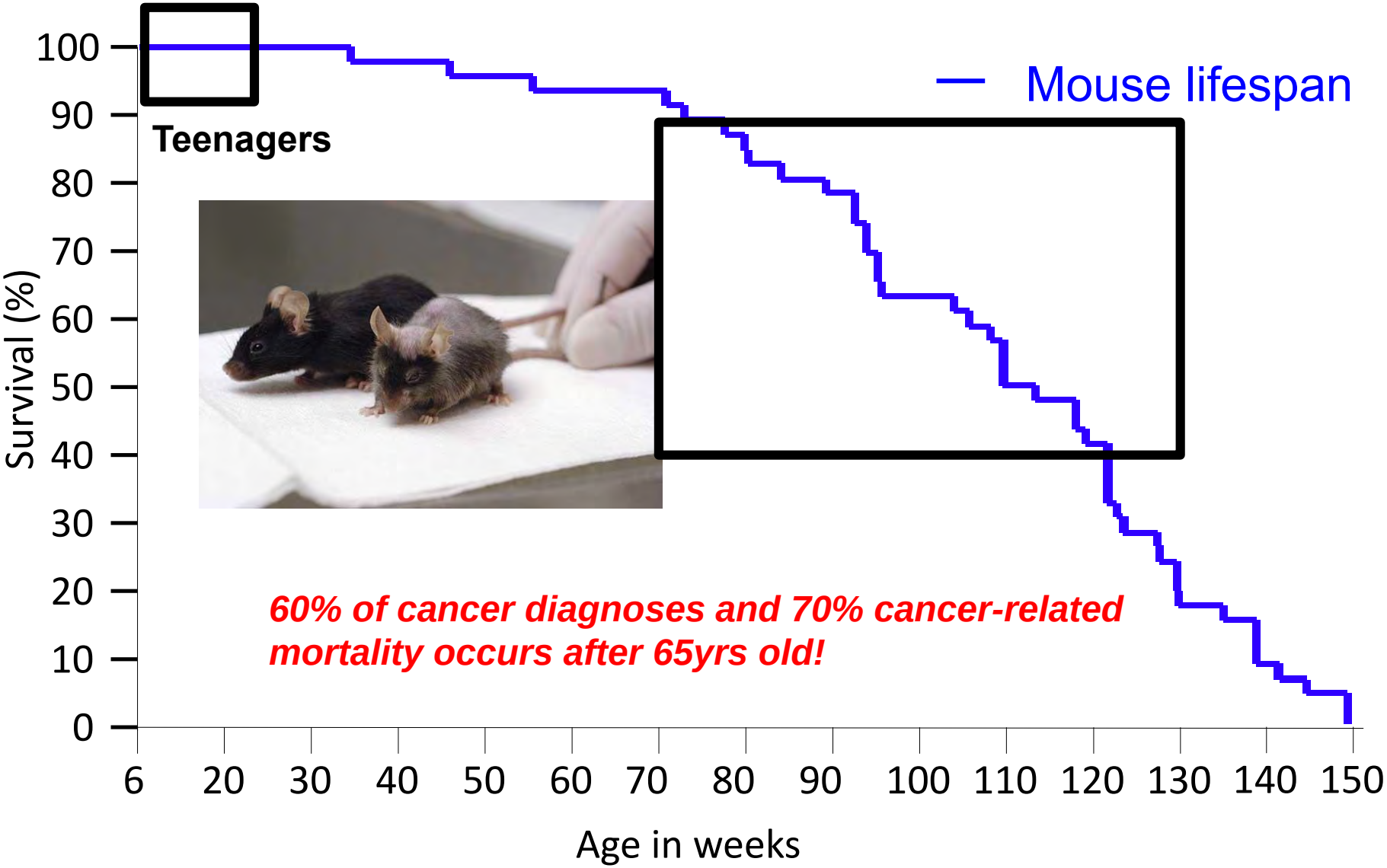


Also, there is an assumption that lowering estrogen tone has no protective effects on aging!

