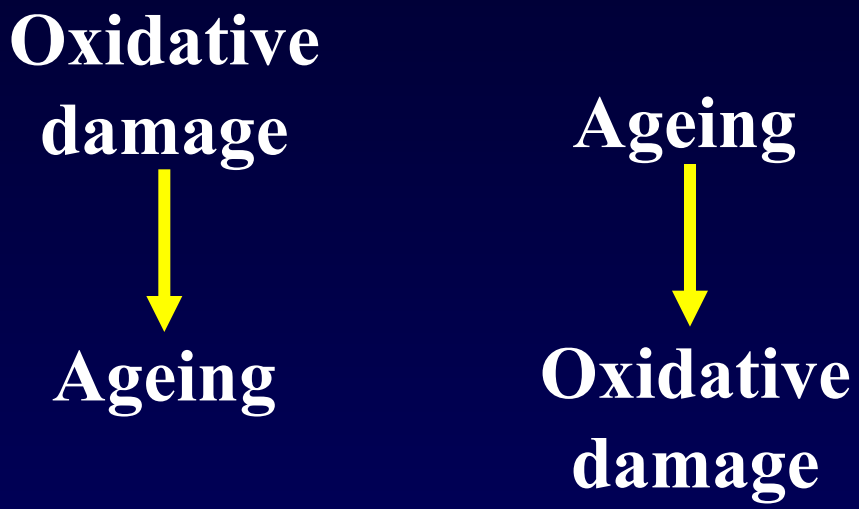
What does the age increase in oxidative damage signify?



- Pathology is typically accompanied by increased oxidative damage
- Ageing entails extensive, severe pathology
- Whatever the cause of ageing, one would expect to see increased levels of oxidative damage

?

Cellular maintenance processes

Stochastic molecular damage

Ageing

Are there any alternatives?

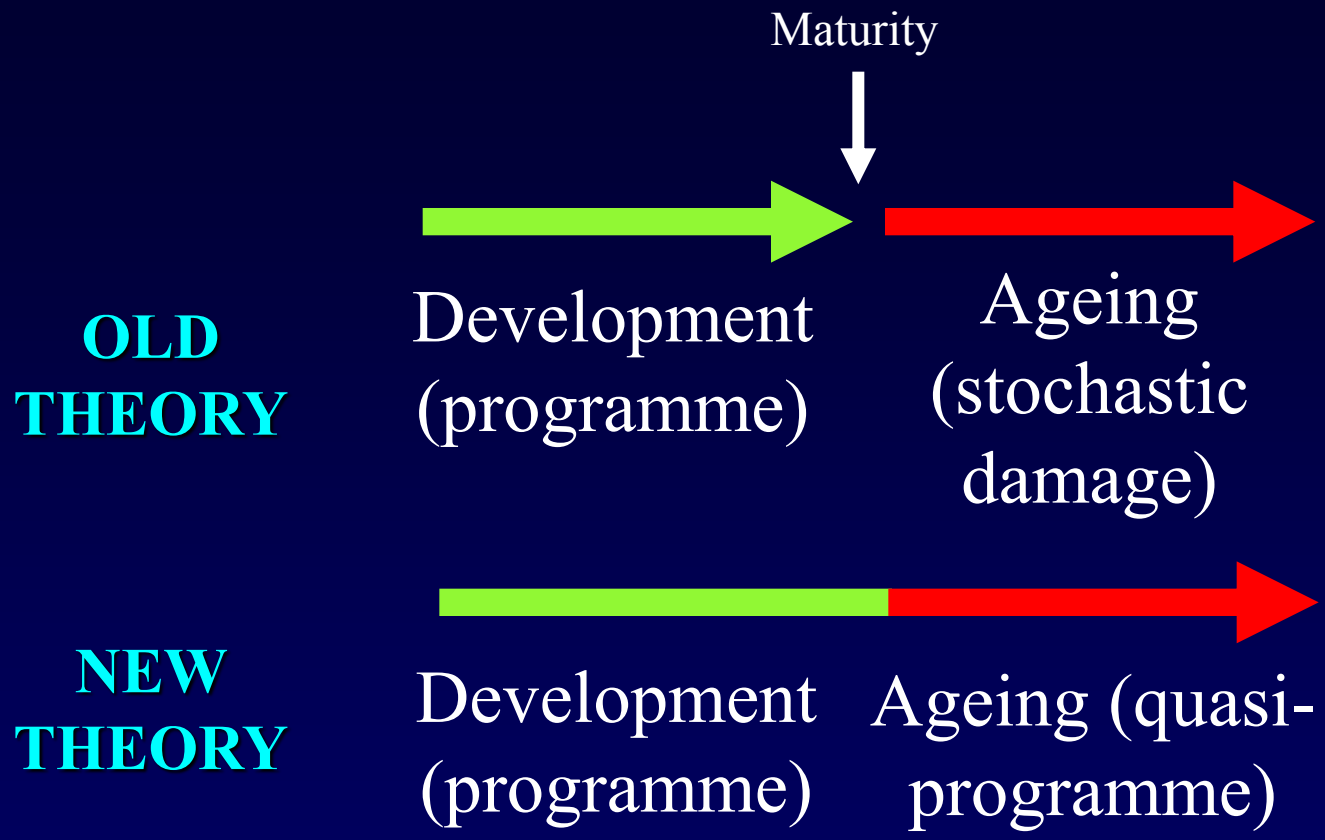
Mikhail V. Blagosklonny
Roswell Park Cancer Institute,
Buffalo NY, USA

