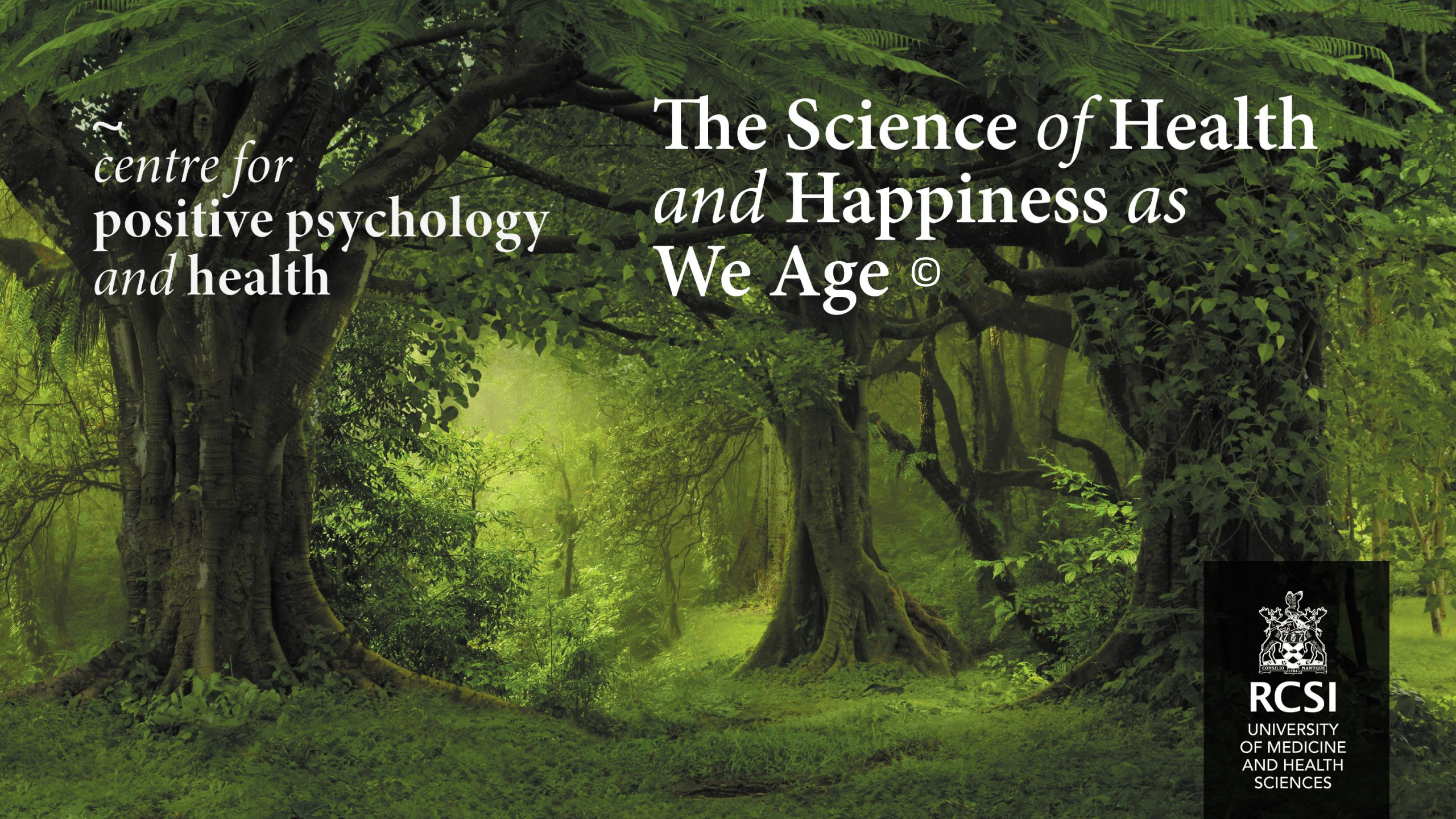
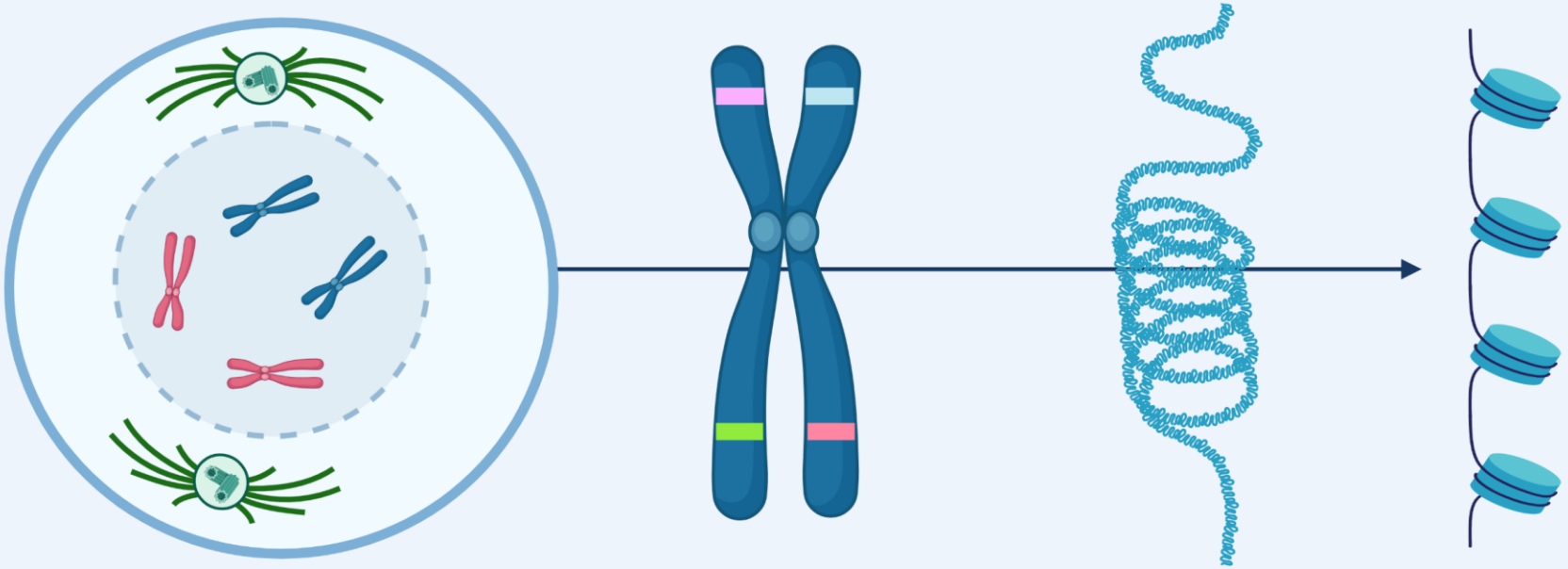

centre for
positive psychology
and health
The Science of Health
and Happiness as
We Age ©
RCSI
UNIVERSITY
OF MEDICINE
AND HEALTH
SCIENCES

Topics for today

- Describe the architecture of chromosomes, genes and DNA
- There is a limit to growth - Hayflick Number
- Telomeres – mechanics of aging cells
- Telomerase – reverse aging and telomeres
- Immune memory is limited
- Inflammation accelerates aging - inflammaging
- Poor lifestyle and disease can accelerate inflammaging
- Your chronological and biological (epigenetic) age are not necessarily the same
- Healthy lifestyle including calorie restriction can decelerate your epigenetic clock

