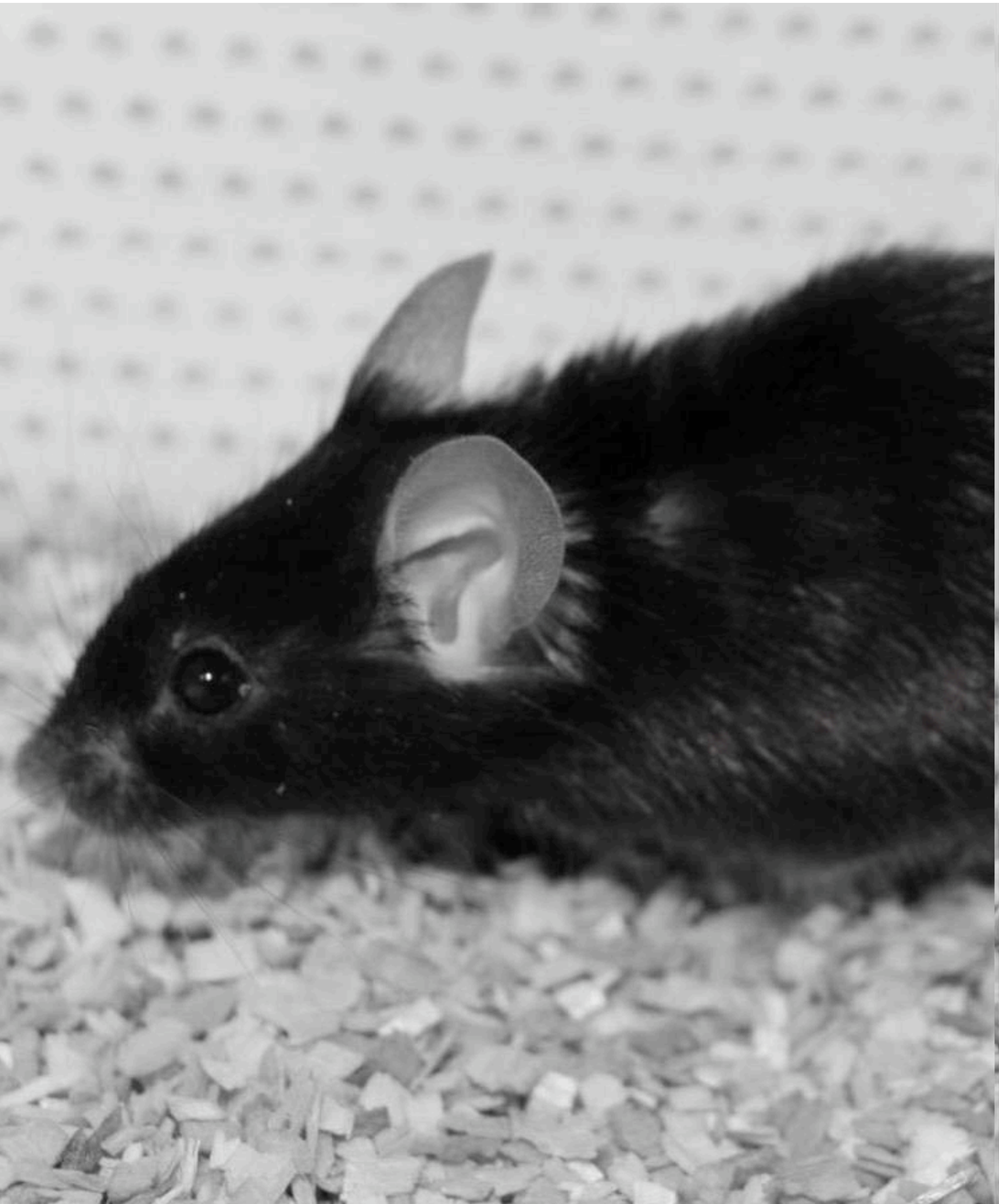
AGING

the mechanisms of getting old and the race for immortality

Steve Knutson March 14, 2023

Dying is a part of living



Dying is a part of living

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An age old pursuit

An age old pursuit

An age old pursuit

Antiquity • 200s B. C.

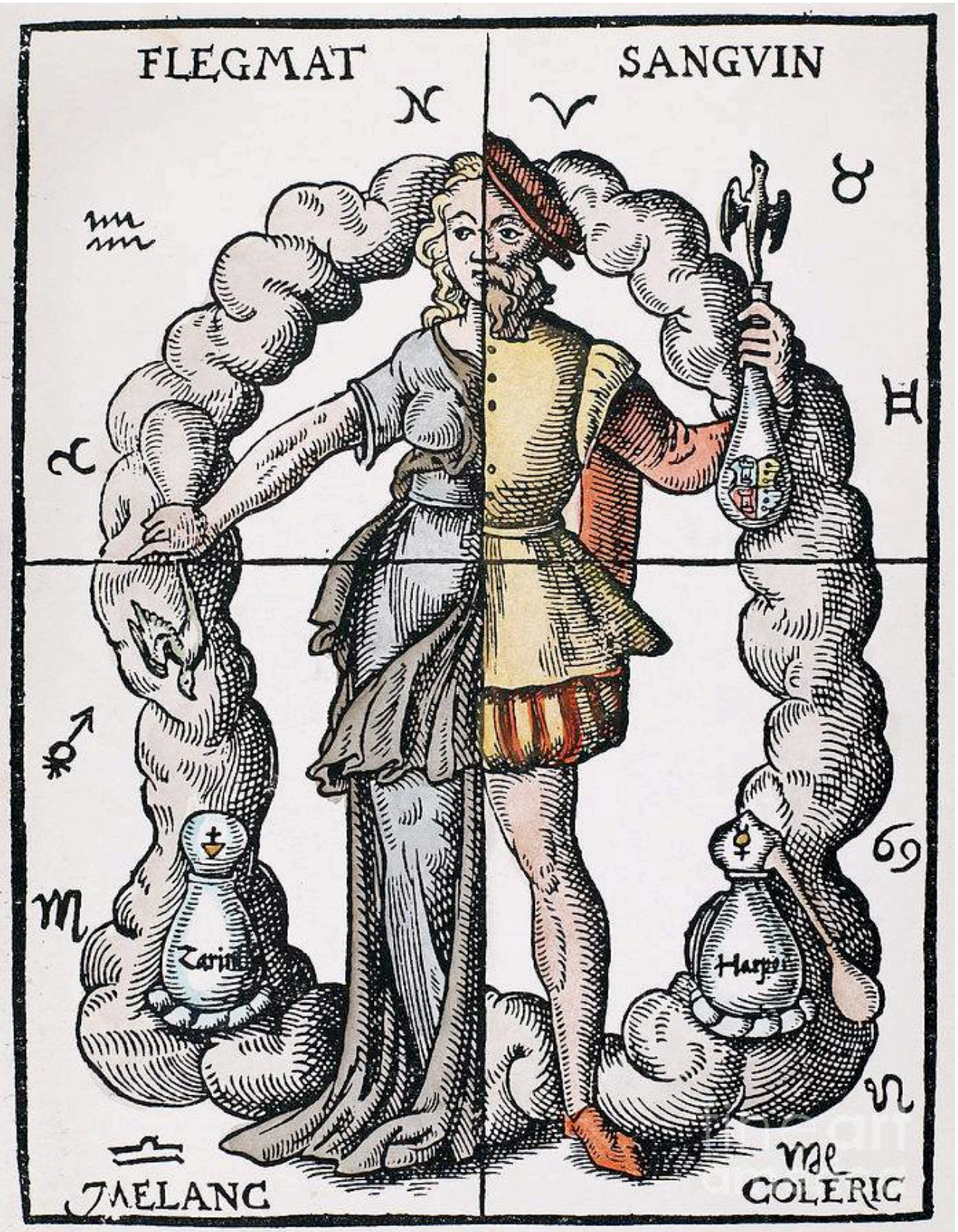
Aristole & Plato
Greece

- aging is a disease
- young = hot and wet
- old = cold and dry?