Stochastic molecular damage

Mikhail V. Blagosklonny
Roswell Park Cancer Institute,
Buffalo NY, USA

Stochastic molecular hyperfunction

Ageing as quasi-programmed



Quasi-programmed ageing: non-adaptive continuation of developmental processes during adulthood

Result: Hyperfunction

Hypertrophy/hyperplasia, atrophy

“If you left water running after taking a bath, then a ‘program’ for filling the bathtub would become a ‘quasi-program’ to flood your apartment”

M.V. Blagosklonny *Cell Cycle*. 2007 6: 2997

Many ageing-related diseases are attributable to hyperfunction

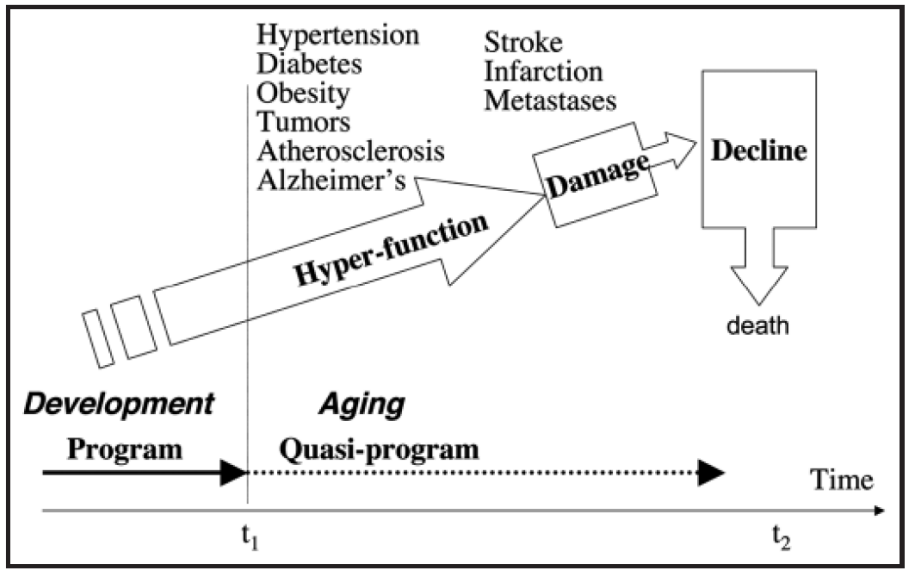


Figure 1. Organism senescence: a quasi-program of post-development. Once development is completed, a program for development is not switched off, thus becoming a quasi-program for aging. This hyper-functional quasi-program is manifested as diseases of aging, leading to damage and secondary decline.

Old theory

Accumulation of molecular damage

↓

Aging

↓

Pathology, death

New theory

Hyperfunction
(hypertrophy, atrophy)

↓

Pathology

↓

Death

Molecular damage

How do insulin/IGF-1/TOR signalling and DR control ageing?