The Biology of Aging – a brief introduction

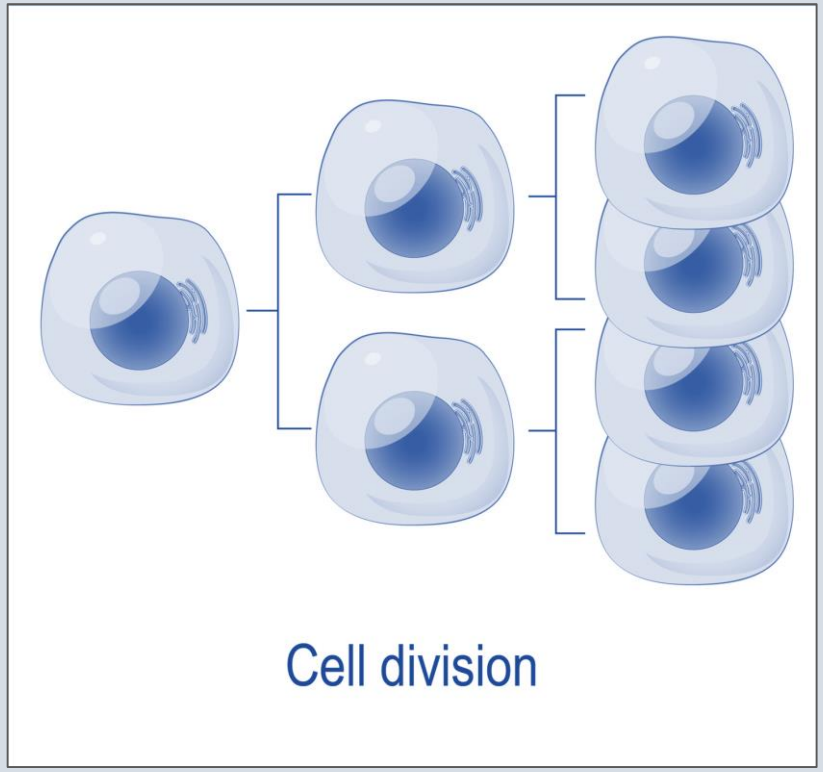
First, the cell and DNA

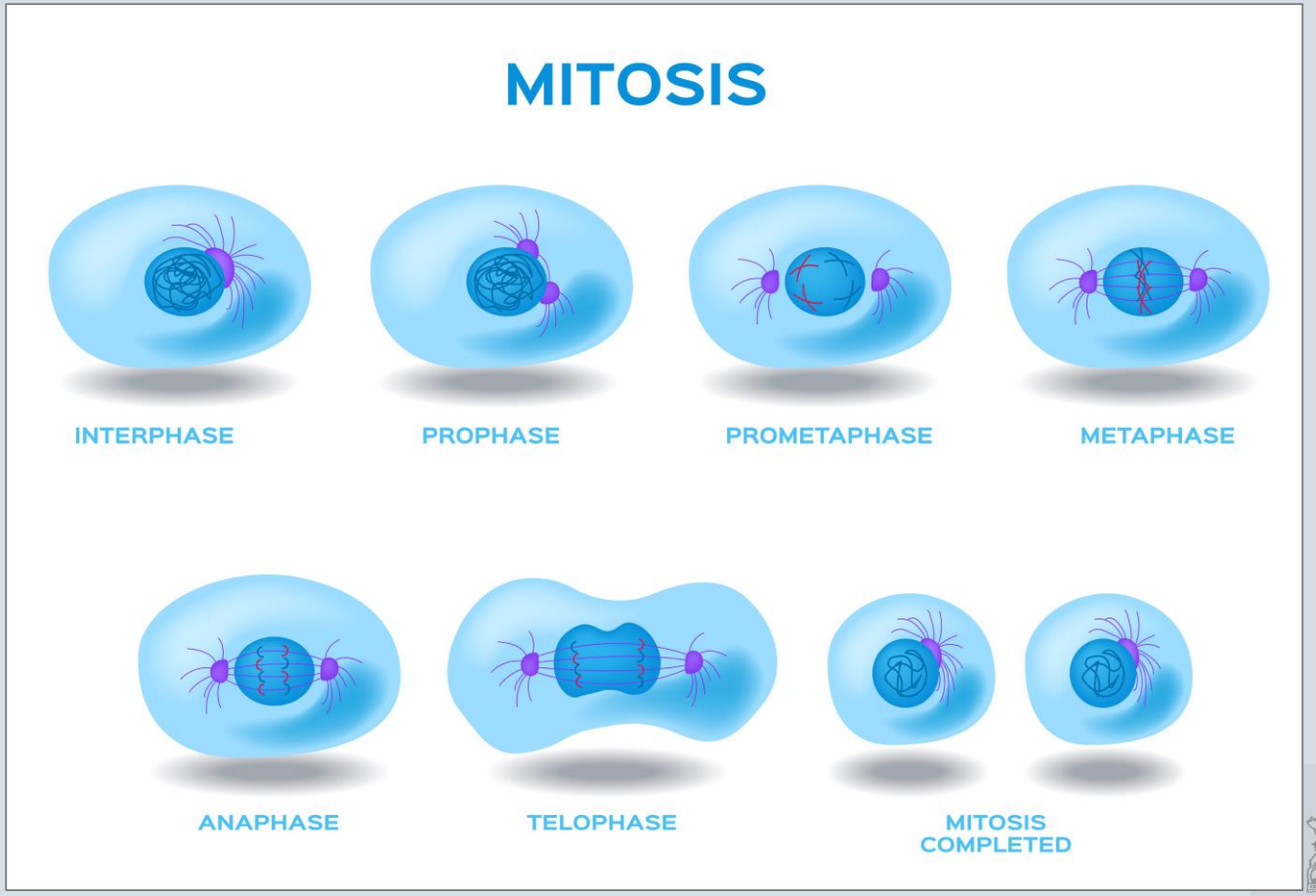


From chromosomes to chromatin to histone-wrapped DNA to DNA

Cell division (mitosis)

– the production of two identical daughter calls from one cell





TIMELINE

Hayflick, his limit, and cellular ageing

Jerry W. Shay and Woodring E. Wright

Almost 40 years ago, Leonard Hayflick discovered that cultured normal human cells have limited capacity to divide, after which they become senescent — a phenomenon now known as the 'Hayflick limit'. Hayflick's findings were strongly challenged at the time, and continue to be questioned in a few circles, but his achievements have enabled others to make considerable progress towards understanding and manipulating the molecular mechanisms of ageing.

To set Hayflick's discoveries in context, we need to go back to 1881 (TIMELINE, overleaf), when the German biologist August Weismann[1] speculated that "death takes place because a worn-out tissue cannot forever renew itself, and because a capacity for increase by means of cell division is not everlasting but finite". This concept, which was almost entirely forgotten by the time Hayflick began his work, was later challenged by the French Nobel-prize-winning surgeon Alexis Carrel, who suggested that all cells explanted in culture are immortal, and that the lack of continuous cell replication was due to ignorance on how best to cultivate the cells. Carrel's view was based on his and Albert Ebeling's work, done at the Rockefeller Institute in New York City, in which they claimed that chick heart fibroblasts grew con-

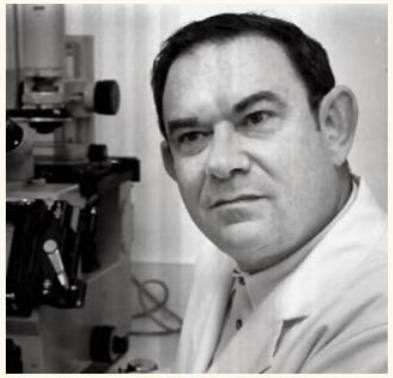
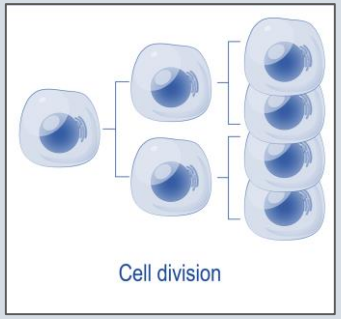


Figure 1 | **Leonard Hayflick in 1988.**
(Photograph: Peter Argentine.)

