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# Advances in Medicine

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## Aging Young: Turning Back the Biologic Clock of Time

Mark Pettus MD
Associate Professor of Medicine
University of Massachusetts Chan Medical School

January 26, 2024

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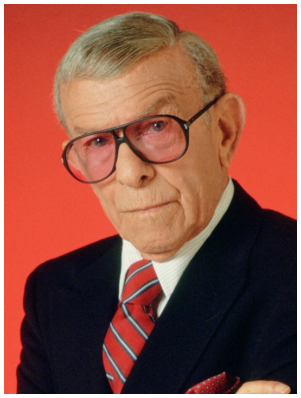

"First you forget names, then you forget faces. Next you forget to pull up your zipper and finally, you forget to pull it down."

George Burns
1896 - 1996

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# Learning Objectives

- Review the current hallmarks (drivers) of aging.
- Review current research on "information theory of aging" and epigenetic clocks
- Distinguish chronologic age from biologic age
- Review the evidence to support health-promoting lifestyle on the modification of biologic age

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## Questions for consideration:

- How long can humans actually live?
- Is getting old always synonymous with poor quality of life?
- What is the difference between chronologic age and biologic age?
- Is aging a disease?
- If so, can it be “treated”?
- As age is most strongly correlated with all advanced chronic diseases, should we focus on treating diseases or treating aging?
- Can age be regressed?

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Person / Earth / Oldest

## Jeanne Calment

At the moment of writing, the overall record for the oldest person living belongs to **Kane Tanaka (Japan)**. Kane, who is now aged 118, is only fours years shy of breaking the record of oldest person ever, which currently belongs to the Jeanne Louise Calment (France), who was born on 21 February 1875 and died aged 122. Sep 30, 2021

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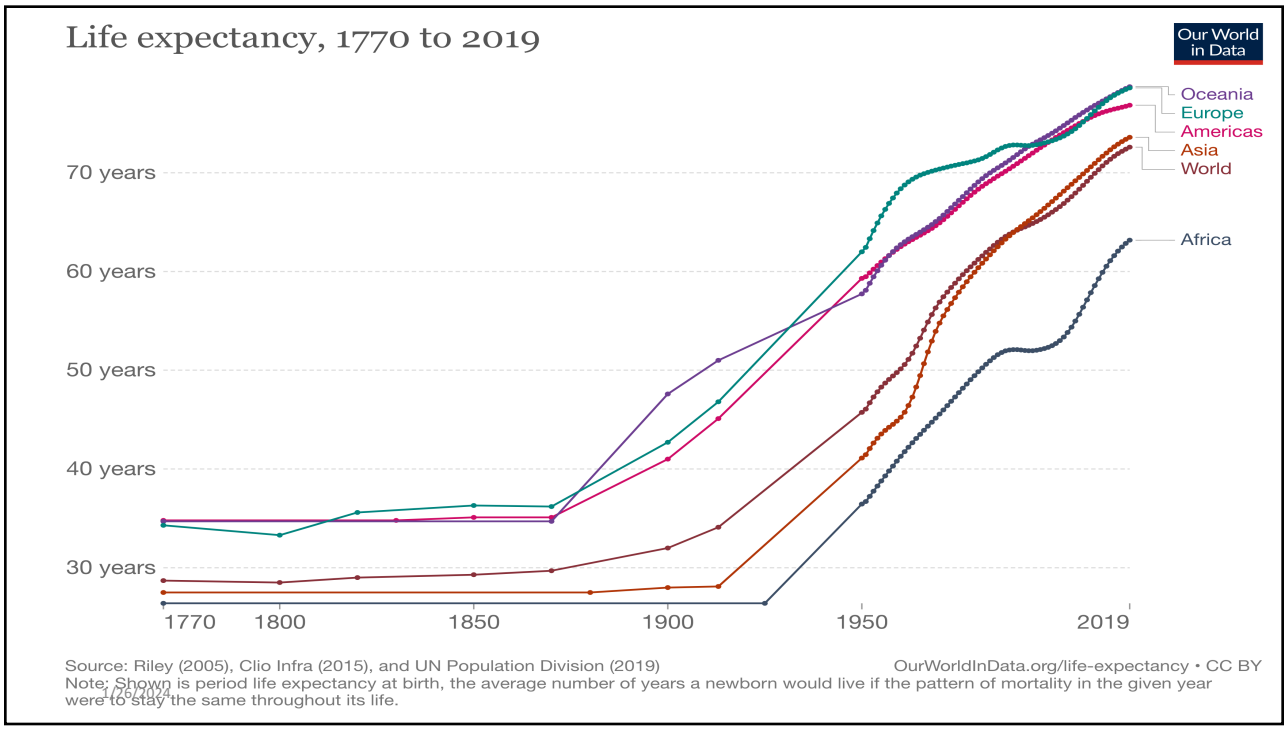


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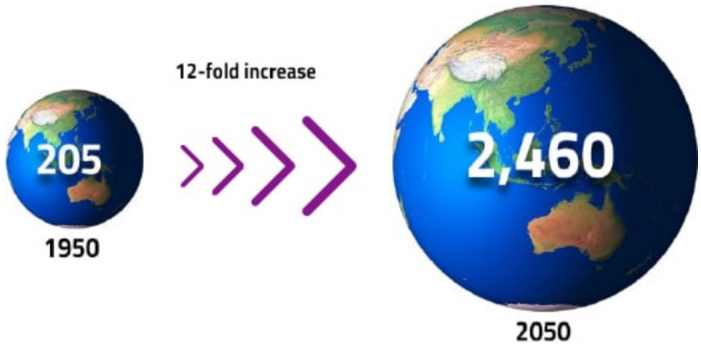
# The silver tsunami




The "silver tsunami" is upon us. The world is experiencing a rapid increase in its aging population and the global population of over 60s will surpass two billion by 2050: a 12-fold increase from 1950 (World Health Organization, 2021).