IIS/TOR

⊣

Somatic maintenance
(e.g. autophagy)

⊣

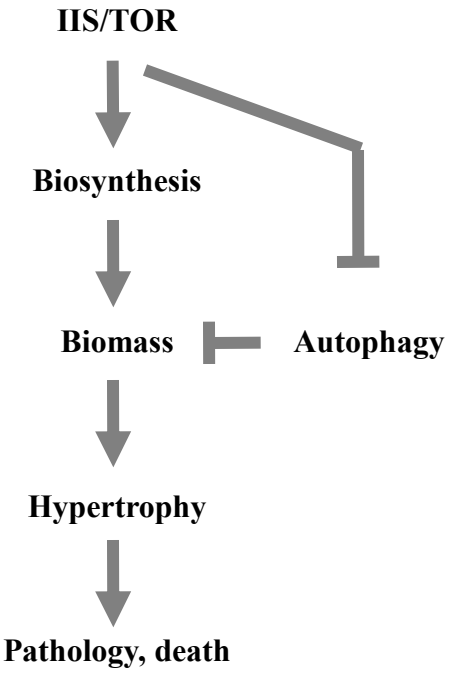
Molecular damage

↓

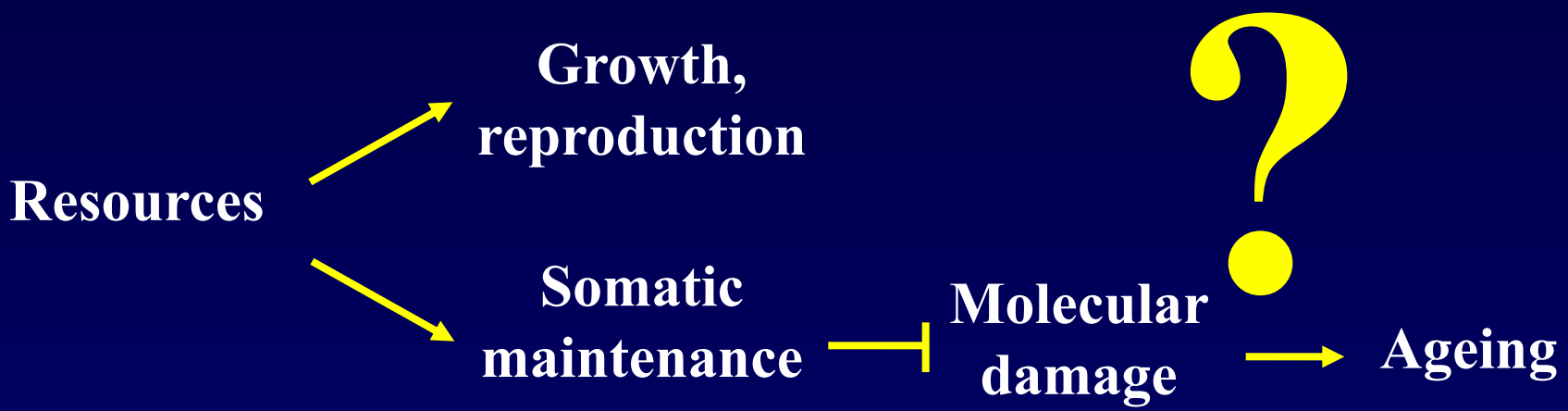
Aging

↓

Pathology, death

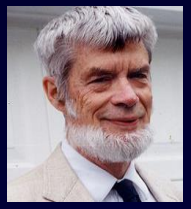


Hyperfunction and the evolution of ageing



Disposable soma theory

Integrating the evolutionary and hyperfunction theories



George C. Williams

Ageing evolves as a side-effect of natural selection in favour of mutations that cause a benefit during youth

Development, early adulthood

Programmed developmental processes, e.g. growth → Quasi-programmed processes, e.g. growth

↓ Reproduction

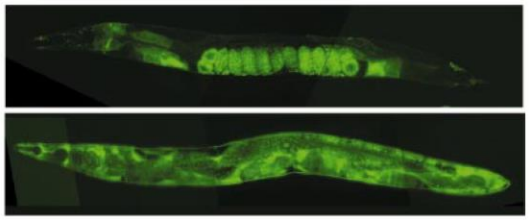
↓ Hypertrophy, hyperplasia, atrophy → Pathology → Death