Qin Shi Huang (秦始皇)
China

- discussion of death outlawed
- interest in sorcery, early alchemy
- died age 49, mercury poisoning

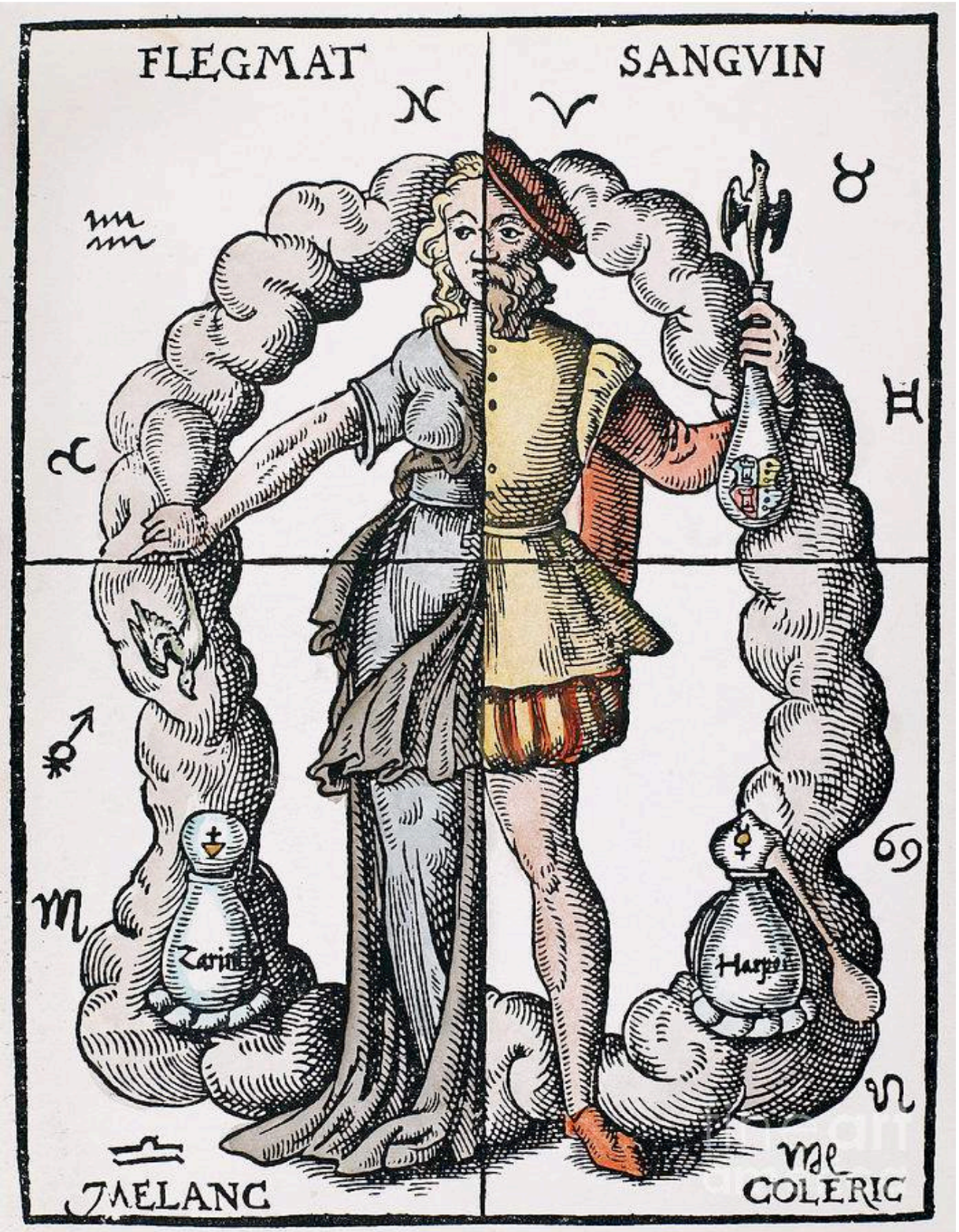
Elizabethan/Renaissance eras • 1400-1600



Diane de Portiers
France

- mistress to King Henry II
- drank gold to preserve looks
- died age 66, gold poisoning

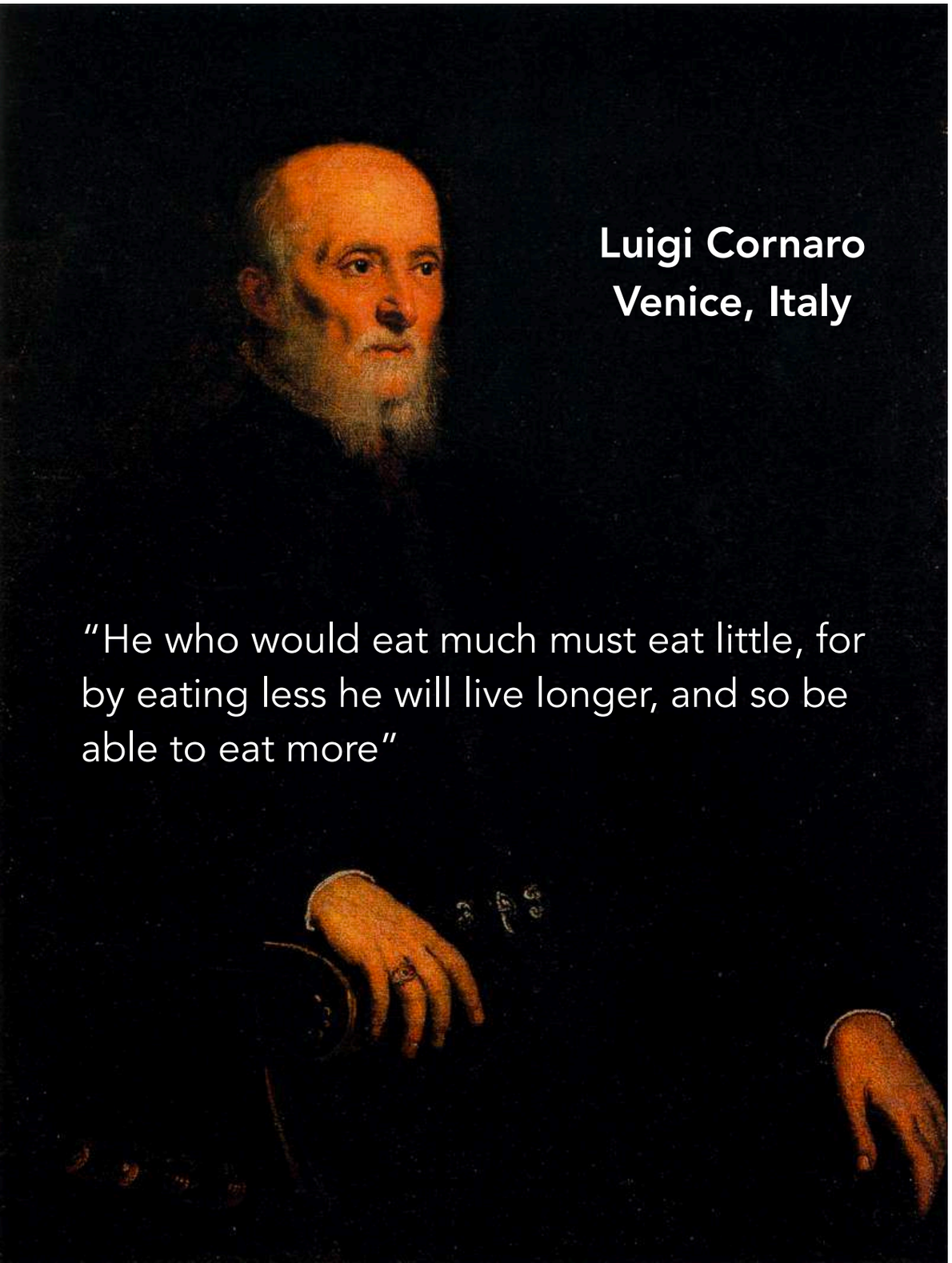
Elizabethan/Renaissance eras • 1400-1600