The Hayflick Limit

By: *Zane Bartlett*
Published: *2014-11-14*
Keywords: Alexey Olovnikov

The Hayflick Limit is a concept that helps to explain the mechanisms behind cellular aging. The concept states that a normal human cell can only replicate and divide forty to sixty times before it cannot divide anymore, and will break down by programmed cell death or apoptosis. The concept of the Hayflick Limit revised Alexis Carrel's earlier theory, which stated that cells can replicate themselves infinitely. Leonard Hayflick developed the concept while at the Wistar Institute in Philadelphia, Pennsylvania, in 1965. In his 1974 book *Intrinsic Mutagenesis*, Frank Macfarlane Burnet named the concept after Hayflick. The concept of the Hayflick Limit helped scientists study the effects of cellular aging on human populations from embryonic development to death, including the discovery of the effects of shortening repetitive sequences of DNA, called telomeres, on the ends of chromosomes. Elizabeth Blackburn, Jack Szostak and Carol Greider received the Nobel Prize in Physiology or Medicine in 2009 for their work on genetic structures related to the Hayflick Limit.

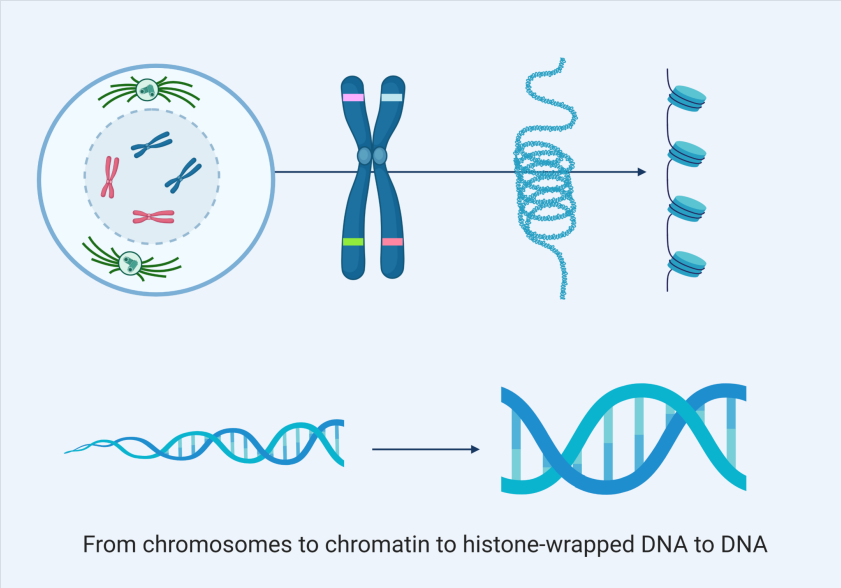


After 40-60 divisions the cell shuts down (senescence) or is programmed to die (apoptosis).

RCSI
UNIVERSITY
OF MEDICINE
AND HEALTH
SCIENCES

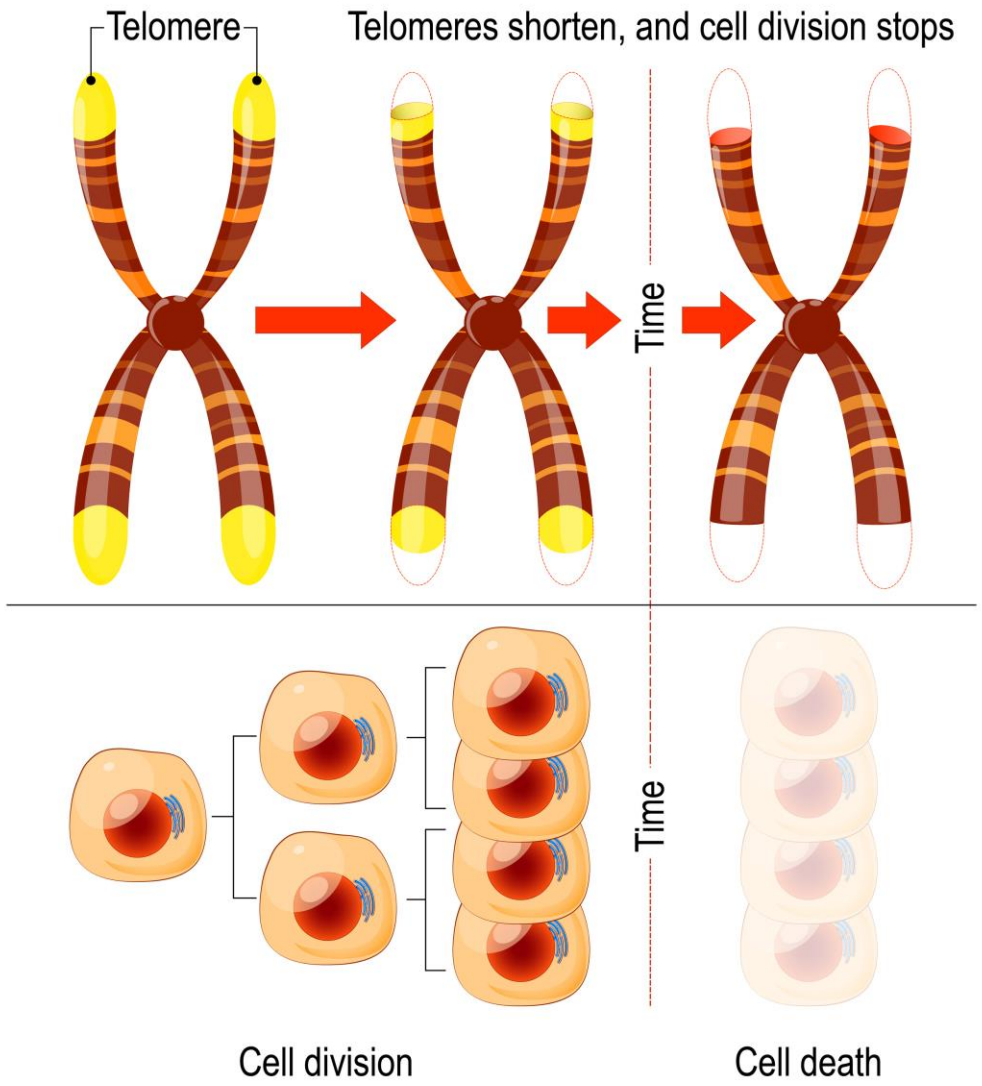
centre for positive psychology and health

Telomeres



From chromosomes to chromatin to histone-wrapped DNA to DNA

Aging process



Aging

RCSI
UNIVERSITY
OF MEDICINE
AND HEALTH
SCIENCES

Telomeres, telomerase and the immune system

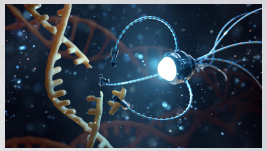
RCSI
UNIVERSITY
OF MEDICINE
AND HEALTH
SCIENCES

Immune cells multiply to fight infection – do they reach the Hayflick Limit?

Telomerase to the rescue!