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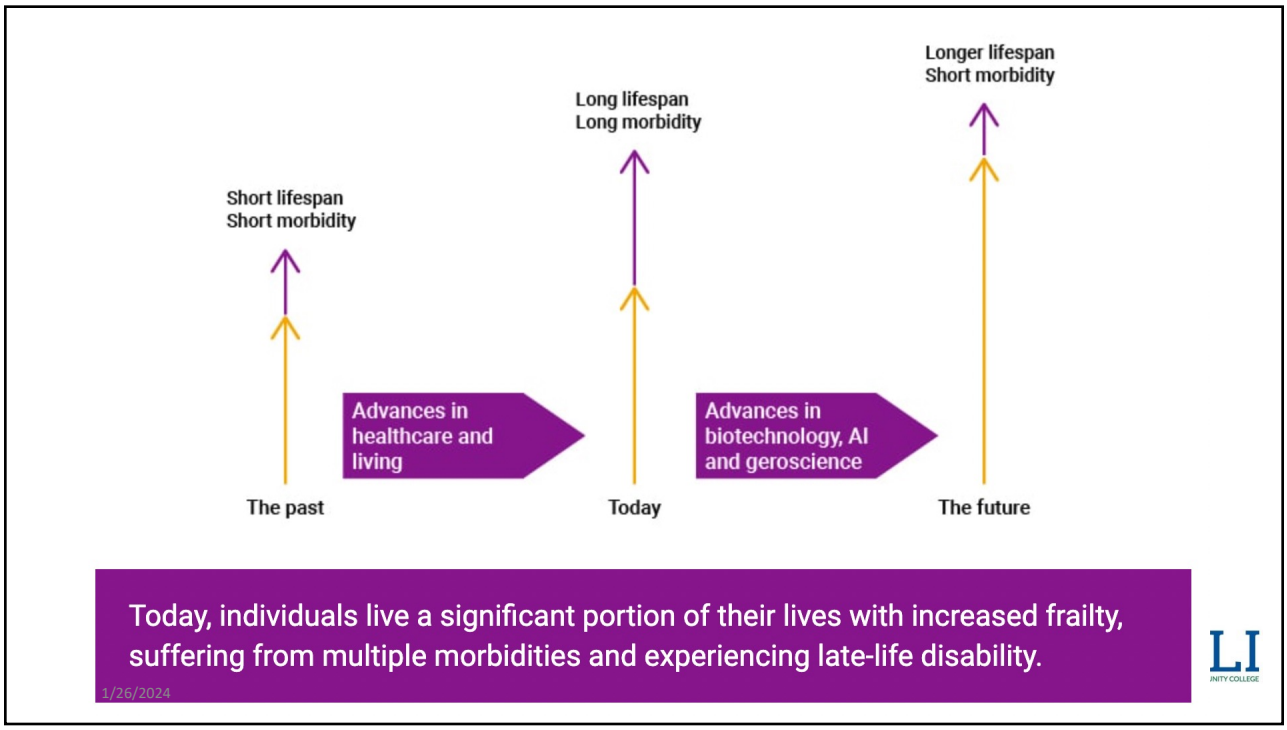
Longer lifespan
Short morbidity
Long lifespan
Long morbidity
Short lifespan
Short morbidity
Advances in healthcare and living
Advances in biotechnology, AI and geroscience
The past
Today
The future
Today, individuals live a significant portion of their lives with increased frailty, suffering from multiple morbidities and experiencing late-life disability.
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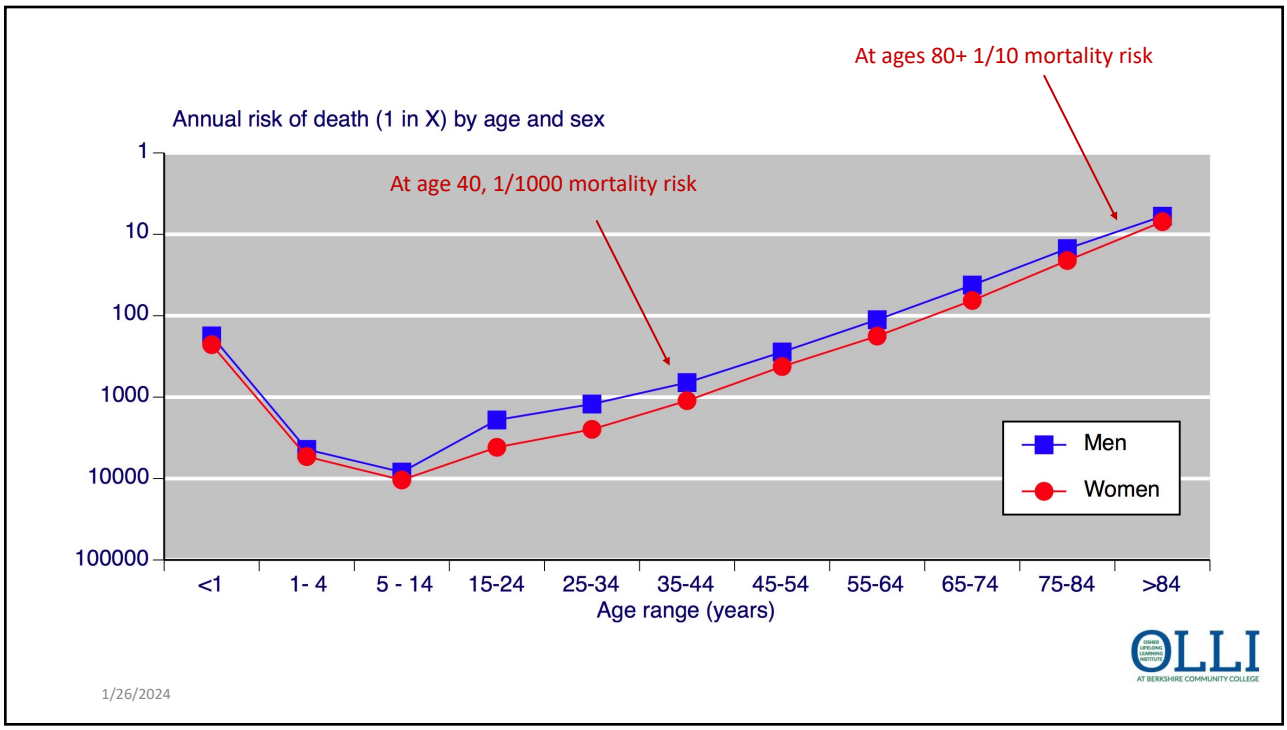
At ages 80+ 1/10 mortality risk
Annual risk of death (1 in X) by age and sex
At age 40, 1/1000 mortality risk
1
10
100
1000
10000
100000
Men
Women
<1
1- 4
5 - 14
15-24
25-34
35-44
45-54
55-64
65-74
75-84
>84
Age range (years)
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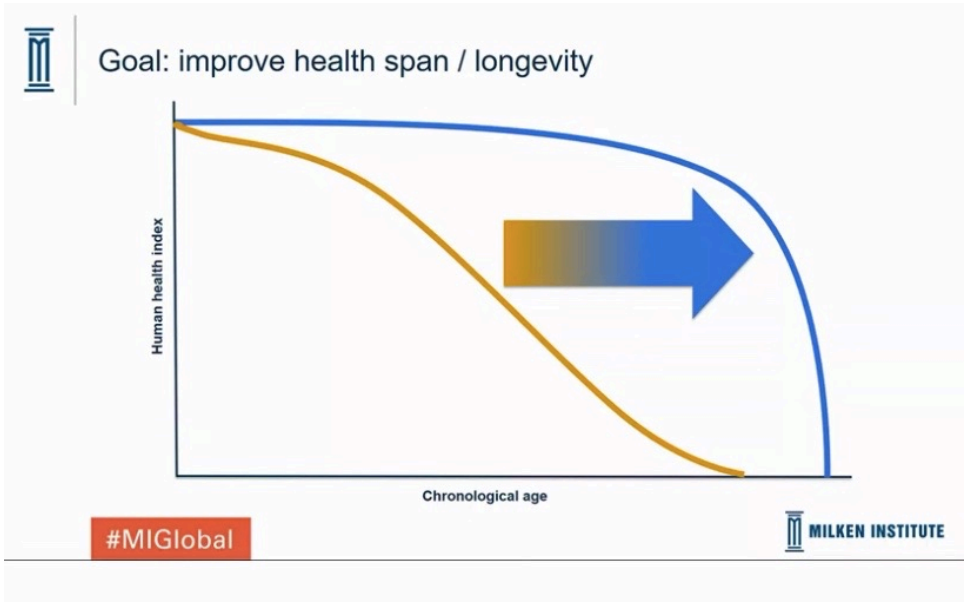


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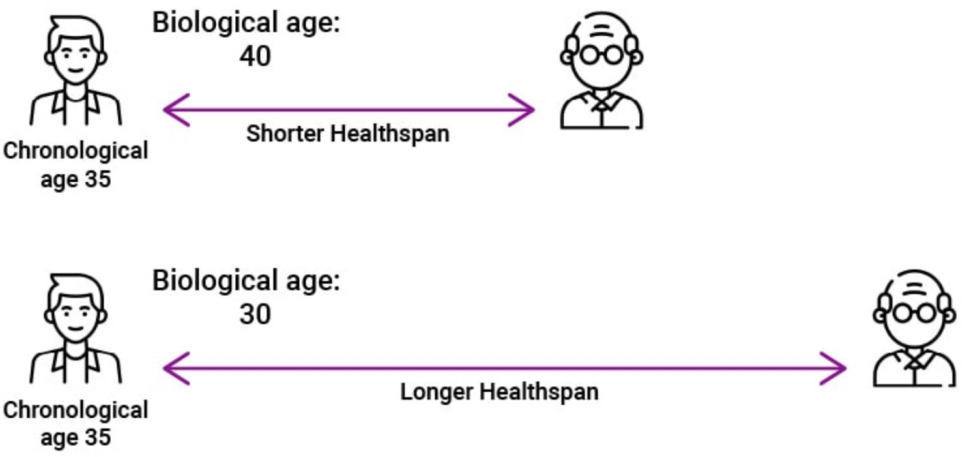


Two individuals with the same chronological age could have very different healthspans. This would be better captured with an accurate biological age, which is a better representation of the individual's internal health status.