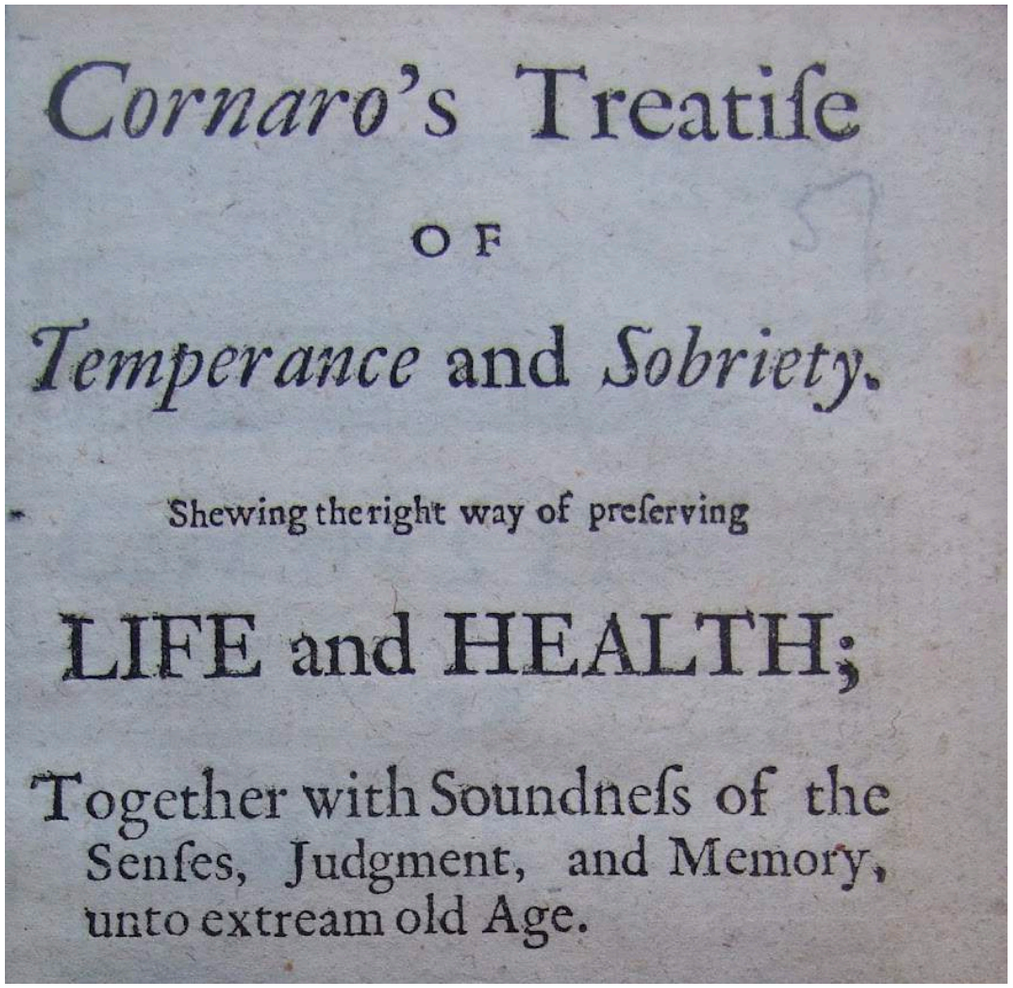


Pope Innocent VIII
Rome, Papal States

- drank blood of young children
- died age 59, unknown cause

Elizabethan/Renaissance eras • 1400-1600

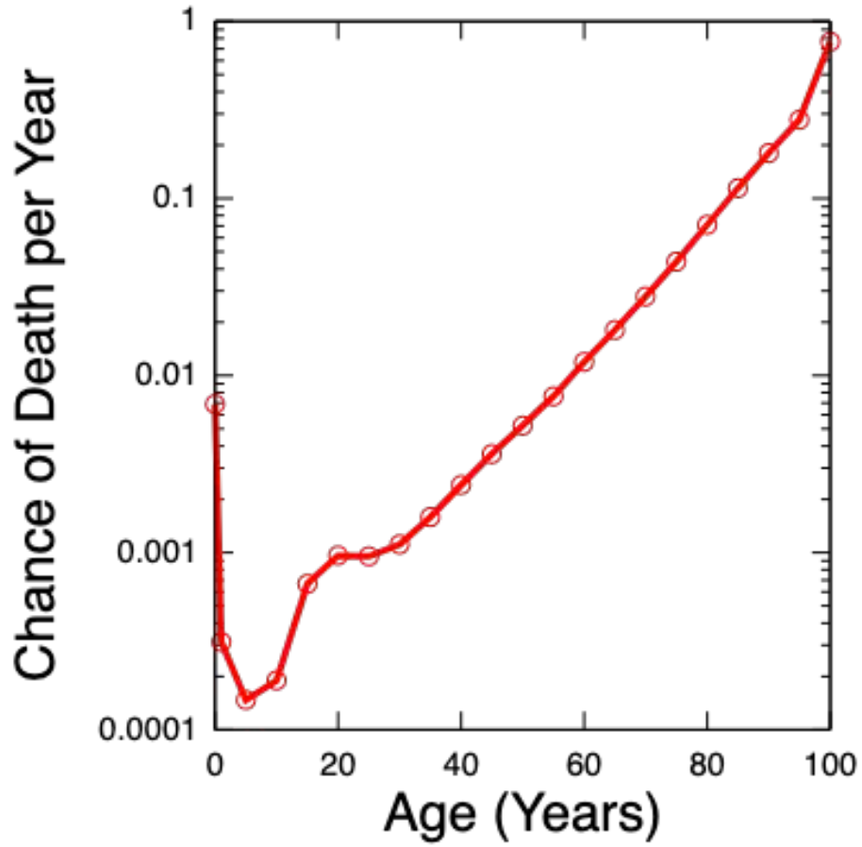



Cornaro's Treatiſe
OF
Temperance and Sobriety.
Shewing the right way of preſerving
LIFE and HEALTH;
Together with Soundneſs of the Senſes, Judgment, and Memory, unto extream old Age.

- first proponent of "moderation"
- died age 102

Age of Reason • 1600-1900

BENJAMIN GOMPERTZ, 1779–1865

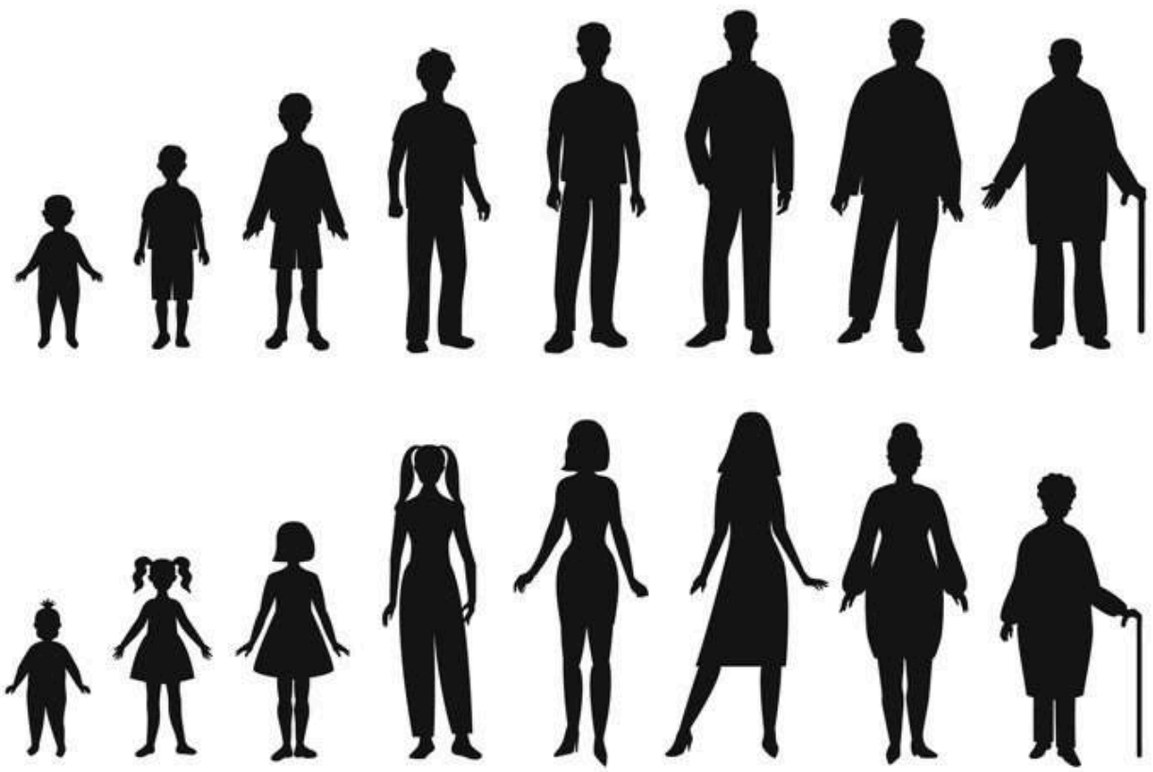


$$p = a + b^x$$

- probability of death increases exponentially with age

Age of Reason • 1800s

- what is the evolutionary purpose of aging?
- **altruistic programmed death:**
  make room for the next generation?