– adds back telomerase repeats to the ends of DNA in the cell

Reverse Aging with telomerase



Only certain cells have telomerase:

Some immune cells and other blood cells

Cells in the embryo

Stem cells (bone marrow)

Cancer cells

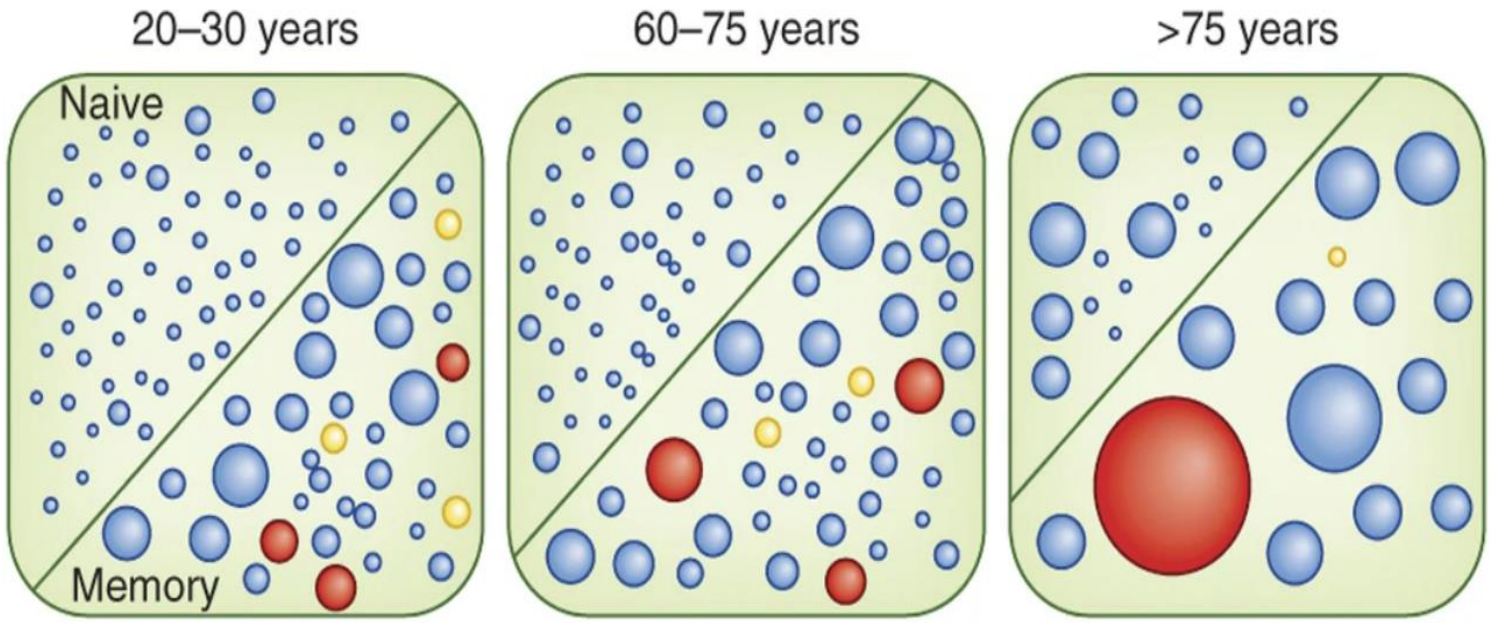
RCSI
UNIVERSITY OF MEDICINE AND HEALTH SCIENCES

Immune memory and aging

- Telomerase can only do so much

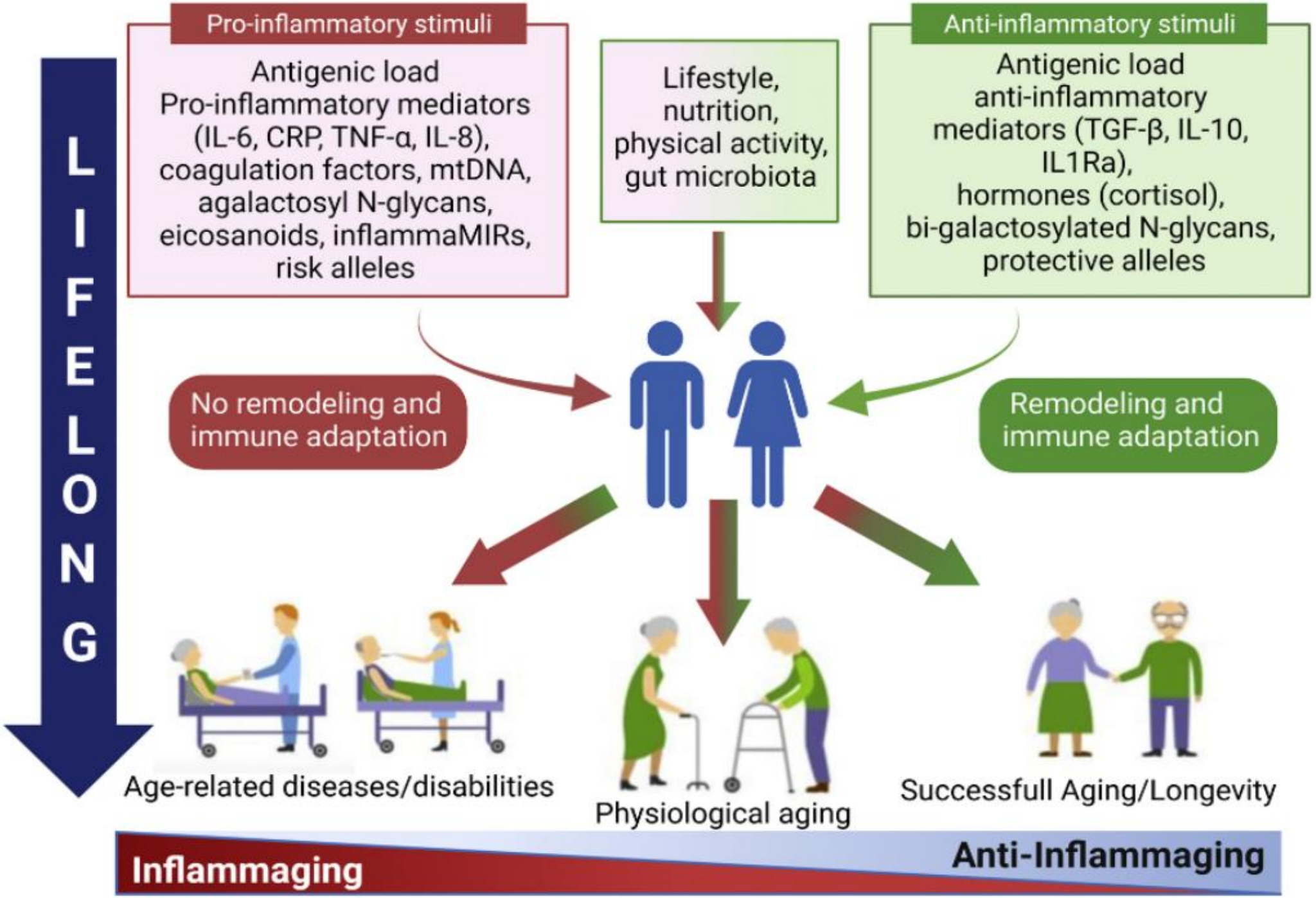
RCSI
UNIVERSITY
OF MEDICINE
AND HEALTH
SCIENCES

From: Understanding immunosenescence to improve responses to vaccines *Nat Immunol* **14,** 428–436 (2013).