Ageing

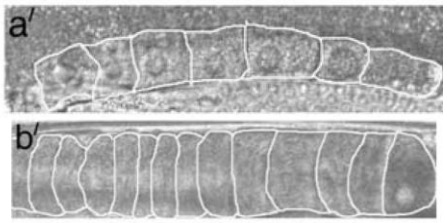
- **Mutations increasing growth may increase reproduction (and therefore fitness), but also increase hyperfunction (e.g. hypertrophy, hyperplasia) later**
- **Trade off between biomass production now (promoting reproduction) and hyperfunction later**

Hyperfunction and ageing in *C. elegans*?

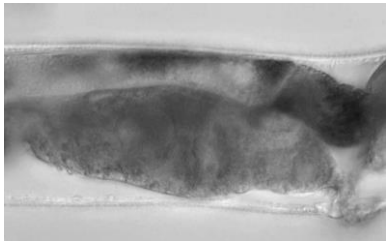
Hypertrophy during aging in *C. elegans*



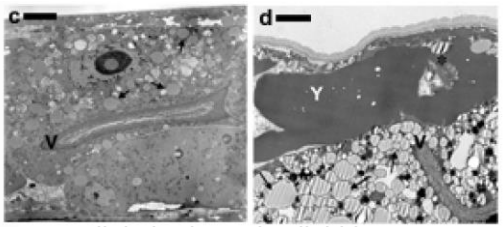
Yolk accumulation after sperm depletion
(Herndon *et al*)



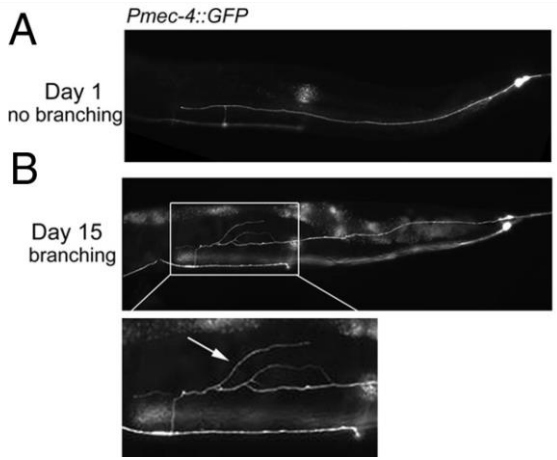
Stacking of oocytes after sperm depletion
(Jud *et al*)



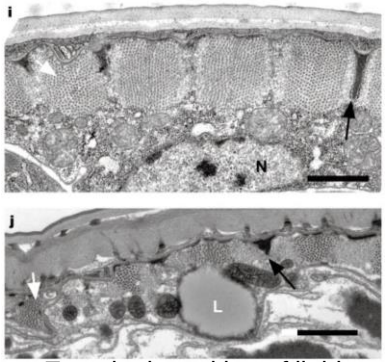
Endoreduplication in oocytes leads to tumour-like intra-uterine masses
(Golden *et al*)



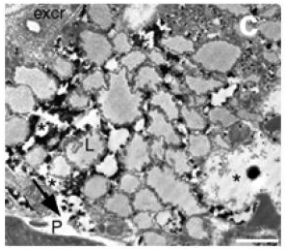
Yolk in body cavity, lipid in intestinal cells
(Herndon *et al*)



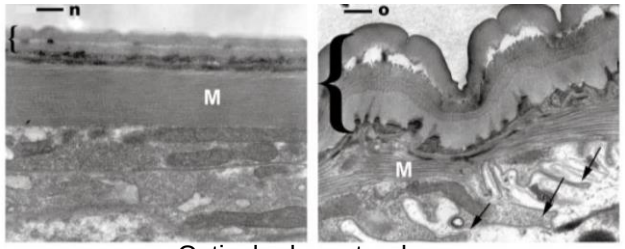
Neurite outgrowth
(Tank et al)



Ectopic deposition of lipid in body wall muscle
(Herndon *et al*)