Alfred Russel Wallace

August Weismann

Age of Reason • 1800s

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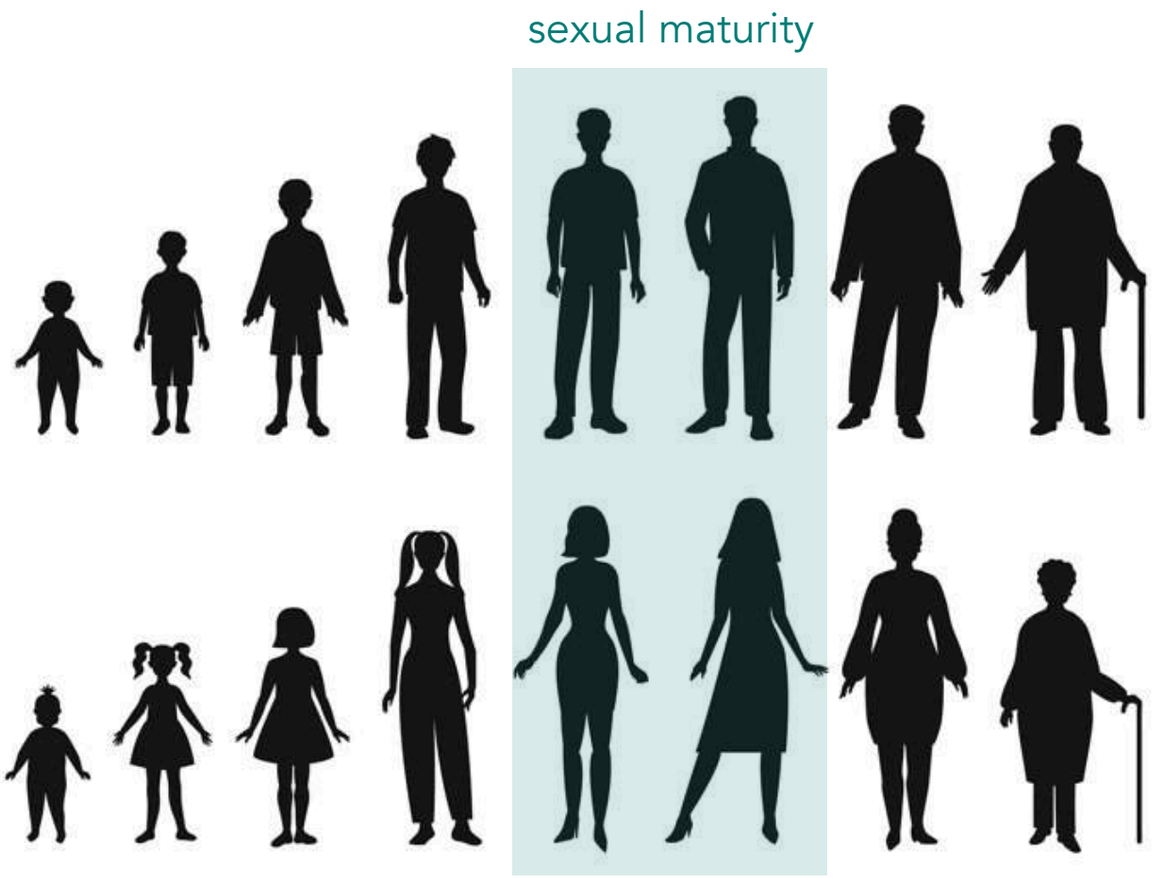


Alfred Russel Wallace

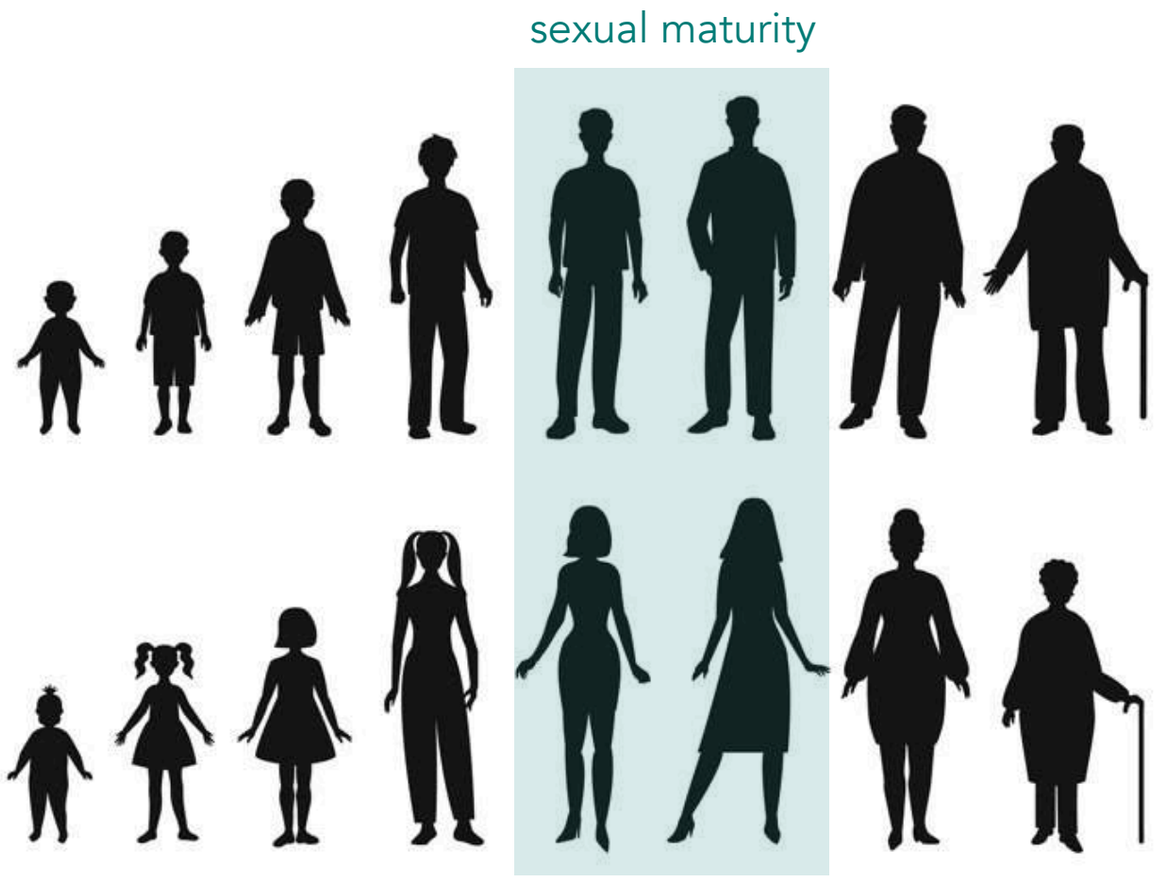
August Weismann

Age of Reason • 1800s

- cost of death to individuals exceeds benefit to the group
- **long-lived individuals would produce more offspring**