- Immune memory cell can recognise billions of pieces of bacteria, virus, fungi, food, plants etc.
- Each memory cell recognises one piece and moves from **naïve** to **memory** once it sees its specific piece
- We can hold a certain number of these cells in our system at any one time
- Chronic inflammation and recurrent infection can expand some memory cells at the expense of others
- This means that our immune memory decreases over time
- Other cells become exhausted, lose their function (senescence) and/or die (apoptosis)

Inflammaging (inflammation + aging)



Source:

Ageing Research Reviews
Volume 71, November 2021, 101422

RCSI UNIVERSITY OF MEDICINE AND HEALTH SCIENCES

In the end, the immune system ages like the rest of the body

- Eventually, our immune memory reduces significantly due to death of specific ells or they lose their function
- Not even telomerase can save us then
- This is one of the reasons why infections can be very dangerous after we reach the age of 80 years

Epigenetics and Aging

RCSI
UNIVERSITY
OF MEDICINE
AND HEALTH
SCIENCES

centre for positive psychology and health

A definition of epigenetics

- Your genes play an important role in your health, but so do your behaviours and environment. E.g. what you eat and physical activity
- Epigenetics is the study of how your behaviours and environment can cause changes that affect the way your genes work
- Unlike genetic changes, epigenetic changes are **reversible** and do not change your DNA sequence
- Epigenetic changes affect gene expression to turn genes **on** and **off**.

Source: www.cdc.gov/genomics/disease/epigenetics.htm

RCSI UNIVERSITY OF MEDICINE AND HEALTH SCIENCES

centre for positive psychology and health

The epigenetic (Horvath) clock

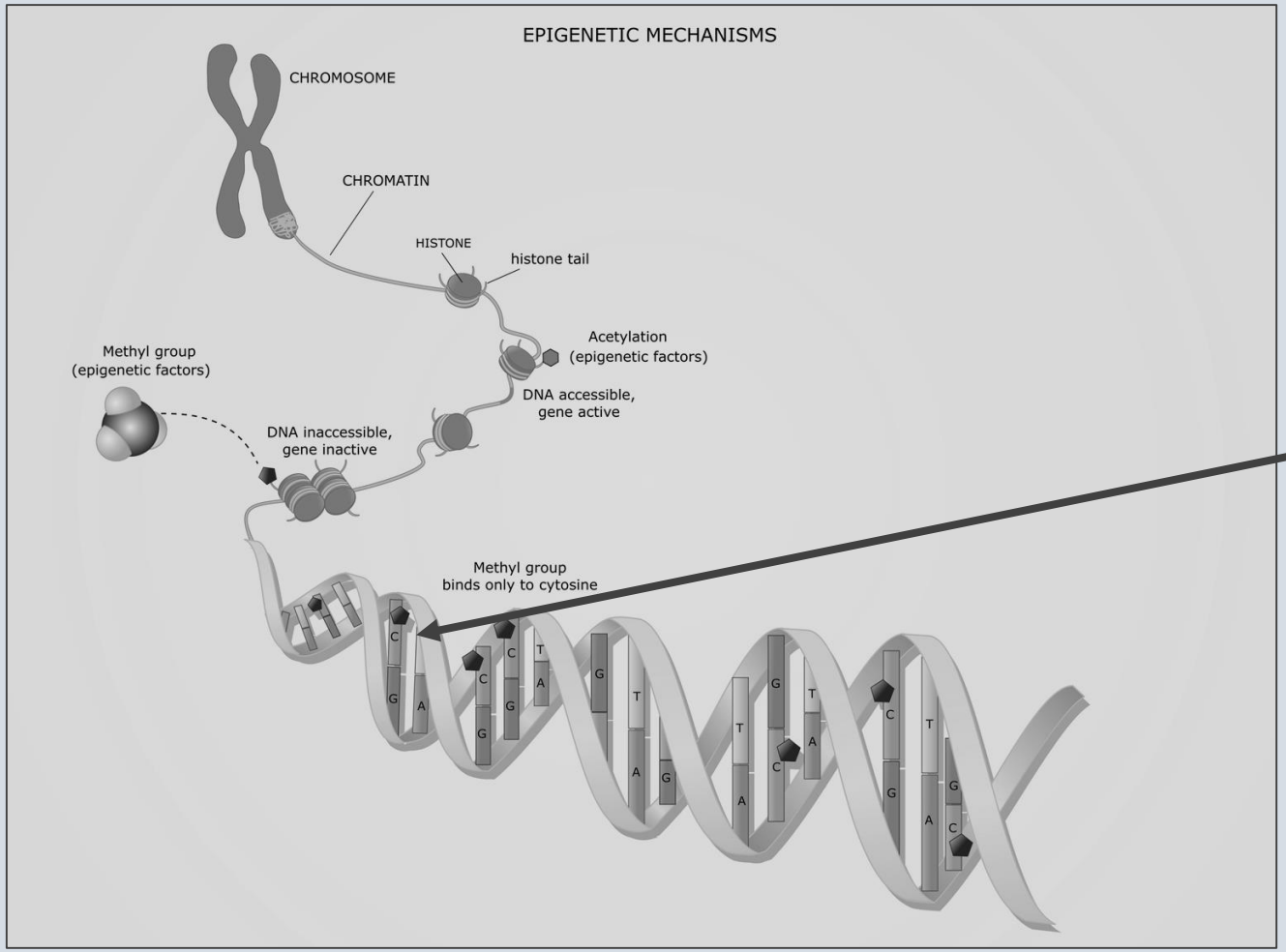
- Your chronological and biological (epigenetic) age are not necessarily the same
- For example, you can be 30 years old but have an older biological age
- Your epigenetic age can be measured by looking at how and where molecules called methyl groups bind to your DNA
- Steven Horvath and colleagues have found that these patterns correlate to how long you will live

Nature **volume 508**, pages168–170 (2014)