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"Only 8% of what contributes to longevity can be traced to genetics. Over 90% of what contributes to longevity and healthy aging is lifestyle."

Eric Verdin MD
President and CEO, Buck Institute

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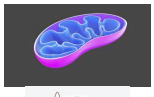
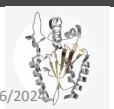
Genetics + Environment

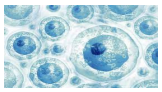
Epigenetic Regulation

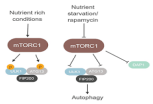

Genomic Instability


Telomere attrition


Mitochondrial Bioenergetics


Loss of Proteostasis


Stem cell depletion


Deregulated Nutrient Sensing


Altered Intercellular Communication


Cellular Senescence

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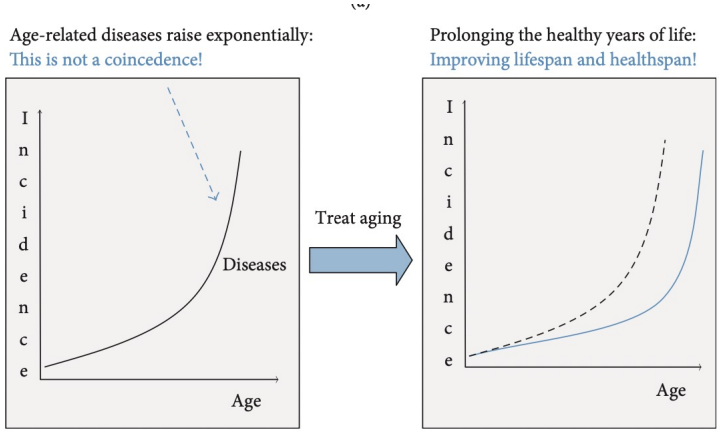
## Treating Diseases vs. Treating Aging

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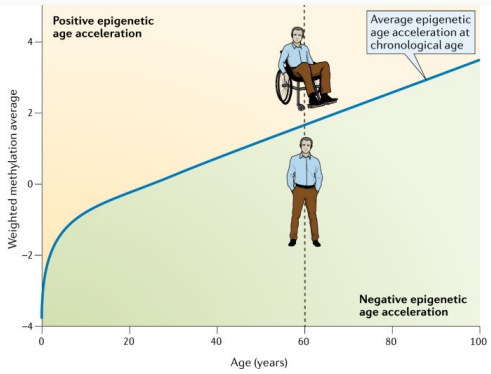
Review Article | Published: 11 April 2018

EPIGENETICS

### DNA methylation-based biomarkers and the epigenetic clock theory of ageing

Steve Horvath & Kenneth Raj

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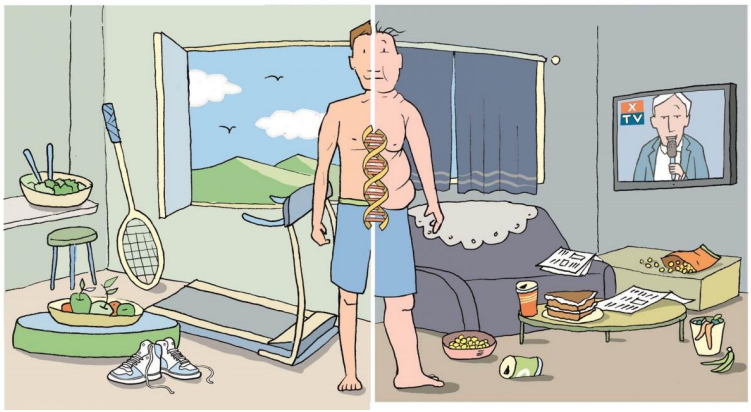
# Epigenetics:

A life with many possibilities.



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## Health as a byproduct of gene-environmental compatibility

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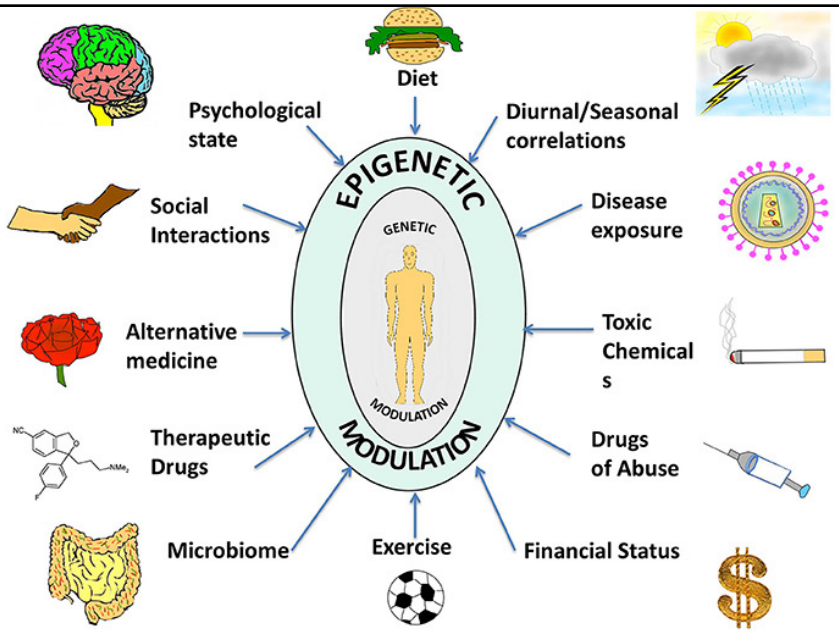


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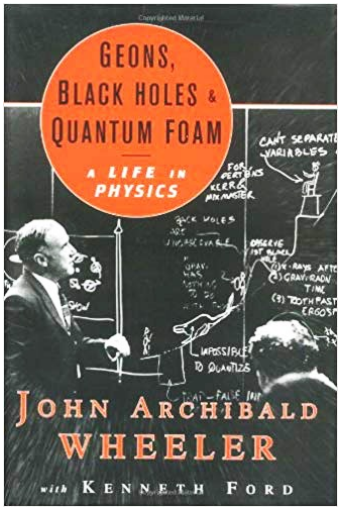


"It from bit symbolizes the idea that every item of the physical world has at bottom…an immaterial source and explanation…that all things physical are information-theoretic in origin and that this is a participatory universe"

**John Archibald Wheeler**

**Particles….Energy….Information**

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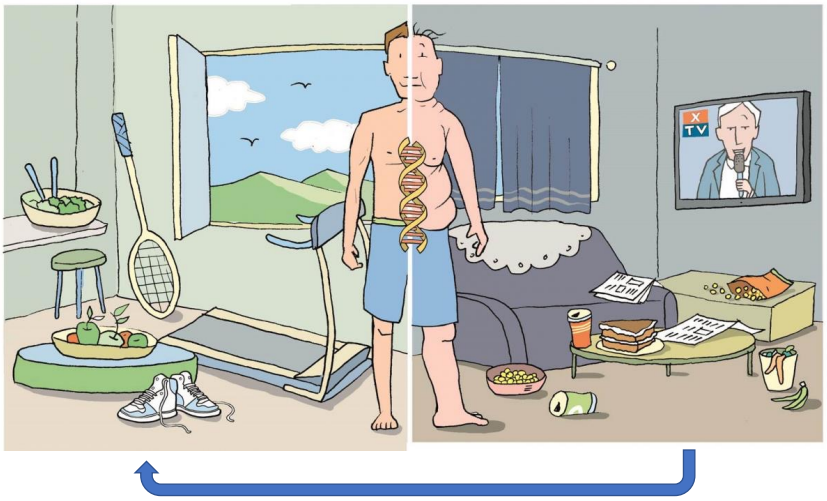


Epigenetic Reprogramming

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Cell Metabolism

CellPress

Available online 4 January 2024

In Press, Corrected Proof What's this?