An Important lesson about interaction of 'young' hormones with an 'old' body



If cancer is a disease of aging, why do we study it in young animals?



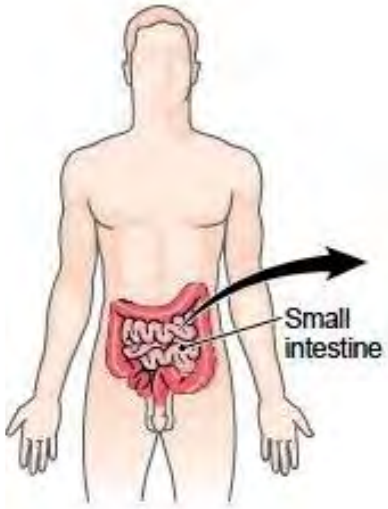
Why is cancer typically studied in young and why does it matter?

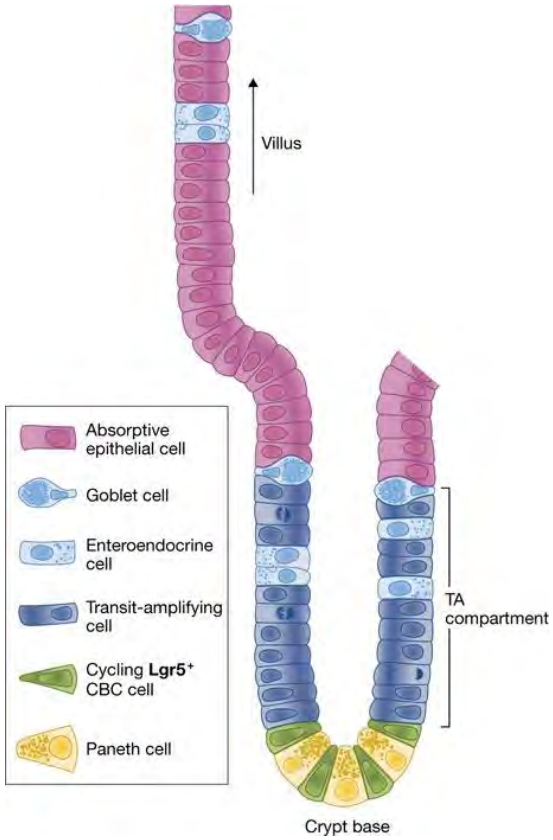
Barriers

- *Normal mice get cancer, but not typically the type that humans get, and the cancers they do develop require 1.5 to 2yrs to manifest*

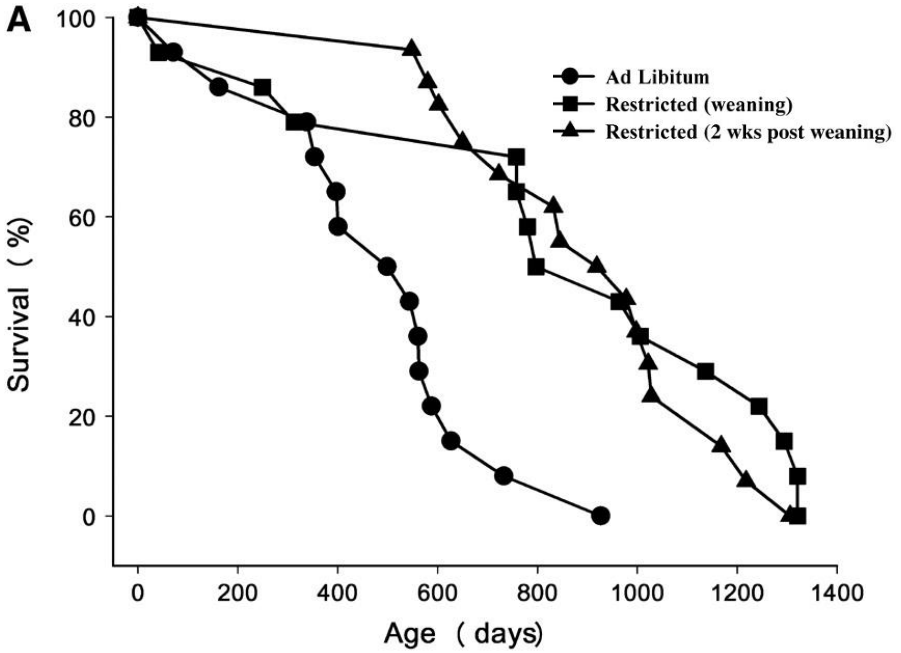
- *Mice have been engineered to get cancer in breast, pancreas, skin and other sites, but these cancers often develop at an early age*