Ectopic deposition of lipid in hypodermis
(Herndon *et al*)



Cuticular hypertrophy
(Herndon et al)

Gems and de la Guardia 2013,
Antioxidants and Redox Signaling

Summary

The hyperfunction theory provides a plausible alternative to molecular damage as a central mechanism of ageing

The evolutionary and hyperfunction theories may readily be integrated: *disposable soma 2*

Growth hormone, IGF-1, insulin/IGF-1 signalling, TOR

↓

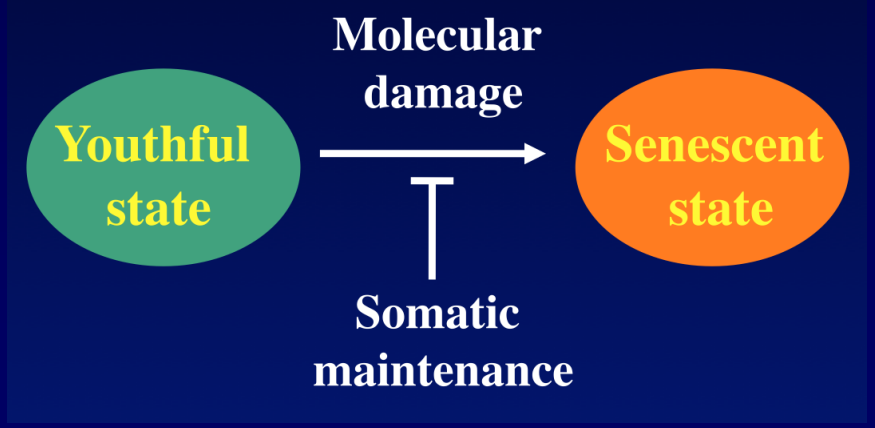
Quasi-programmes, hyperfunction

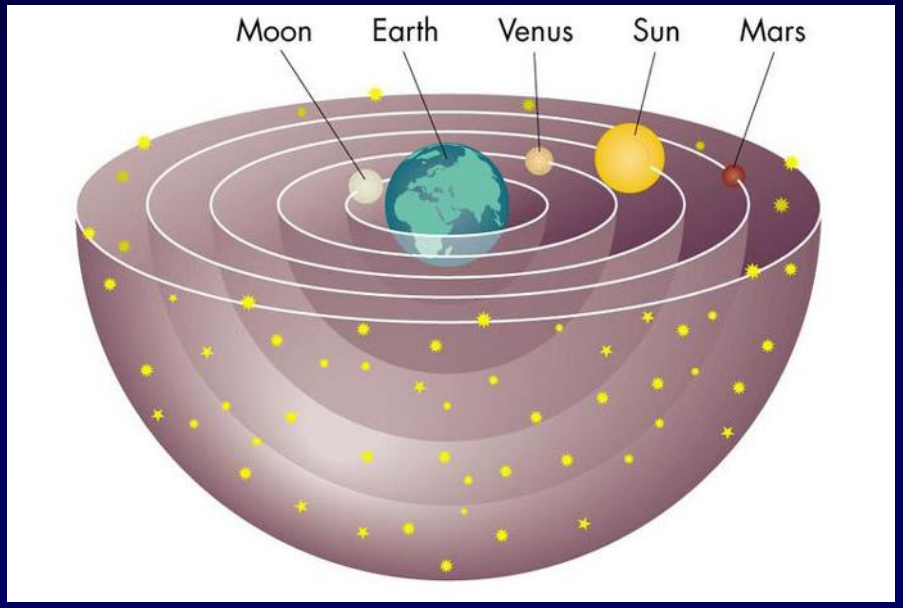
?

↓

AGEING

Damage maintenance paradigm as folk theory?





Geocentric solar system model

Is there going to be a cure for ageing?