Review

# Human trials exploring anti-aging medicines

Leonard Guarente [1 2], David A. Sinclair [2 3], Guido Kroemer [2 4 5 6]

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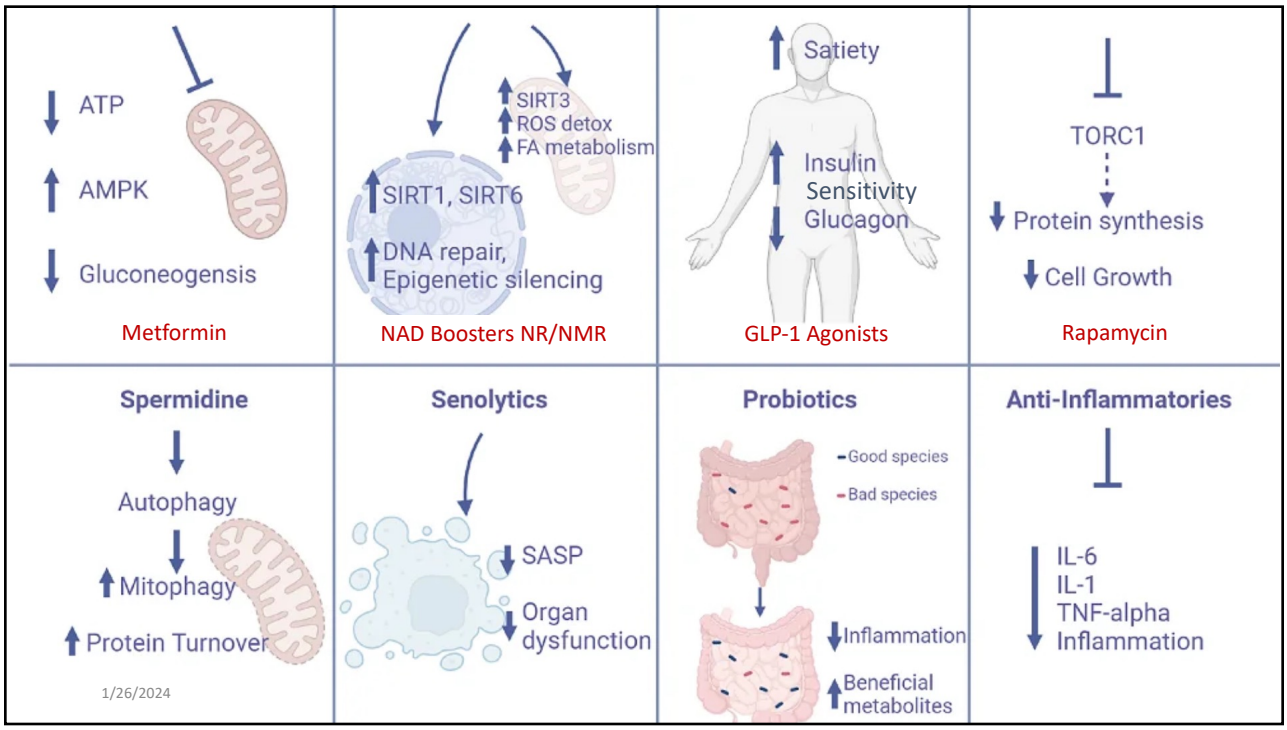


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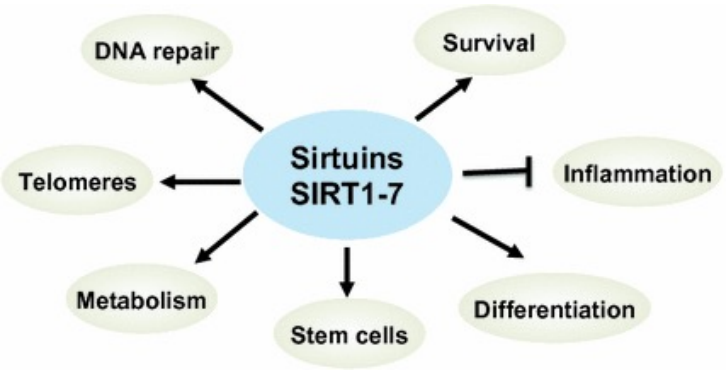
# Sirtuins

- A class of enzymes that influence aging and longevity through multiple molecular pathways. Sirtuins regulate a variety of metabolic processes, including the release of insulin, response to stress, and modulation of lifespan. They also influence circadian clocks and mitochondrial biogenesis. Sirtuins are activated when NAD levels rise. Plant-based molecules e.g. resveratrol, pterostilbene and quercetin can activate sirtuins, designated as Sirt1 to Sirt7.

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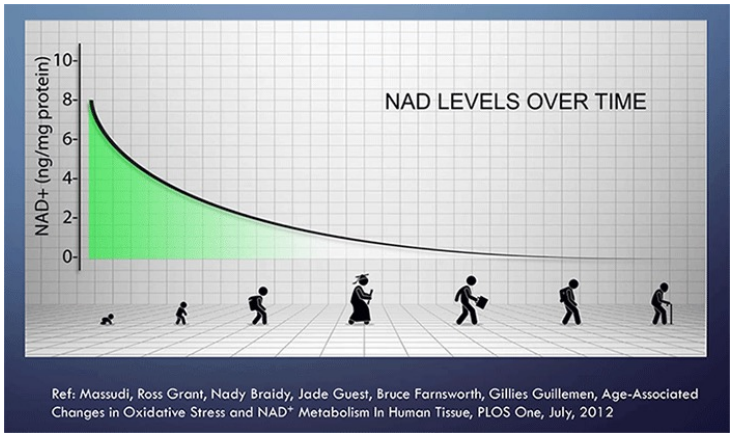
## Hallmarks of Aging Associated with Cellular depletion of NAD+

- Altered DNA repair (PARP activity NAD-dependent)
- Altered epigenetics
- Mitochondrial dysfunction
- Disrupted metabolic-nutrient sensing e.g. Insulin resistance with glucose intolerance
- Cellular senescence
- Decreased autophagy

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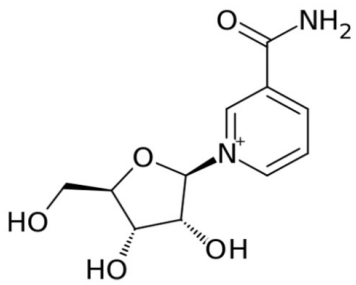
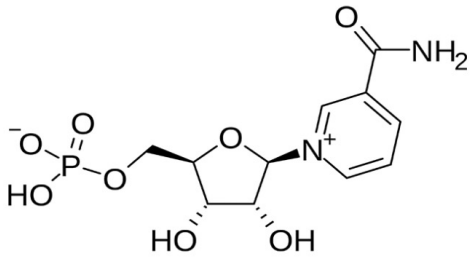
## NAD boosters:

Dietary supplements that purportedly increase cellular levels of nicotinamide adenine dinucleotide (NAD+). Examples of potential NAD+ boosters include nicotinamide riboside and nicotinamide mononucleotide.