Watch a Ted Talk video by Prof Horvath here

RCSI UNIVERSITY OF MEDICINE AND HEALTH SCIENCES

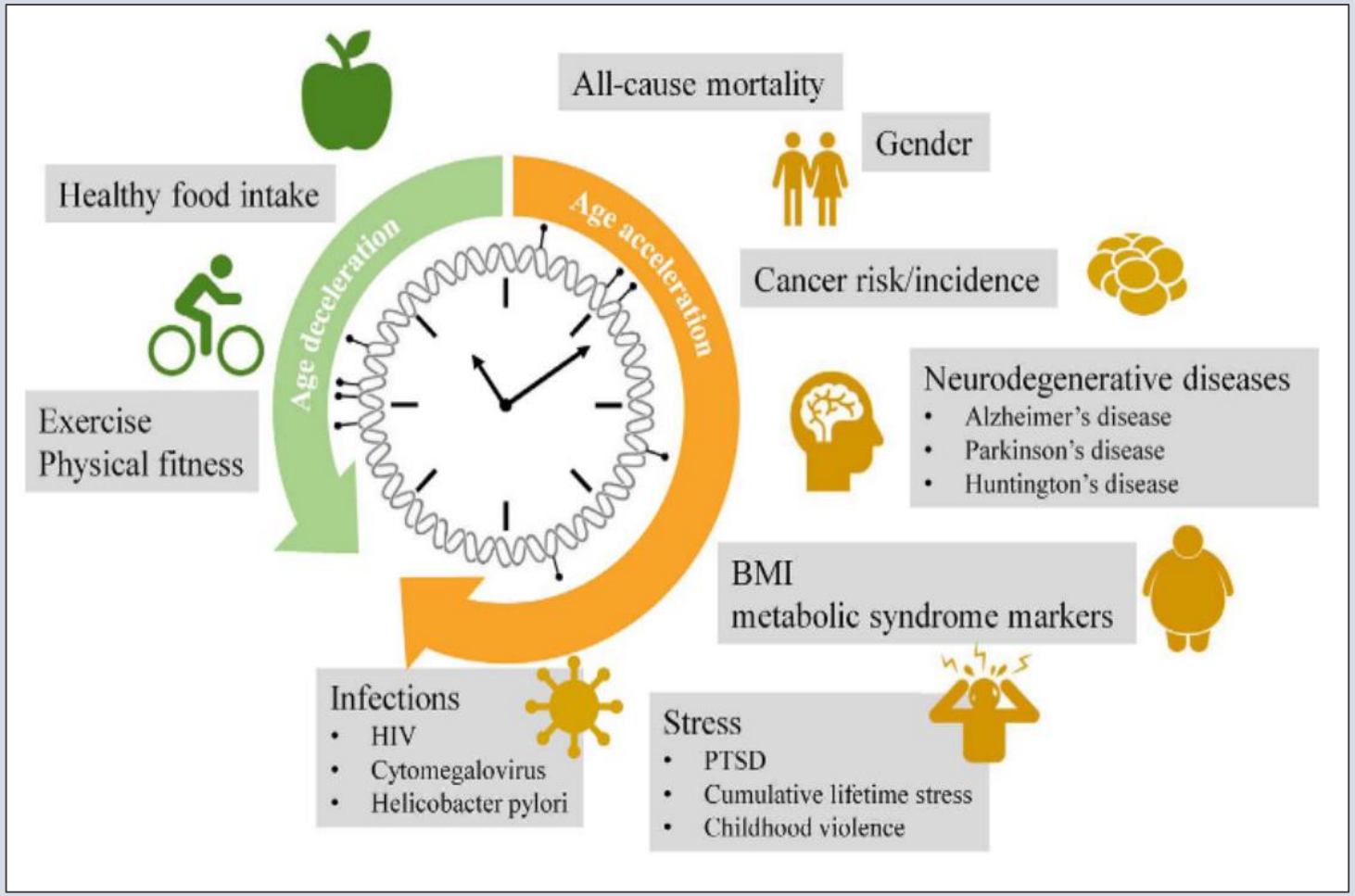
The epigenetic (Horvath) clock



- Small molecules called methyl groups (CH3) attach to DNA in certain patterns
- These patterns can be used to identify the age of an organ or a mammal (including humans)

centre for positive psychology and health

The epigenetic (Horvath) clock



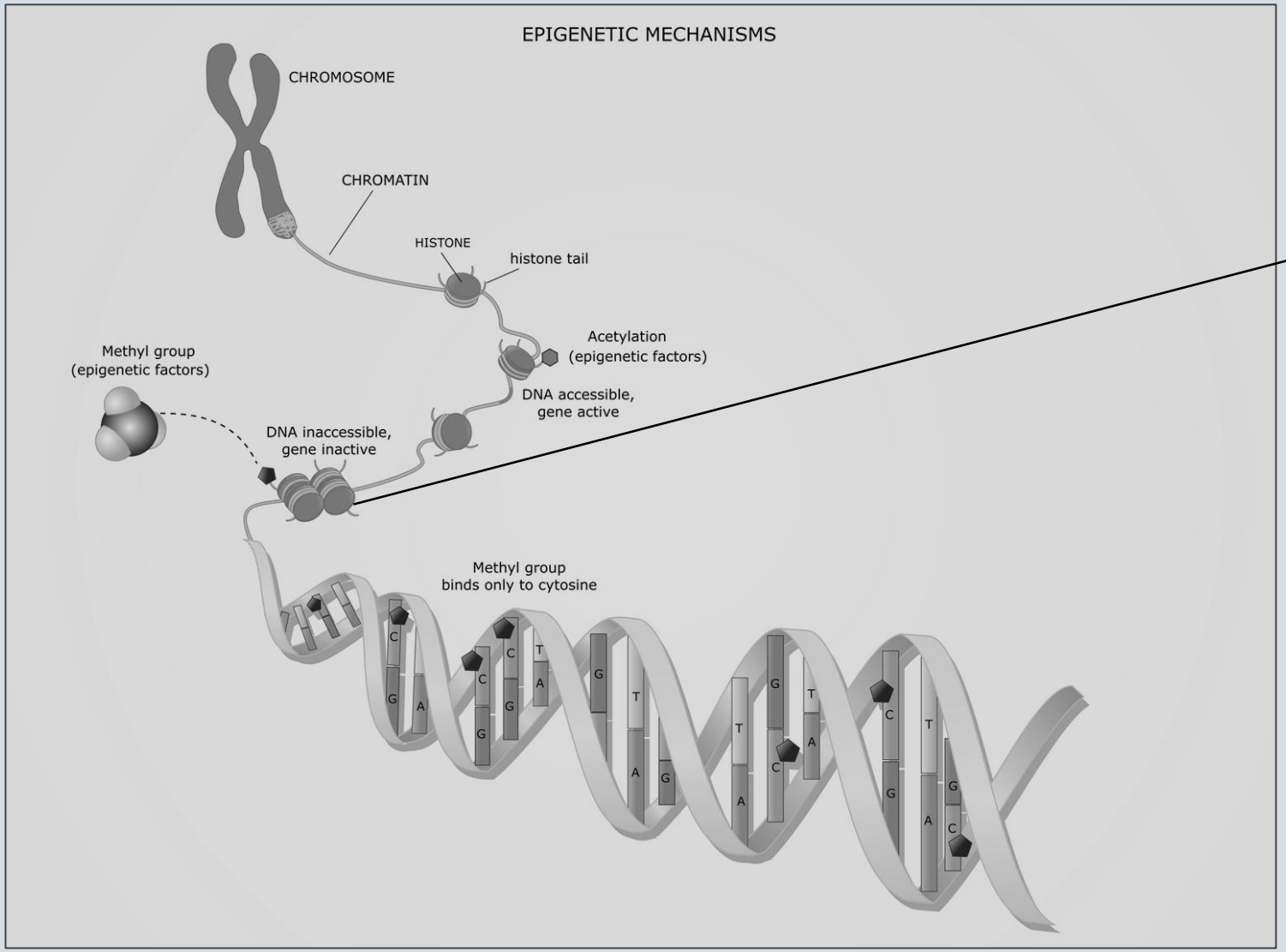
Source: Mechanisms of Ageing and Development Volume 174, September 2018, Pages 18-29

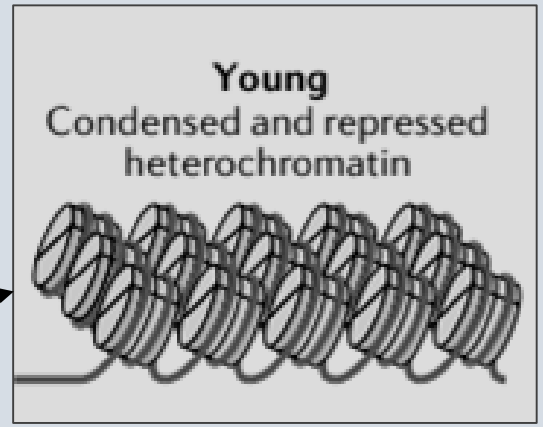
Highlights

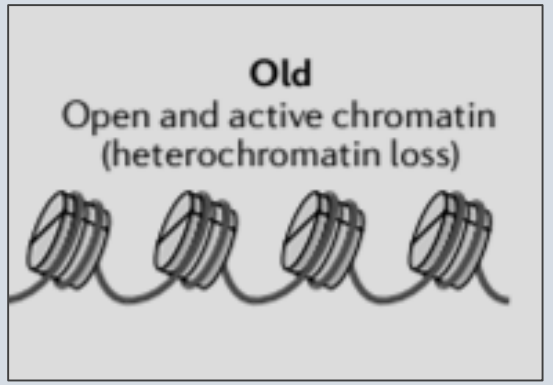
- The epigenetic clock DNA methylation signature can be used as biomarker to predict biological age
- Age associated DNA methylation drift is highly conserved across mammalian species
- Epigenetic clock acceleration promotes lifestyle diseases and mortality risk
- Lifestyle interventions are developed to extend healthy lifespan by slowing down the epigenetic clock progression

RCSI UNIVERSITY OF MEDICINE AND HEALTH SCIENCES

What else can we do to slow the epigenetic clock?