Developments within Biogerontology

1983: First long lived *C. elegans* mutant described
1996: First long-lived mouse mutant, first longevity genes sequenced in *C. elegans*
2001: Long-lived insulin/IGF-1 mutant fruitflies
2003: Long-lived insulin/IGF-1 mutant mice
2005: Drugs extending lifespan in *C. elegans*, growth hormone gene variation linked to human longevity
2007: Hyperfunction theory of ageing proposed
2008: 10-fold increase of lifespan in *C. elegans*
2009: Mutational or pharmacological inhibition of mTor pathway increases mouse lifespan, evidence that dietary restriction increases primate lifespan
2008-12: Crisis in molecular damage theory

Rapid progress

Proven treatments for human ageing derived from biogerontology

Average life expectancy may decrease due to epidemic of obesity

The Future

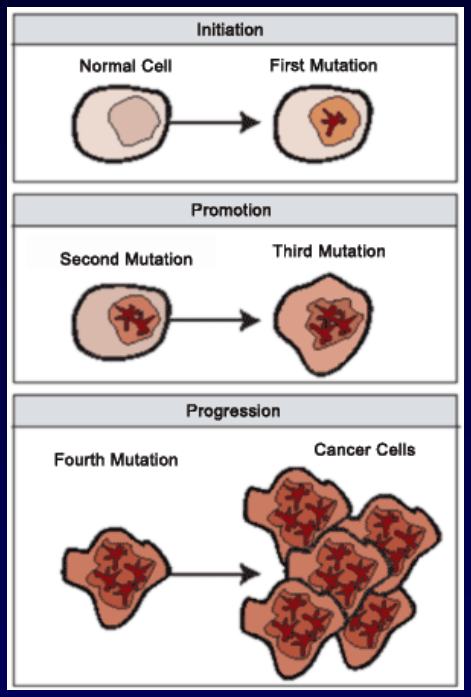
- Effective treatments for human ageing are not imminent
- The genetics of ageing is rapidly identifying potential drug targets
- The fundamental biology of ageing is probably in the process of being solved
- Treatments for ageing are very likely to be devised at some point
- When, what level of efficacy?

A magic bullet for ageing?

Bacterial pathogens

Antibiotics = broad spectrum treatment

Magic bullet



Cancer

Chemotherapy
Radiotherapy
Surgery

No magic bullet

Ageing

One probable mechanism: quasi-programmed hyperfunction

Magic bullet unlikely?

Looking into the future

2015: Drugs targeting longevity control pathways identified and proven effective in nematodes, fruitflies and mice

2007-2025: Underlying biology of ageing is understood

2020-2040: First successful human trials, show reduction in age-related pathology at advanced ages

However: effects are small (+1-3 yrs) relative to benefits e.g. of exercise, controlled diet, social engagement

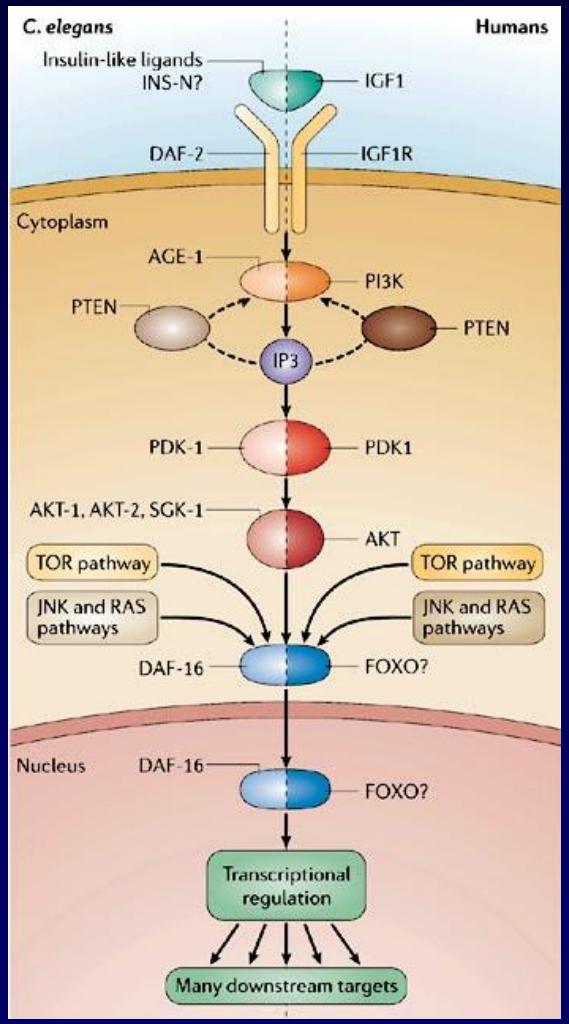
2015-2040: More powerful treatments from full understanding of ageing, effective in nematodes, fruitflies and mice