Alfred Russel Wallace

August Weismann



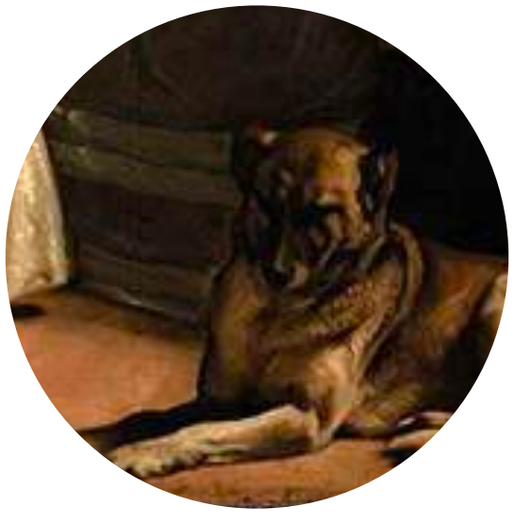
The aging paradox

animals have very different lifespans

mouse

Mus musculus

2-3 years



dog

Canis lupus familiaris

10-13 years

human

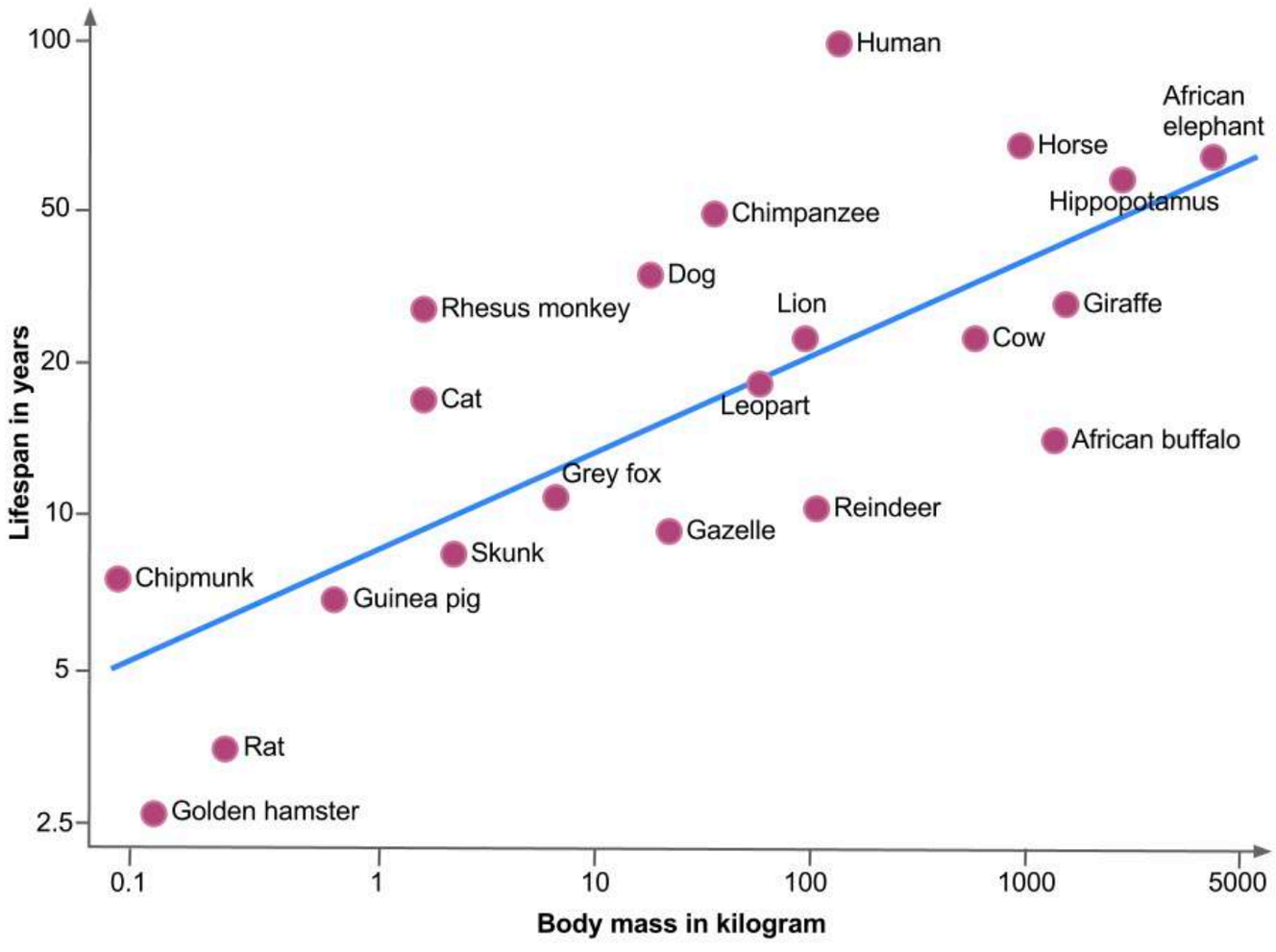
Homo sapiens

~40 years (late 19th c)

~80 years (today)

The aging paradox

bigger animals live longer



The aging paradox

except when they don't

small dogs

big dogs

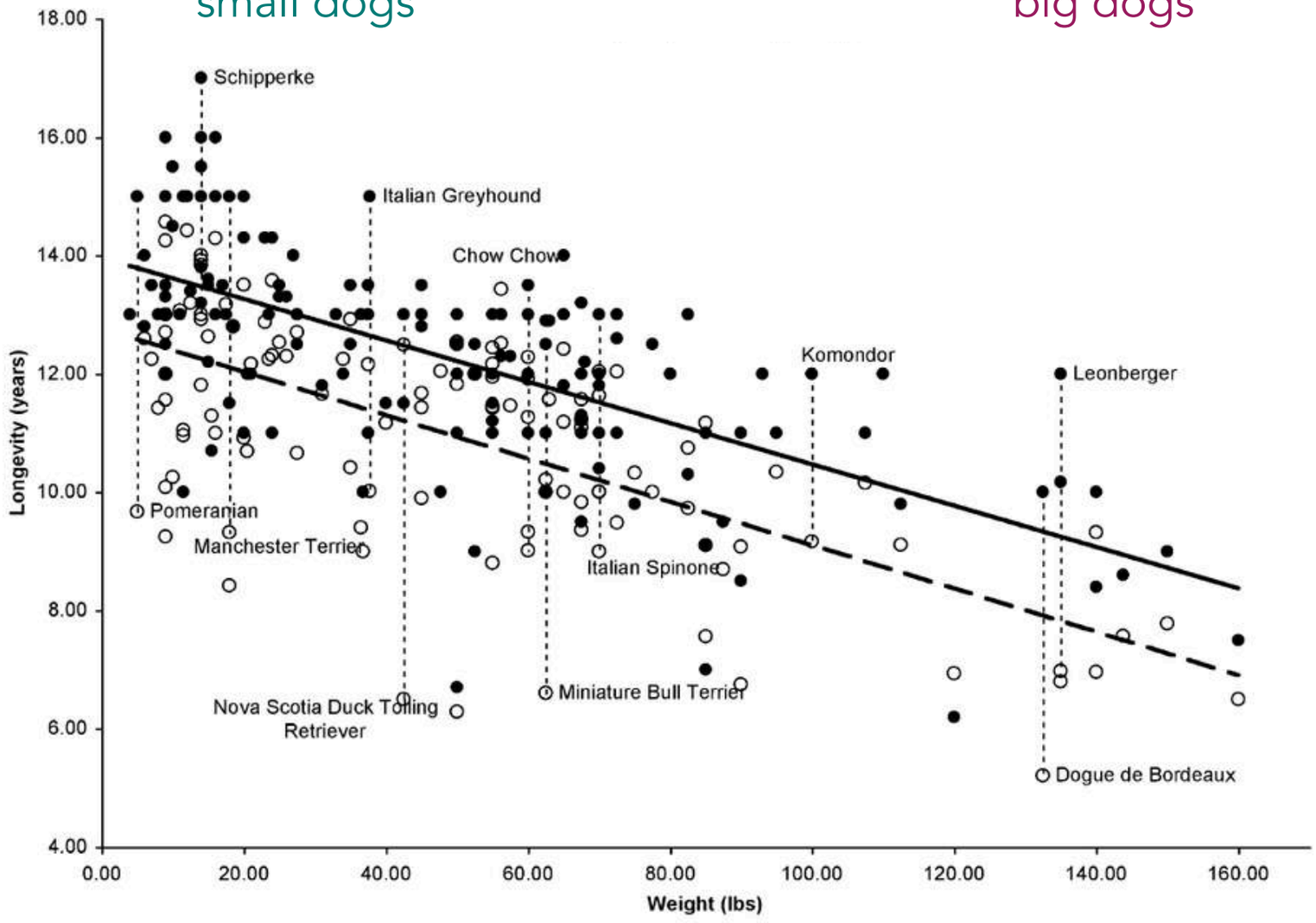


FIGURE 4.—Longevity or AOD as a function of body weight in pounds. For details, see text. Solid symbols represent the database created from websites (see supplemental Table 3). Open symbols are data from the database of Cassidy (http://users.pullman.com/lostriver/longhome.htm). A few dog breeds with extreme values are noted.

The “wear and tear” theory

- body parts and cells “wear out” like machine parts
- continued use + environment insults, outpaces the body’s capacity for repairing and replenishing

Alfred Russel Wallace

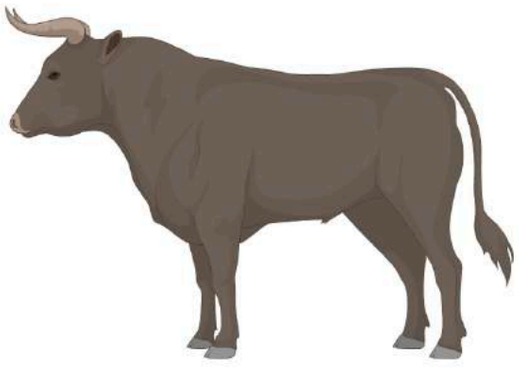
August Weismann

Replacement “therapy” • 1890 - 1920s

Charles-Édouard Brown-Séquard

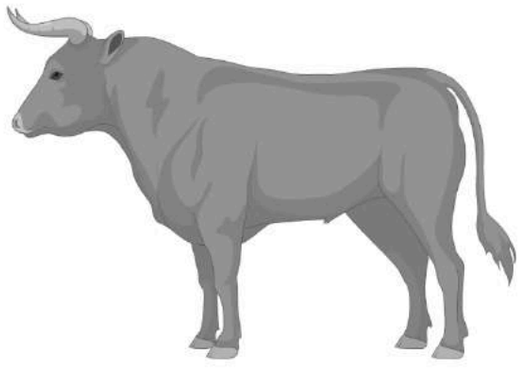
Serge Voronoff
Сергей Воронов

Leo Leonidas Stanley



young bull

testicular
transplant



old bull

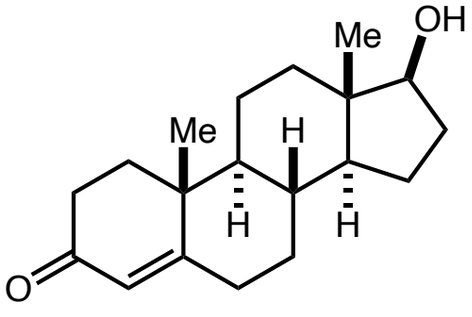
restored
mating “virility”