**NR:** Nicotinamide Riboside

Wikipedia contributors. "Nicotinamide riboside." *Wikipedia, The Free Encyclopedia*, 20 Nov. 2019. Web. 26 Nov. 2019.




**NMN:** Nicotinamide Mononucleotide

Wikipedia contributors. "Nicotinamide mononucleotide." *Wikipedia, The Free Encyclopedia*, 14 Nov. 2019. Web. 26 Nov. 2019.

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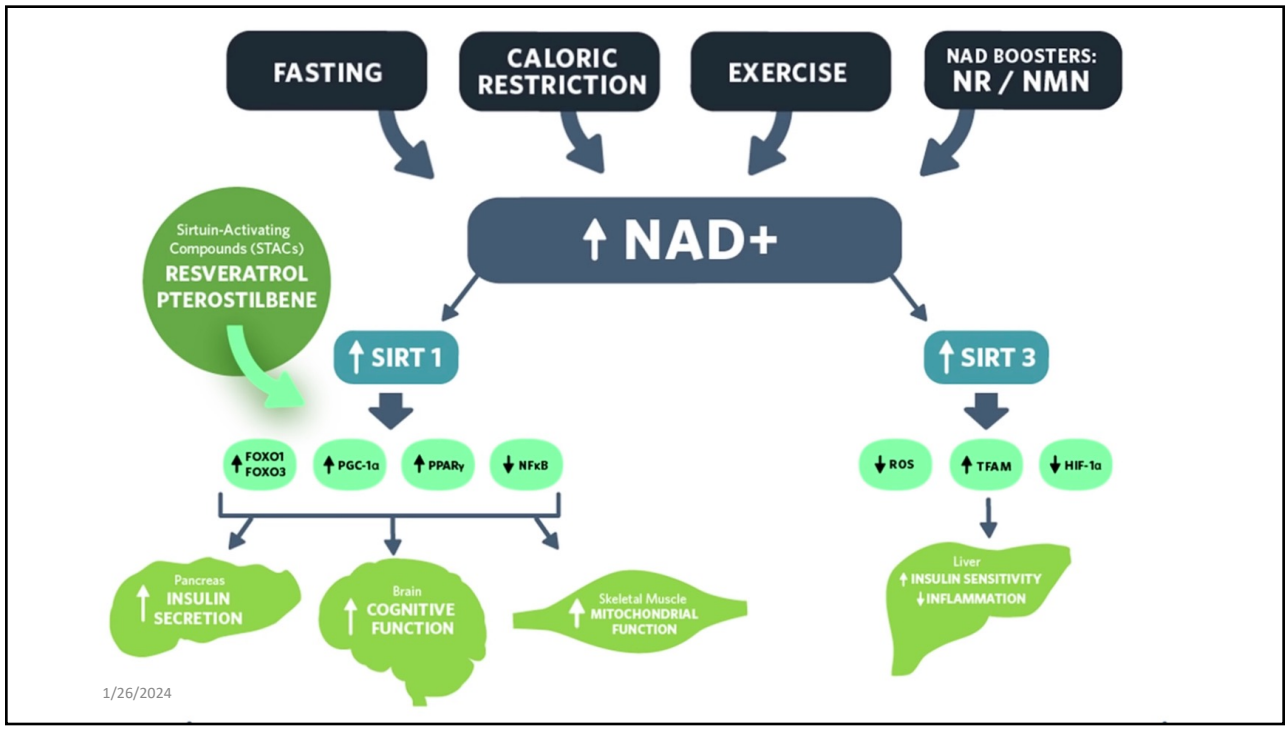


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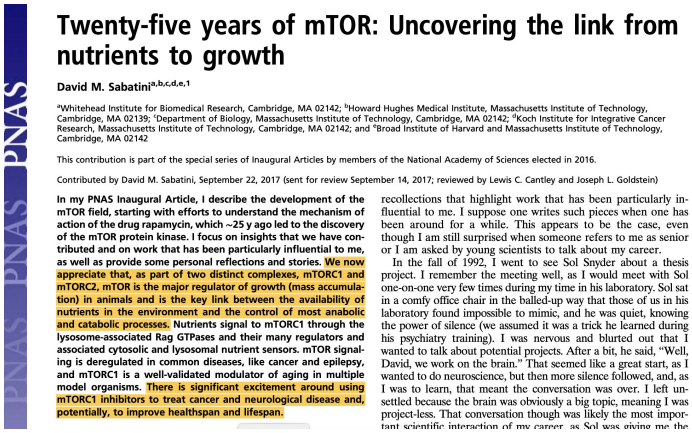
# mTOR – Mammalian Target of Rapamycin

- mTOR is the major nutrient-sensitive regulator of growth in animals and plays a central role in physiology, metabolism, the aging process, and common diseases.



PNAS PNAS PNAS

## Twenty-five years of mTOR: Uncovering the link from nutrients to growth

David M. Sabatini[a,b,c,d,e,1]

[a]Whitehead Institute for Biomedical Research, Cambridge, MA 02142; [b]Howard Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, MA 02139; [c]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02142; [d]Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02142; and [e]Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, MA 02142

This contribution is part of the special series of Inaugural Articles by members of the National Academy of Sciences elected in 2016.

Contributed by David M. Sabatini, September 22, 2017 (sent for review September 14, 2017; reviewed by Lewis C. Cantley and Joseph L. Goldstein)

**In my PNAS Inaugural Article, I describe the development of the mTOR field, starting with efforts to understand the mechanism of action of the drug rapamycin, which ~25 y ago led to the discovery of the mTOR protein kinase. I focus on insights that we have contributed and on work that has been particularly influential to me, as well as provide some personal reflections and stories. We now appreciate that, as part of two distinct complexes, mTORC1 and mTORC2, mTOR is the major regulator of growth (mass accumulation) in animals and is the key link between the availability of nutrients in the environment and the control of most anabolic and catabolic processes. Nutrients signal to mTORC1 through the lysosome-associated Rag GTPases and their many regulators and associated cytosolic and lysosomal nutrient sensors. mTOR signaling is deregulated in common diseases, like cancer and epilepsy, and mTORC1 is a well-validated modulator of aging in multiple model organisms. There is significant excitement around using mTORC1 inhibitors to treat cancer and neurological disease and, potentially, to improve healthspan and lifespan.**

recollections that highlight work that has been particularly influential to me. I suppose one writes such pieces when one has been around for a while. This appears to be the case, even though I am still surprised when someone refers to me as senior or I am asked by young scientists to talk about my career.

