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.
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.
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)

The diagram shows the decline in 'Youthfulness' (%) with age. Key factors include Sex Hormones (estrogen, testosterone) and Growth Hormone.
Can we delay or even reverse aging by replacing young factors?

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

Estrogen replacement?

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

Graph showing the decrease in ‘youthfulness’ (%) with age, with a significant increase in CVD, Cognitive Decline, and Breast Ca after age 60.
If cancer is a disease of aging, why do we study it in young animals?

60% of cancer diagnoses and 70% cancer-related mortality occurs after 65yrs old!
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!
Drug X

Genetic "scissors" only expressed in intestinal stem cells

The Apc gene, which is required to prevent tumorigenesis, is engineered to have sites that the scissors recognize and cut it out.

Scissors only work when we give a specific drug Apc.
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

- Treatment began at 18 mo of age
- Improved longevity observed in males and females
No cancer

H-Ras

Skin hyperplasia

Young

Rapid hair growth

H-Ras

Dysplasia

Old

Squamous cell carcinoma
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.

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