EPIGENETIC MECHANISMS
CHROMOSOME
CHROMATIN
HISTONE
histone tail
Acetylation
(epigenetic factors)
Methyl group
(epigenetic factors)
DNA accessible,
gene active
DNA inaccessible,
gene inactive
Methyl group
binds only to cytosine


Young
Condensed and repressed
heterochromatin


Old
Open and active chromatin
(heterochromatin loss)

Calorie restriction - fasting

The ageing epigenome and its rejuvenation

Weiqi Zhang[1,2,3,4], Jing Qu[4,5], Guang-Hui Liu[1,4,6] and Juan Carlos Izpisua Belmonte[2]**

Abstract | Ageing is characterized by the functional decline of tissues and organs and the increased risk of ageing-associated disorders. Several 'rejuvenating' interventions have been proposed to delay ageing and the onset of age-associated decline and disease to extend healthspan and lifespan. These interventions include metabolic manipulation, partial reprogramming, heterochronic parabiosis, pharmaceutical administration and senescent cell ablation. As the ageing process is associated with altered epigenetic mechanisms of gene regulation, such as DNA methylation, histone modification and chromatin remodelling, and non-coding RNAs, the manipulation of these mechanisms is central to the effectiveness of age-delaying interventions. This Review discusses the epigenetic changes that occur during ageing and the rapidly increasing knowledge of how these epigenetic mechanisms have an effect on healthspan and lifespan extension, and outlines questions to guide future research on interventions to rejuvenate the epigenome and delay ageing processes.

Ten–eleven translocation enzymes
TET enzymes. A family of dioxygenases, including TET1, TET2, and TET3, involved in DNA demethylation. They function by converting 5-methylcytosine into 5-hydroxymethylcytosine.

Constitutive heterochromatin
Constitutive heterochromatin encompasses highly repetitive DNA sequences, is enriched around the pericentromeric and telomeric regions of chromosomes and is consistently stable in many cell types of most eukaryotes.

Epigenetic drifts
Age-associated heterogeneity of the epigenome which will lead to increased noise of gene expression during ageing.

A recent analysis of global demographic data suggested that there is a limit to the human maximum lifespan[1]. However, human life expectancy has increased steadily over the past century in most countries[2]. Environmental factors such as changes in lifestyle and improvements in health-care provision are the major contributors to this increase in life expectancy for elderly individuals. Environmental conditions can affect molecular mechanisms and may affect the cellular epigenome to regulate gene expression and control cell fate, which might eventually contribute to the aggravation or alleviation of the ageing process. For example, the progressive accumulation of ageing-associated epigenetic changes could lead to aberrant gene expression regulation, metabolic instability, stem cell senescence and/or exhaustion and tissue homeostasis imbalance, all of which contribute to ageing.

Recent studies based on animal models have shown that alterations in DNA methylation, histone post-translational modification and chromatin organization and remodelling influence healthspan and lifespan[3]. The most abundant type of DNA methylation in eukaryotes is cytosine 5-methylation, which is regulated by DNA methyltransferases (DNMTs) and ten–eleven translocation enzymes (TET enzymes)[4,5] (FIG. 1). It has been recently shown that DNA methylation levels and, in particular, the pattern of 5-methylcytosine are altered during ageing[6–8]. This DNA methylation status can be used to predict chronological age in a variety of tissues, such as blood, kidney and liver and has therefore been termed the 'epigenetic clock'[6]. Histones are subject to post-translational modifications such as lysine methylation and acetylation (FIG. 1). All of these modifications are crucial to chromatin function, modulating the availability of DNA to transcriptional complexes. Nucleosome positioning also regulates chromatin accessibility (that is, whether chromatin is in an open or a closed state) and is associated with cell type-specific gene expression programmes and varies with ageing[9–11]. Furthermore, non-coding RNAs, including long non-coding RNAs, microRNAs and circular RNAs, provide additional layers of epigenetic regulation that are important in the context of ageing[12].

Recent studies have found that substantial chromatin changes that are typically accompanied by progressive loss of constitutive heterochromatin occur during ageing[9,10] (FIG. 1). Moreover, the notion that epigenetic factors regulate the ageing process is supported by numerous lines of evidence. For example, it was found that epigenetic drifts occur during ageing, that transgenerational inheritance mediated by epigenetic mechanisms has an effect on ageing and, most importantly, that environmental and epigenetic factors (such as sirtuins) can directly modulate ageing kinetics[13].

Ageing hallmarks can be modulated by genetic, nutritional or pharmacological interventions, and stabilization of chromatin structure is crucial in delaying ageing in model systems. Indeed, analyses of global DNA methylation patterns in mouse liver cells have demonstrated that the acquisition of ageing-associated

*e-mail: ghliu@ioz.ac.cn; belmonte@salk.edu

https://doi.org/10.1038/s41580-019-0204-5

Source: Zhang W, Qu J, Liu GH, Belmonte JCI. The ageing epigenome and its rejuvenation. Nat Rev Mol Cell Biol. 2020 Mar;21(3):137-150. doi: 10.1038/s41580-019-0204-5. Epub 2020 Feb 4. PMID: 32020082.

centre for positive psychology and health

Can we use drugs to reverse aging?

A person's biological age, measured by the epigenetic clock, can lag behind or exceed chronological age.

EPIGENETICS

Trial hints at age–clock reversal

In a small trial, a drug cocktail seemingly rolled back the epigenetic clock, which tracks a person's biological age.

- Ten healthy men, given a cocktail of **human growth hormone (hGH), metformin (treats diabetes),** and **DHEA** (Dehydroepiandrosterone is a steroid hormone produced by the adrenal gland)
- Self-injected up to 4 times weekly
- Plus 3000 IU of vitamin D3, and 50 mg zinc daily for 1-year

The result?