- *Recent advances in mouse genetics have allowed us more control for when cancer starts……but*
- It takes *time*
- It takes *resources*
- It takes *patience*
- It takes *awareness*
- ***Less than 5% of cancer drugs tested in mice work in humans!***

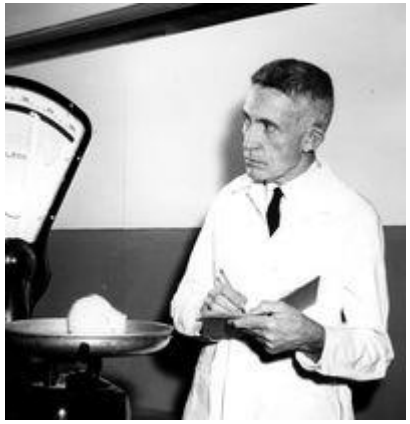

Small intestine

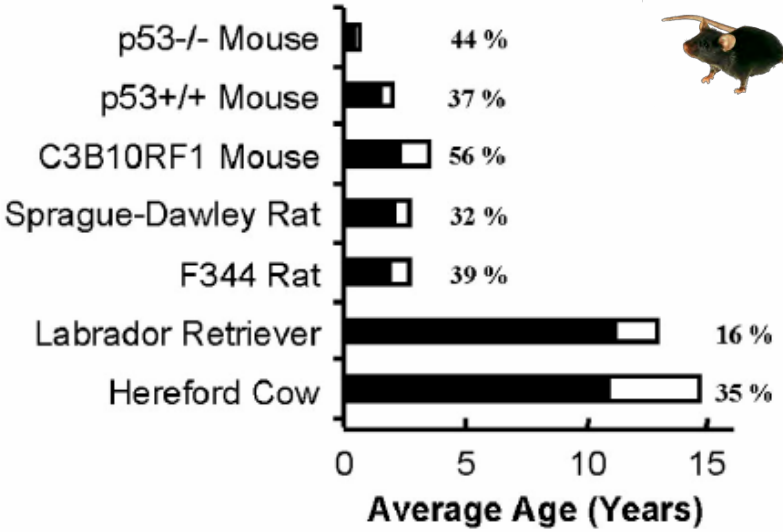

Absorptive epithelial cell
Goblet cell
Enteroendocrine cell
Transit-amplifying cell
Cycling Lgr5+ CBC cell
Paneth cell
Villus
TA compartment
Crypt base