In the fall of 1992, I went to see Sol Snyder about a thesis project. I remember the meeting well, as I would meet with Sol one-on-one very few times during my time in his laboratory. Sol sat in a comfy office chair in the balled-up way that those of us in his laboratory found impossible to mimic, and he was quiet, knowing the power of silence (we assumed it was a trick he learned during his psychiatry training). I was nervous and blurted out that I wanted to talk about potential projects. After a bit, he said, "Well, David, we work on the brain." That seemed like a great start, as I wanted to do neuroscience, but then more silence followed, and, as I was to learn, that meant the conversation was over. I left unsettled because the brain was obviously a big topic, meaning I was project-less. That conversation though was likely the most important scientific interaction of my career, as Sol was giving me the

11818–11825 | PNAS | November 7, 2017 | vol. 114 | no. 45

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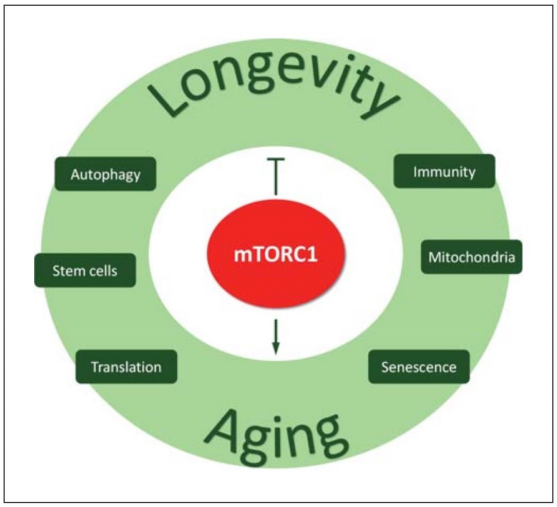


**Fig. 2.** The role of mTORC1 in longevity and aging. The mechanisms of how mTORC1 regulates longevity and aging.

Gerontology 2018;64:127–134

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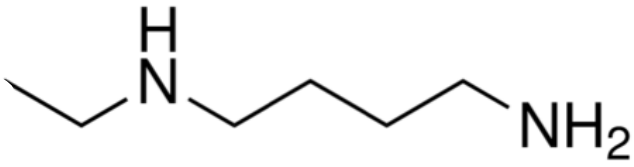
# Spermadine

- Polyamine that is found in foods and produced endogenously
- May have effects of delayed aging in humans (*Aging. 2018 Aug; 10(8): 2209-2211.)*
- Autophagy is upregulated and may be an anti-aging mechanism
- All-cause Mortality inversely related to spermidine intake in observational studies (*Am J Clin Nutr. 2018 Aug 1;108(2): 371-380)*
- Improved cognition in older adults (*Alzheimer's Res Ther. 2019;11:36.)*
- SmartAge Study recruitment
- Dietary sources are plant and fungi derived (*Ann Rev Nutr. 2020 Sep 23;40:135-159)*
- Great sources include vegetable sprouts, mushrooms, peas, legumes, broccoli, cauliflower
- Safety and tolerability in older adults at doses 1.2 mg/day (*Aging. 2018 Jan; 10(1): 19-33)*

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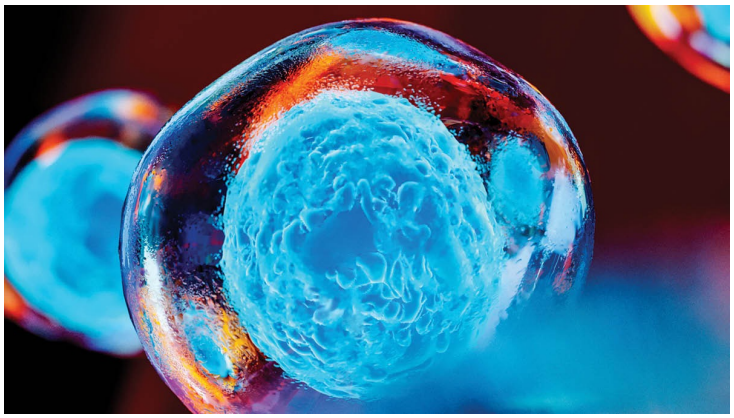
# Stem cells and regenerative medicine

- Embryonic: pluripotent, can form almost any cell type in the human body
- Tissue specific: can form only limited types of cells
- Induced pluripotent: engineered by scientists to behave like embryonic stem cells



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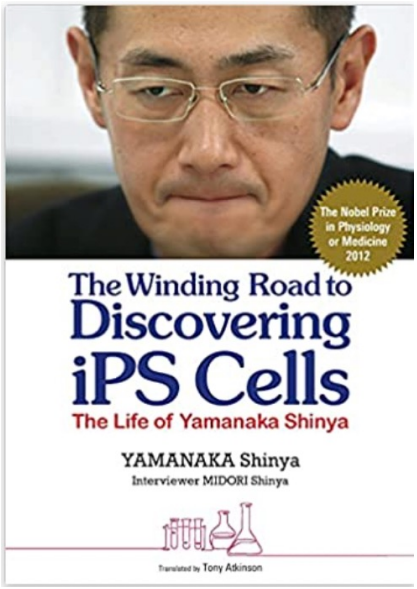


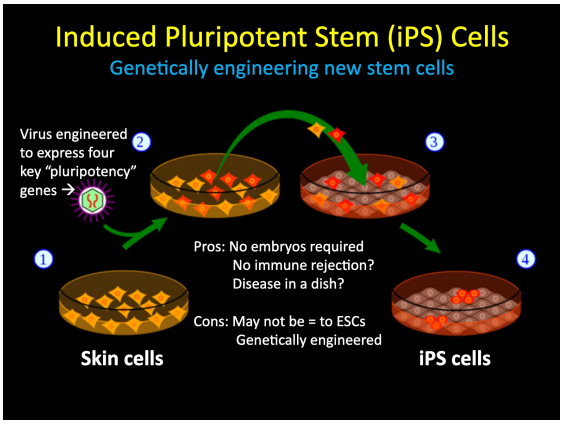


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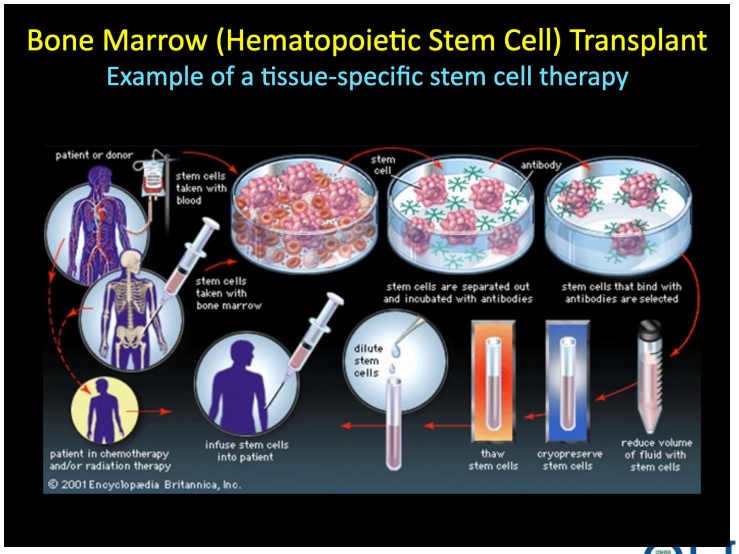
## Diseases that stem cells have the potential to treat

- Blood diseases
- Heart diseases
- Parkinson's
- Alzheimer's
- ALS
- Multiple sclerosis
- Macular degenerations
- Cancer
- HIV/AIDS
- Spinal cord injury
- Stroke

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## Telomere Attrition

- Too much telomere erosion causes cells to malfunction and die.
- Telomeric DNA partially shortens during the decades of human lifetimes


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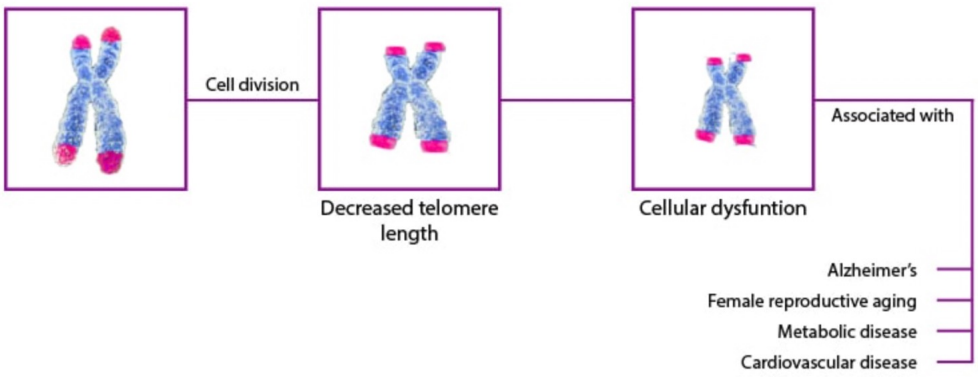