Replacement “therapy” • 1890 - 1920s

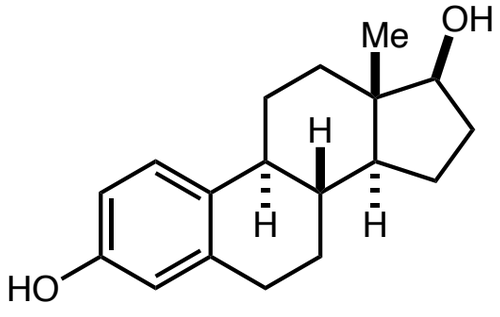
Charles-Édouard Brown-Séquard

Serge Voronoff
Сергей Воронов

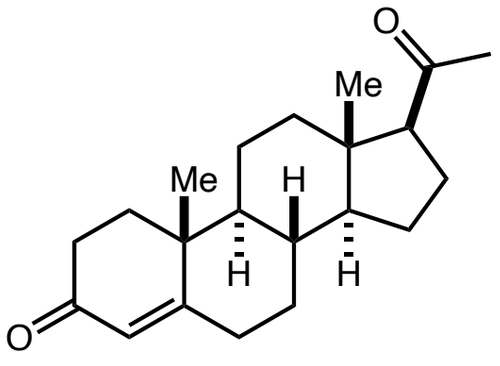
Leo Leonidas Stanley



testosterone



estrogen



progesterone

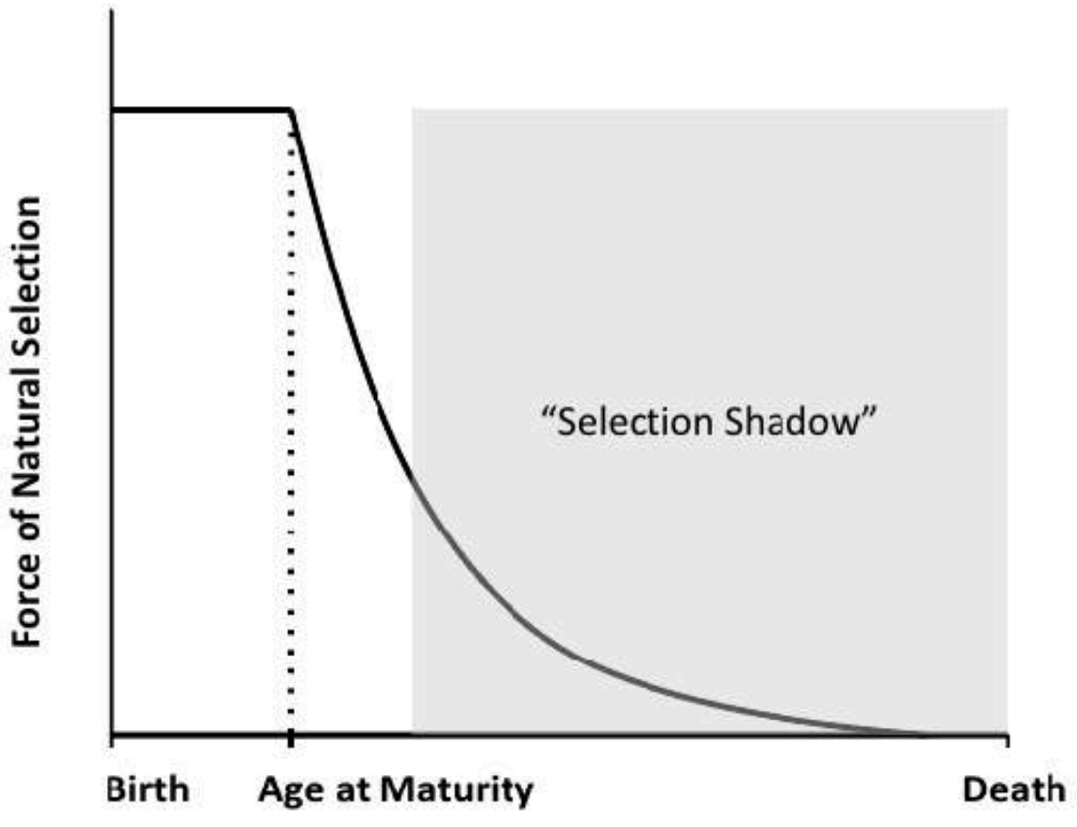
The aging paradox - extrinsic mortality

Peter Medawar

George C. Williams

J. B. S. Haldane

- few **old** animals exist in wild - predation, competition, disease, starvation, etc
- most animals die soon after genes already passed on, long before “aging” occurs
- natural selection is increasingly ineffective with age



The aging paradox - extrinsic mortality

mouse

Mus musculus

2-3 year lifespan

extremely high extrinsic mortality

Brandt's bat

Myotis brandtii

40 year lifespan

extremely low extrinsic mortality

Meanwhile, during the Great Depression

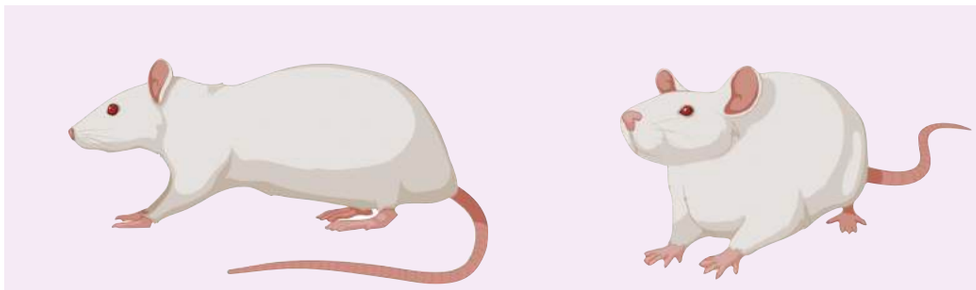
- 1930s - life expectancy was 53
- starvation, malnutrition commonplace
- lack of any real scientific data on nutritional impacts on overall health
- assess how and why malnutrition/ starvation was bad for the body

Clive McCay

Cornell University

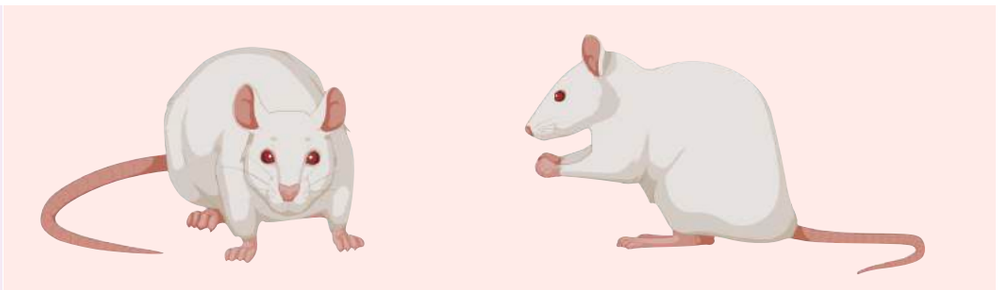
Caloric restriction

group 1



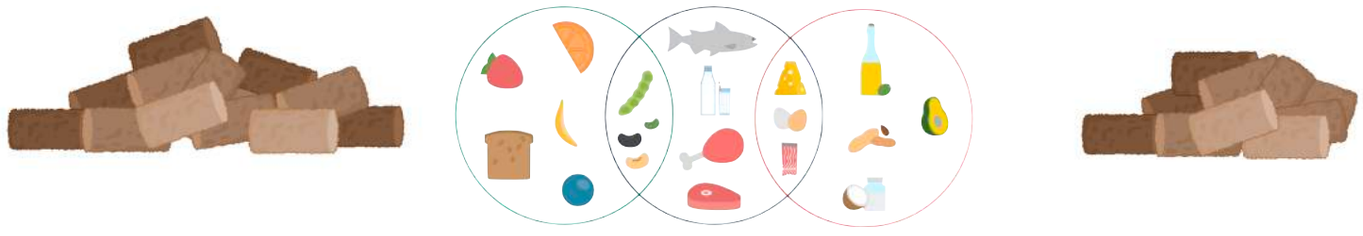
ad libitum (unlimited eating)