Caloric Restriction: Eat less, live more



Clive McCay
1935





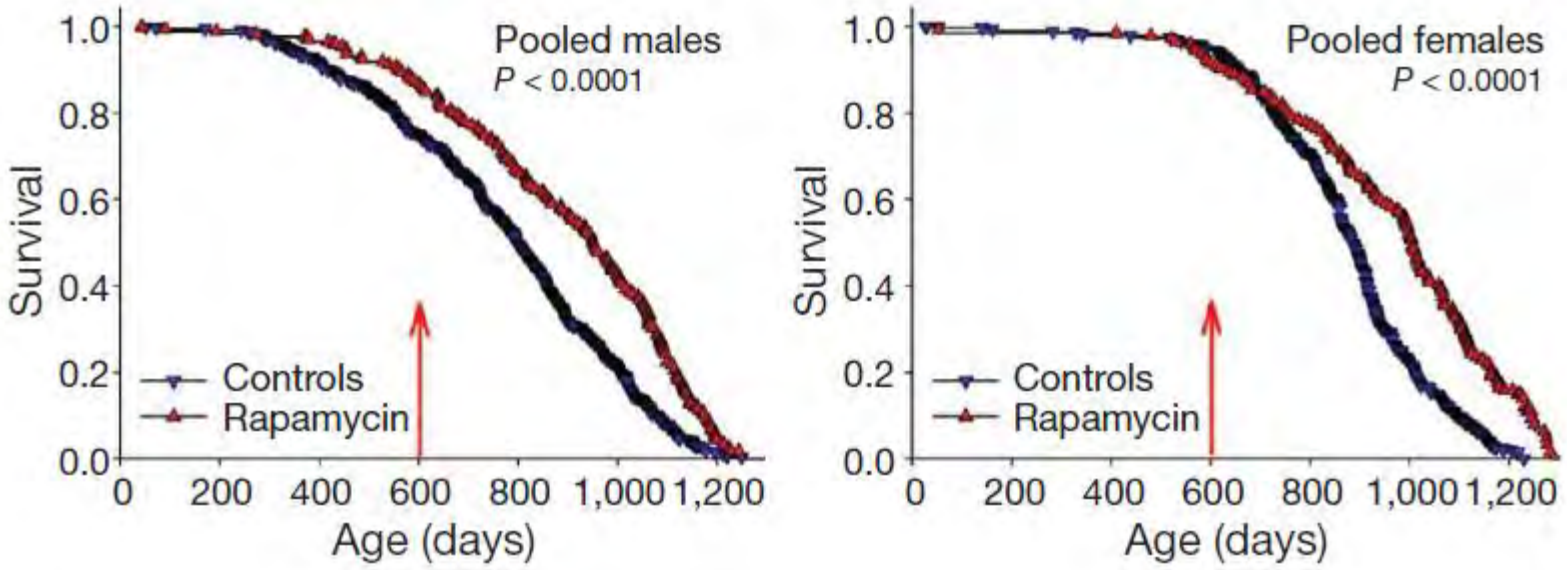
Rapamycin

- Also known as sirolimus, rapa is a macrolide produced by the bacterium Streptomyces hygroscopicus

- Has side effects in humans including:
  - -glucose intolerance
  - -slowed wound healing
  - -edema
  - -immunosuppression
  - -may promote sarcopenia

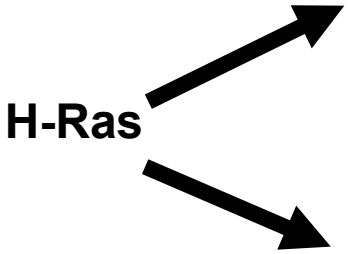
Rapamycin fed late in life extends lifespan in genetically heterogeneous mice

David E. Harrison[1]*, Randy Strong[2]*, Zelton Dave Sharp[3], James F. Nelson[4], Clinton M. Astle[1], Kevin Flurkey[1], Nancy L. Nadon[5], J. Erby Wilkinson[6], Krystyna Frenkel[7], Christy S. Carter[8], Marco Pahor[8]†, Martin A. Javors[9], Elizabeth Fernandez[2] & Richard A. Miller[10]*



- **Treatment began at 18 mo of age**
- **Improved longevity observed in males and females**

Young



Cell Death and Differentiation (2015) 22, 1764–1774

www.nature.com/cdd

Age-associated inflammation connects RAS-induced senescence to stem cell dysfunction and epidermal malignancy

L Golomb[1], A Sagiv[1], IS Pateras[2], A Maly[3], V Krizhanovsky[1], VG Gorgoulis[4,5,6,7], M Oren*[,1] and A Ben-Yehuda*[,3]

Summary

-Aging is the major underlying risk factor for cancer risk

-Aging may be an important modifier of how cancer prevention and treatment strategies respond

-Geroscience seeks to understand the molecular and cellular mechanisms responsible for aging as a major driver of common chronic conditions and diseases of older people.

Trans-NIH Geroscience Interest Group (GSIG)

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