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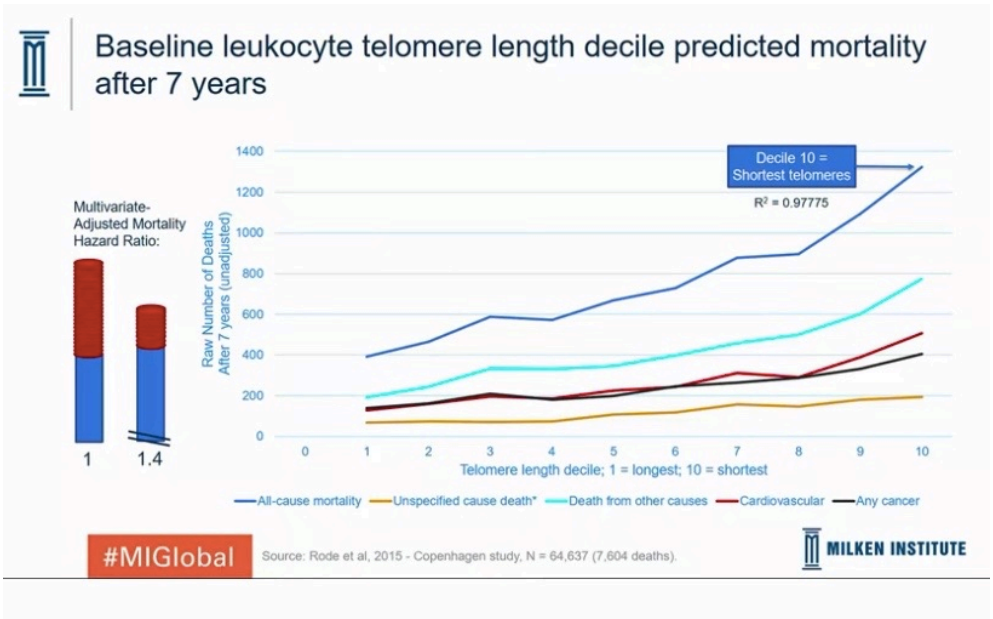


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Received: 11 May 2019 | Revised: 16 July 2019 | Accepted: 4 August 2019
DOI: 10.1111/acel.13028

ORIGINAL ARTICLE

Aging Cell WILEY

# Reversal of epigenetic aging and immunosenescent trends in humans

Gregory M. Fahy[1] | Robert T. Brooke[1] | James P. Watson[2] | Zinaida Good[3] | Shreyas S. Vasanawala[4] | Holden Maecker[5] | Michael D. Leipold[5] | David T. S. Lin[6] | Michael S. Kobor[6] | Steve Horvath[7]

[1]Intervene Immune, Los Angeles, CA, USA
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[3]Departments of Microbiology and Immunology, Stanford University, Stanford, CA, USA
[4]Stanford Medical Center, Stanford, CA, USA
[5]Institute for Immunity, Transplantation and Infection, Stanford School of Medicine, Human Immune Monitoring Center, Stanford, CA, USA
[6]Department of Medical Genetics, BC Children's Hospital Research Institute, Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, BC, Canada
[7]Human Genetics, David Geffen School of Medicine, University of California, Los

**Abstract**

Epigenetic "clocks" can now surpass chronological age in accuracy for estimating biological age. Here, we use four such age estimators to show that epigenetic aging can be reversed in humans. Using a protocol intended to regenerate the thymus, we observed protective immunological changes, improved risk indices for many age-related diseases, and a mean epigenetic age approximately 1.5 years less than baseline after 1 year of treatment (−2.5-year change compared to no treatment at the end of the study). The rate of epigenetic aging reversal relative to chronological age accelerated from −1.6 year/year from 0–9 month to −6.5 year/year from 9–12 month. The GrimAge predictor of human morbidity and mortality showed a 2-year decrease in epigenetic vs. chronological age that persisted six months after discontinuing treatment. This is to our knowledge the first report of an increase, based on an epigenetic age estimator, in predicted human lifespan by means of a currently accessible aging intervention.



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# Maybe We Can!

September 8, 2019:
We published the first strong evidence that ***aging can be reversed in humans.***


ORIGINAL ARTICLE | Open Access

Reversal of epigenetic aging and immunosenescent trends in humans

"This is to our knowledge the first report of an increase . . . in predicted human lifespan by means of a ***currently accessible*** aging intervention."

Greg Fahey MD, UCLA

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www.aging-us.com AGING 2023, Vol. 15, No. 6

Research Paper

## Potential reversal of biological age in women following an 8-week methylation-supportive diet and lifestyle program: a case series

**Kara N. Fitzgerald[1], Tish Campbell[2], Suzanne Makarem[2], Romilly Hodges[3]**

[1]Institute for Functional Medicine, Federal Way, WA 98003, USA
[2]Virginia Commonwealth University, Richmond, VA 23284, USA
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**Correspondence to:** Kara N. Fitzgerald; **email:** kf@drkarafitzgerald.com
**Keywords:** DNA methylation, epigenetic, aging, lifestyle, biological clock
**Received:** January 1, 2023 **Accepted:** March 1, 2023 **Published:** March 22, 2023



**ABSTRACT**

**Here we report on a case series of six women who completed a methylation-supportive diet and lifestyle program designed to impact DNA methylation and measures of biological aging. The intervention consisted of an 8-week program that included diet, sleep, exercise and relaxation guidance, supplemental probiotics and**

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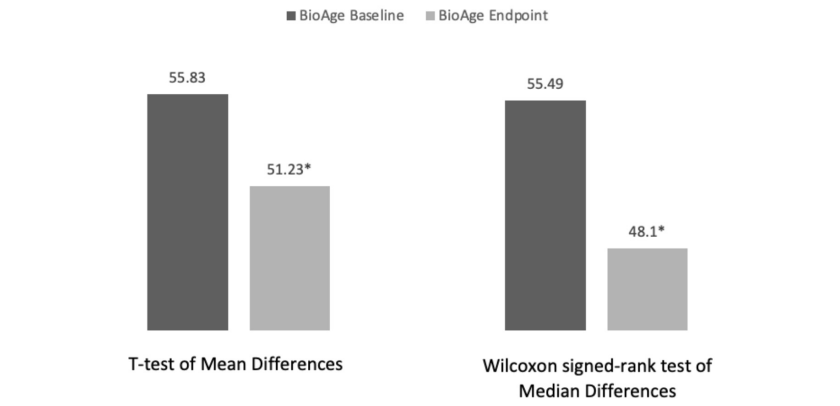


**Figure 1. Participants' average biological age change analysis.** *Significant difference with p-value < .05.





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Research Paper

# Potential reversal of epigenetic age using a diet and lifestyle intervention: a pilot randomized clinical trial

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**Correction:** This article has been corrected. Please see Aging 2022: https://doi.org/10.18632/aging.204197



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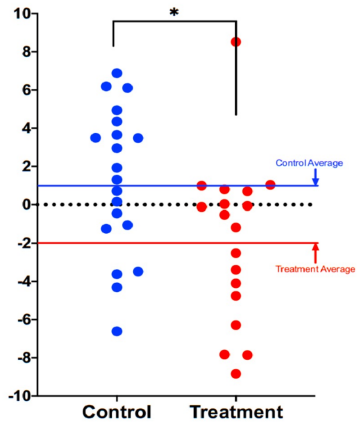


**Figure 2. Comparison of DNAmAge change between treatment and control groups.** Each dot is a subject, and the vertical axis represents difference in DNAmAge from the beginning to the end of the eight-week term. Participants scored an average 1.96 years younger, controls an average 1.27 years older. The age reduction of the treatment group strongly trended towards significance (p=0.066), while the age increase of the control group itself was not significant (p=0.153). The difference between control and treatment groups was significant at the level p=0.018 (unpaired two-tailed t-test). Long red and blue lines represent group averages (mean).