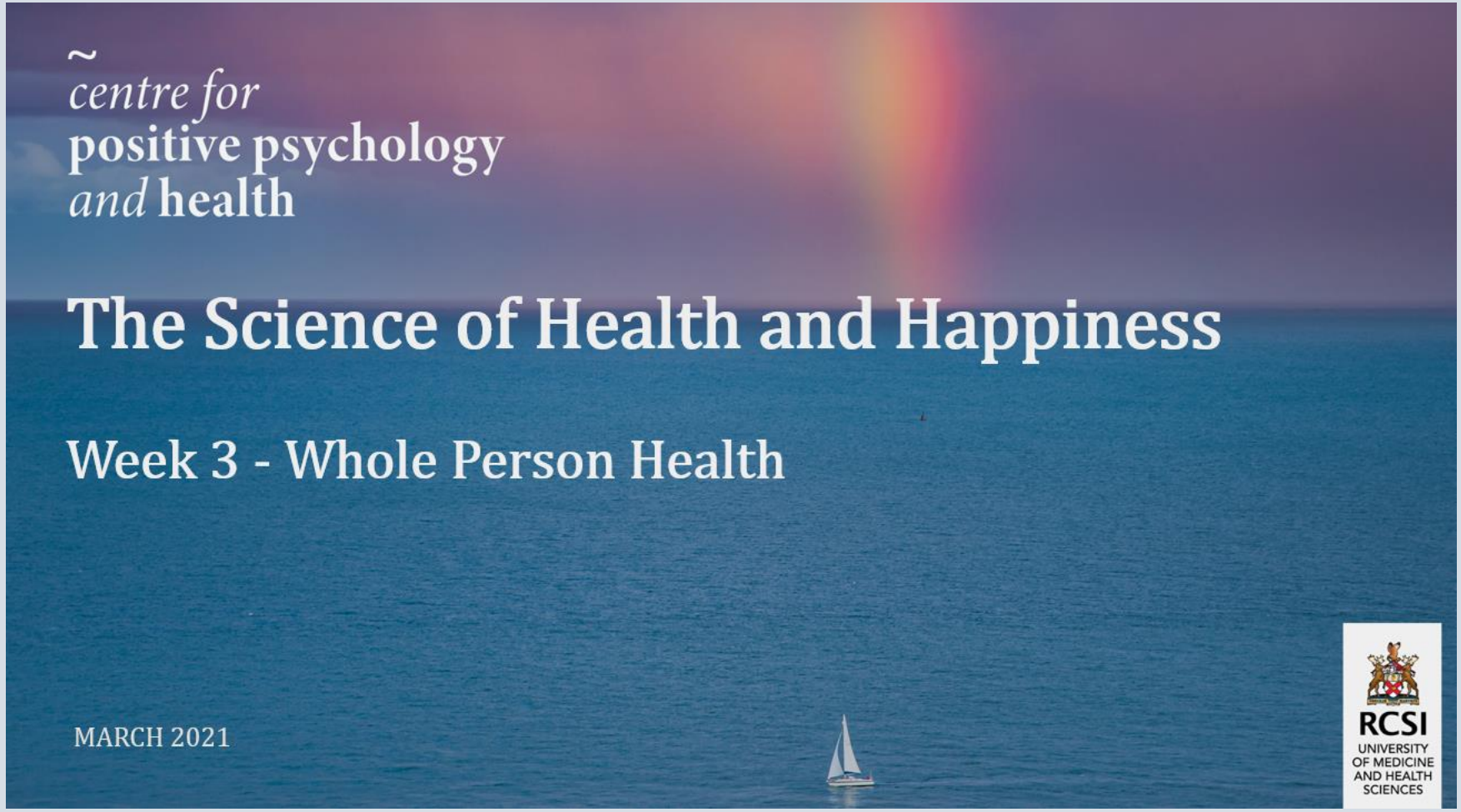
Lost approximately 2.5 years off the biological age of their blood cells, according to an analysis of their epigenome. In other words, their blood was on average 2.5 years younger.

Source: Fahy, G. M. *et al. Aging Cell* https://doi.org/10.1111/acel.13028 (2019).

Dr Greg Fahy Ted Talk video on reversing aging

RCSI UNIVERSITY OF MEDICINE AND HEALTH SCIENCES


centre for
positive psychology
and health
RCSI
UNIVERSITY
OF MEDICINE
AND HEALTH
SCIENCES
Is there anything else we can do?


~
centre for
positive psychology
and health
The Science of Health and Happiness
Week 3 - Whole Person Health
MARCH 2021
RCSI
UNIVERSITY
OF MEDICINE
AND HEALTH
SCIENCES


LOMA LINDA
UNITED STATES
NICOYA
COSTA RICA
SARDINIA
ITALY
ICARIA
GREECE
OKINAWA
JAPAN
BLUE
ZONES
Blue zones are regions where a higher than usual number of
people live much longer than average.
There are five blue zone areas in the world.

~
centre for
positive psychology
***and* health**

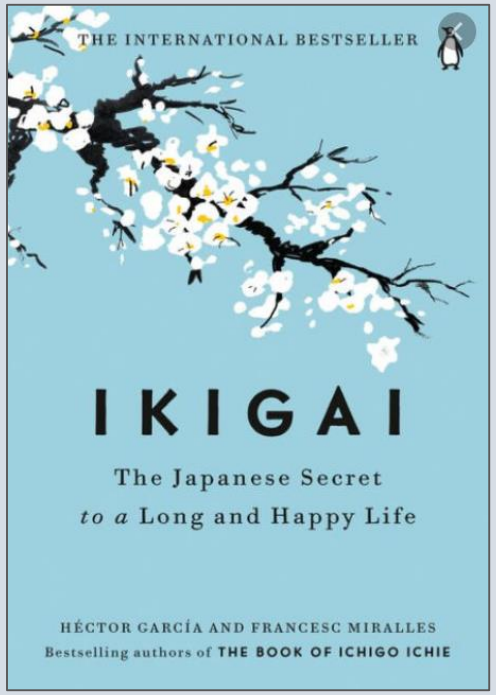
Summary of whole person health

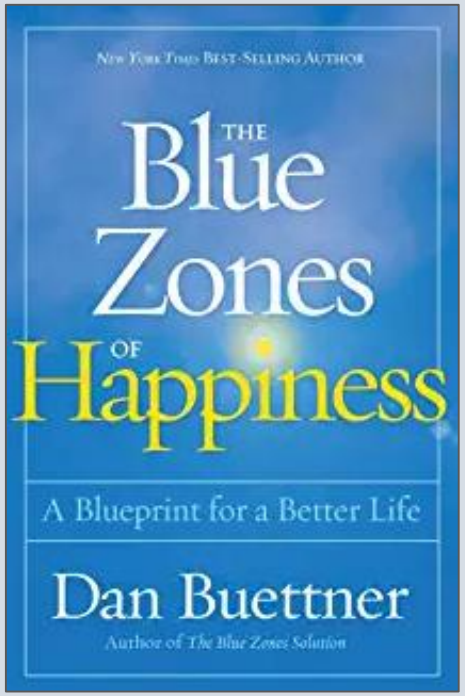
If you want to live to be a healthy and happy 100 year old:

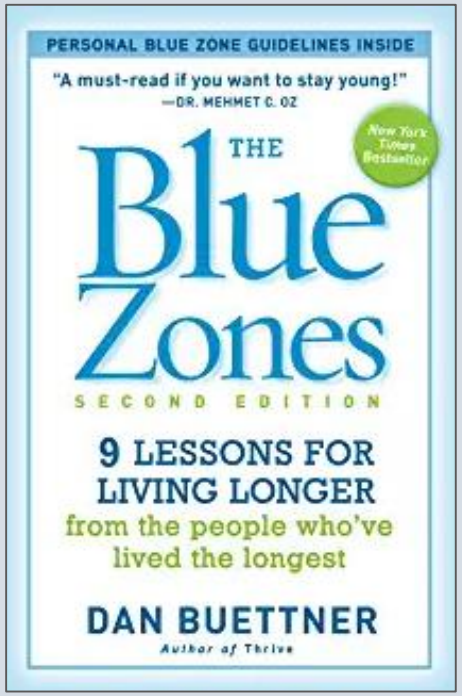
- "Eat food. Not too much. Mostly plants." – Michael Pollen (food author & journalist)
- Look after your gut
- Move naturally – household chores can be viewed as exercise
- Value your family and your community as equally as food and exercise
- Cultivate meaning and purpose, plus creativity in your life

RCSI
UNIVERSITY
OF MEDICINE
AND HEALTH
SCIENCES

Future Reading







In summary

- There is a limit to growth - Hayflick Number
- Telomeres – mechanics of aging cells
- Telomerase – reverse aging and telomeres
- Immune memory is limited
- Inflammation accelerates aging - inflammaging
- Poor lifestyle and disease can accelerate inflammaging
- Your chronological and biological (epigenetic) age are not necessarily the same
- Healthy lifestyle including calorie restriction can decelerate your epigenetic clock