2030- : Successful human trials further slowing ageing, initially +2-5 years, but increasing slowly decade by decade

2100- : Treatments coming into use that can add several decades to life expectancy

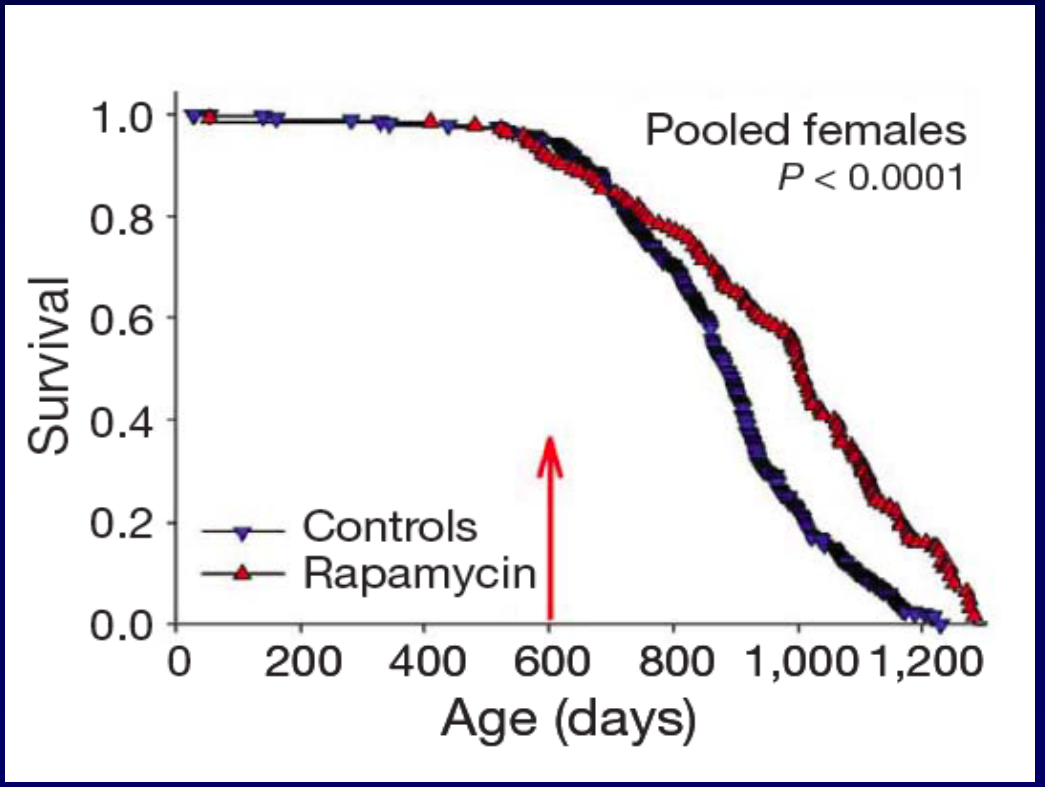
Lifespan control pathways include drug targets

TOR = target of rapamycin



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]*



Nature 2009

The Institute of HEALTHY AGEING

UCL

Catherine Au
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Marina Ezcurra
Inna Feyst
Ann Gilliat
Yila de la Guardia
Rosina Pryor
Michele Riesen
Jennifer Tullet
Eleanor Tyler

Mikhail Blagosklonny

Thank you!

Blagosklonny MV. Aging and immortality: quasi-programmed senescence and its pharmacologic inhibition. *Cell Cycle* 2006 5: 2087.

Blagosklonny MV. Paradoxes of aging. *Cell Cycle* 2007 6: 2997.

Blagosklonny MV. Aging: ROS or TOR. *Cell Cycle* 2008 7: 3344.

Gems D, Partridge L. Genetics of longevity in model organisms: Debates and paradigm shifts. *Annual Review of Physiology* 2013 75: 621.