group 2



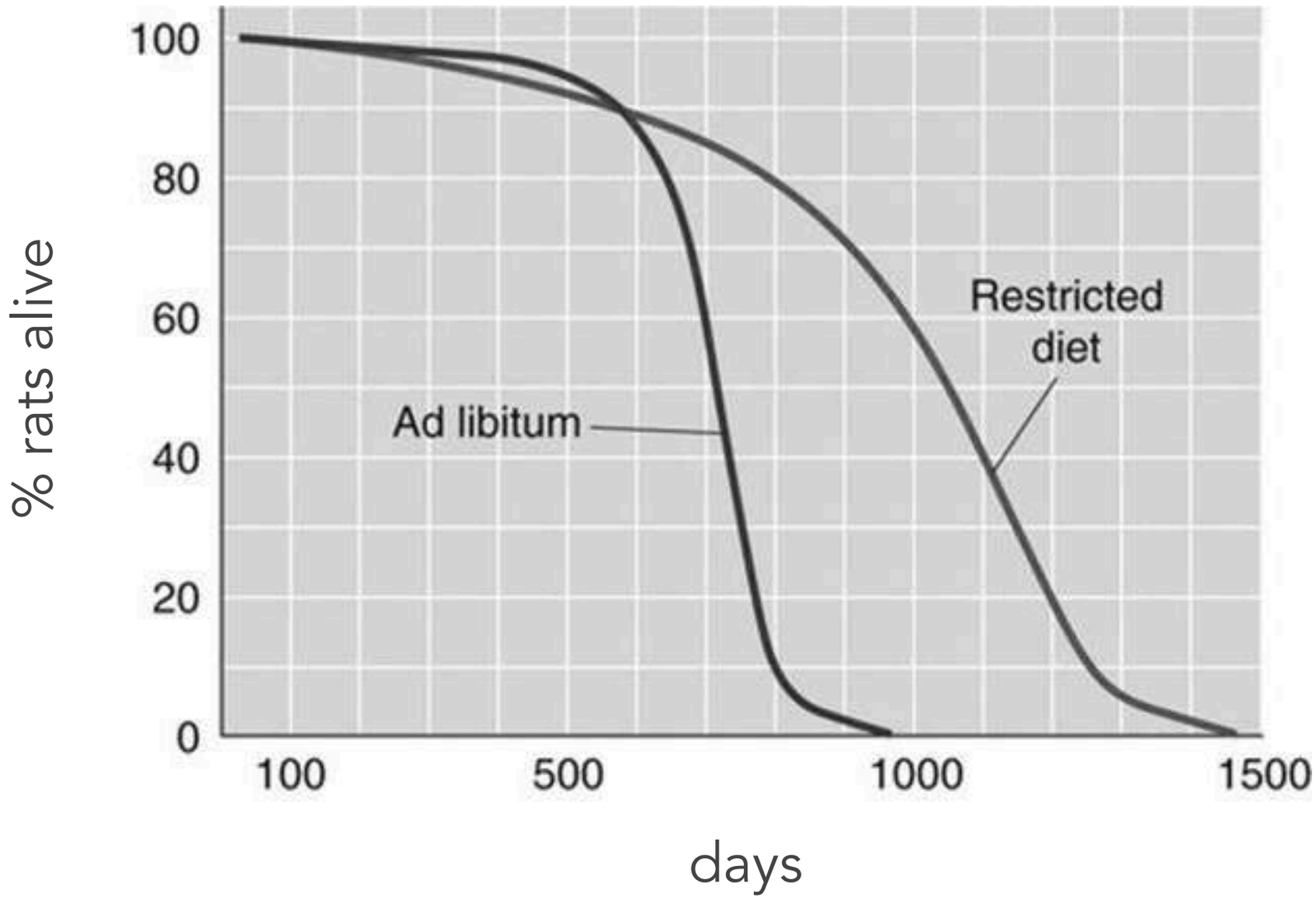
calorie restricted (30-50%)

identical macronutrient chow



McCay, C. M., Crowell, M. F., & Maynard, L. A. *J. Nutrition*, **1935**, *10*(1), 63-79.

Caloric restriction



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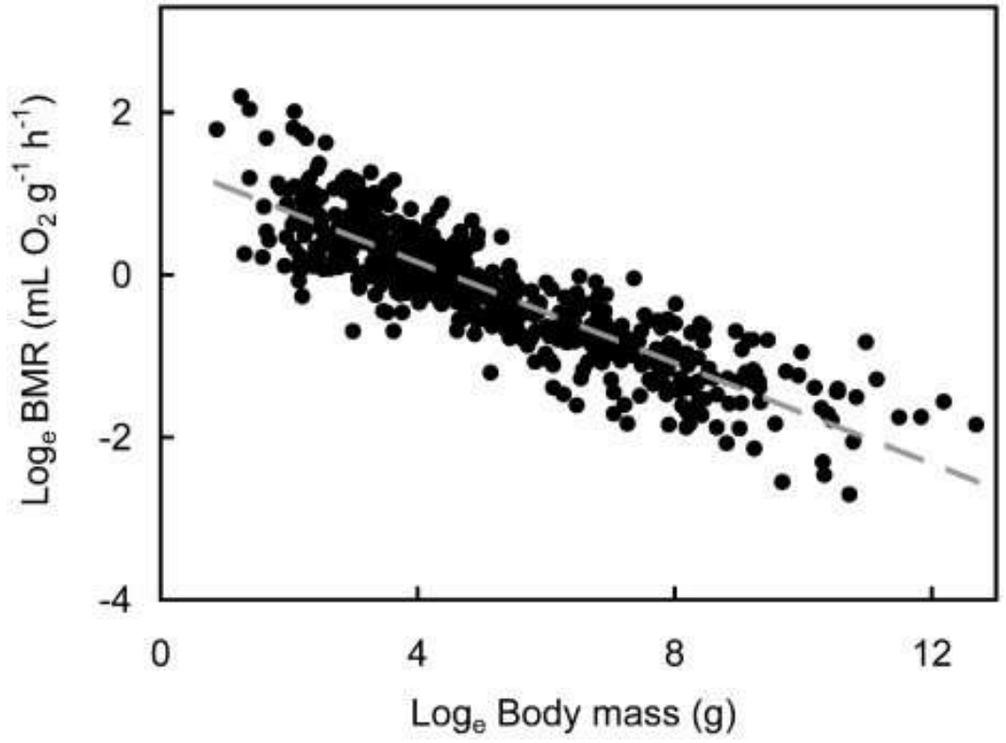
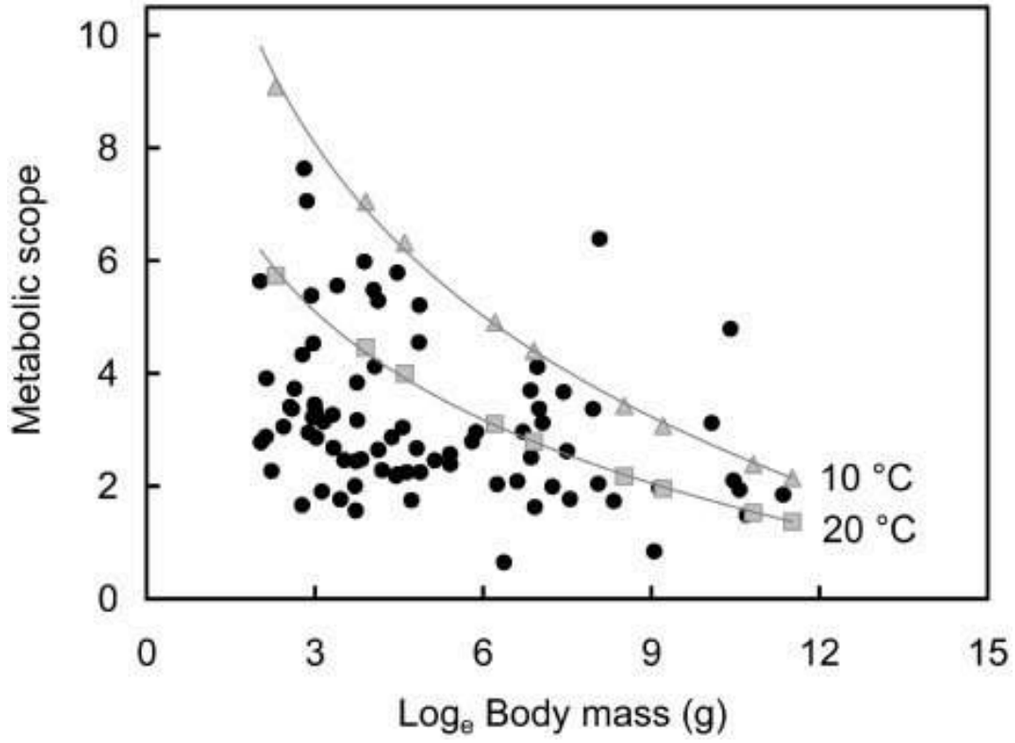
Caloric restriction

- overall “slowing” of the body’s processes/breakdown
- **~100 years later, we are still figuring out why calorie restriction extends lifespan**





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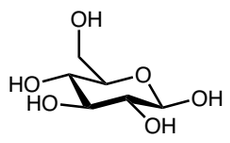
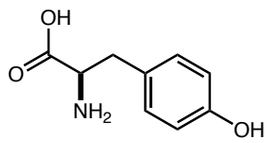
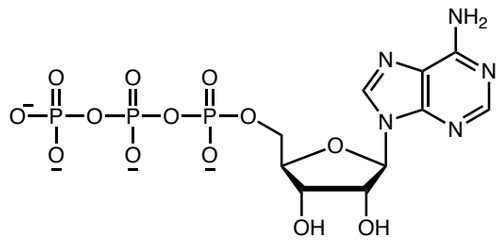
The “disposable soma”

resources are finite







perfect maintenance

(repair, regeneration)

imperfect maintenance

(good enough to mate)

immortal

net degeneration

The “disposable soma”