***After 1-year, treatment group with healthy lifestyle interventions regressed biologic age 1.96 years compared to control group who aged 1.27 years***



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Priority Research Paper

# Chemically induced reprogramming to reverse cellular aging

**Jae-Hyun Yang[1,*], Christopher A. Petty[1,*], Thomas Dixon-McDougall[1,*], Maria Vina Lopez[4], Alexander Tyshkovskiy[2,3], Sun Maybury-Lewis[1], Xiao Tian[1], Nabilah Ibrahim[1], Zhili Chen[1], Patrick T. Griffin[1], Matthew Arnold[1], Jien Li[1], Oswaldo A. Martinez[1,5], Alexander Behn[1], Ryan Rogers-Hammond[1], Suzanne Angeli[4], Vadim N. Gladyshev[2], David A. Sinclair[1]**

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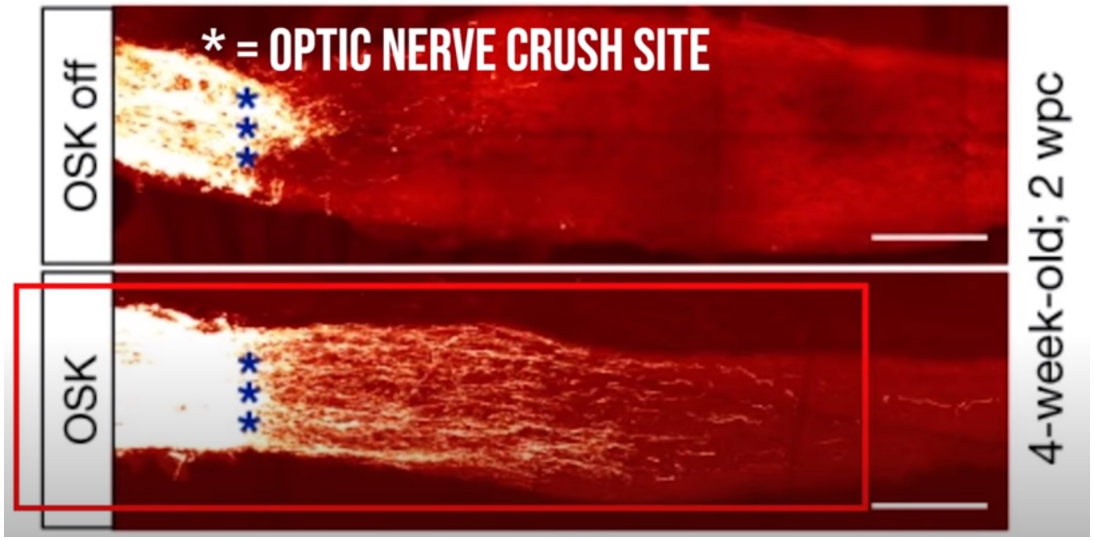


David Sinclair PhD, Harvard Medical School

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## How can I translate this science into my day-to-day routine in 2024?


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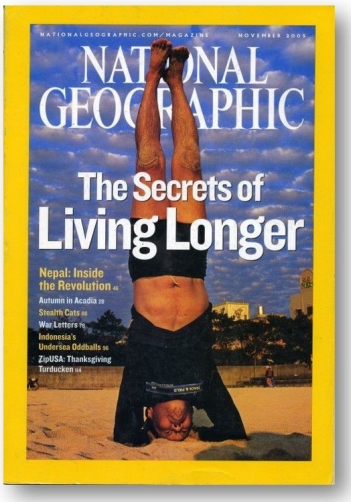



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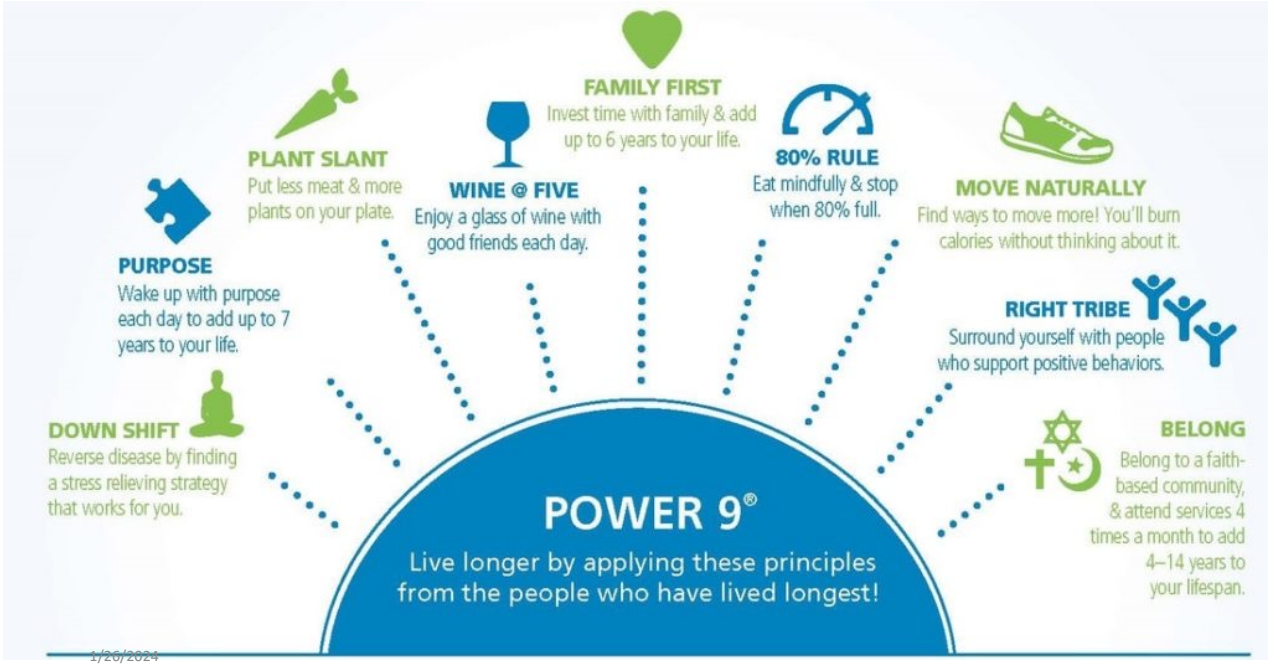




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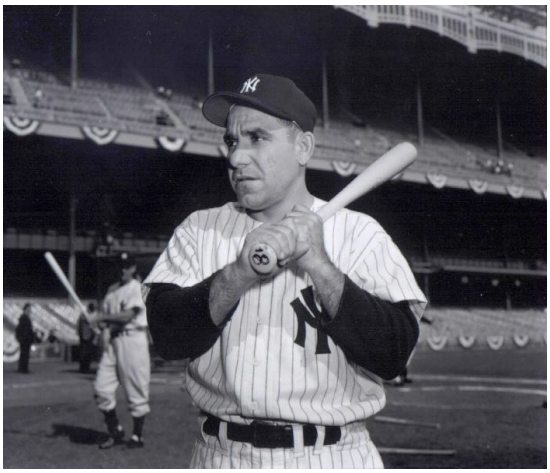

"The future ain't what it used to be."
Yogi Berra

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