The “disposable soma”

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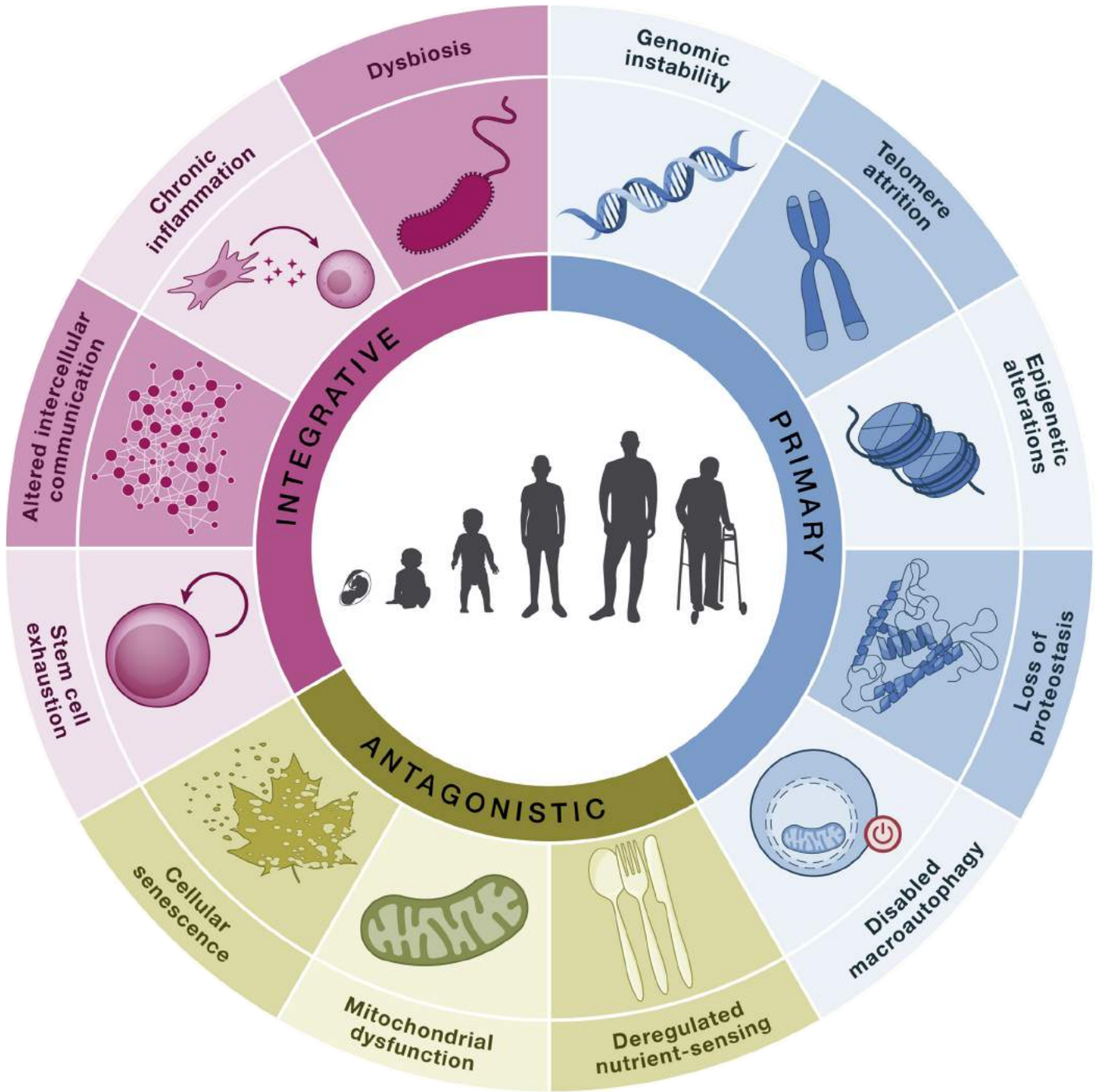
The “disposable soma”

The “disposable soma”

The 12 hallmarks of aging

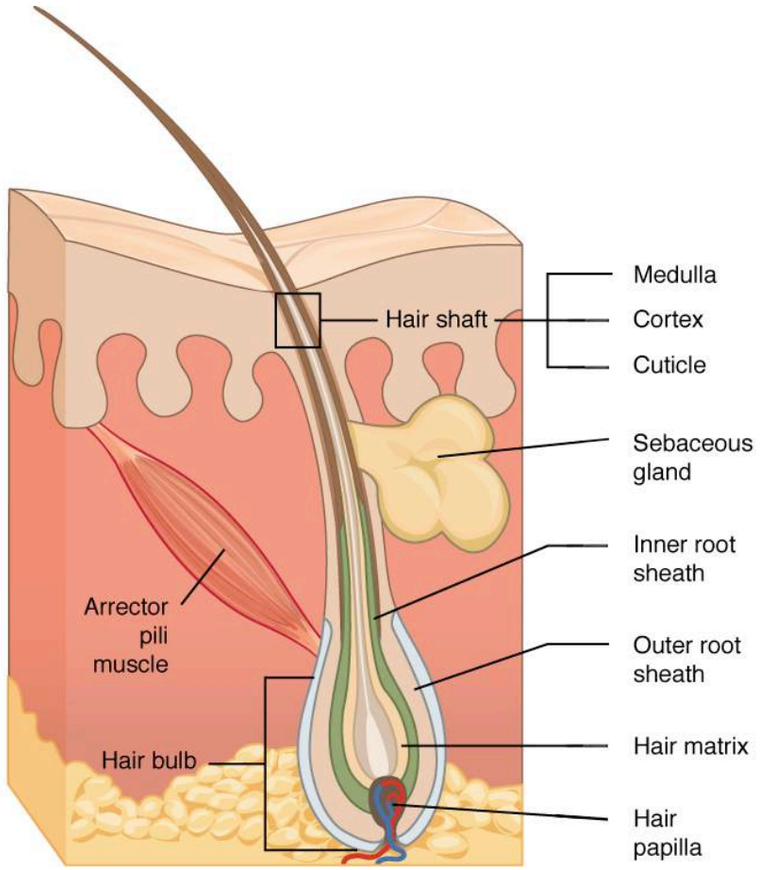


Lopez, Otin, C. et al., *Cell*, **2023,** in press

The 12 hallmarks of aging

Lopez, Otin, C. et al., *Cell*, **2023,** in press

Cellular aging



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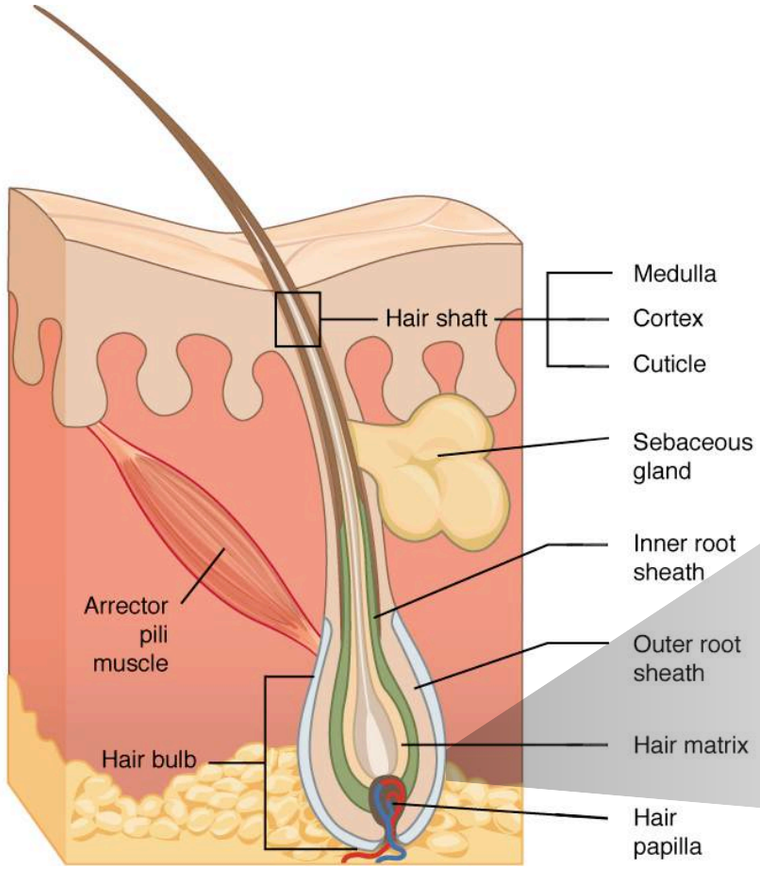

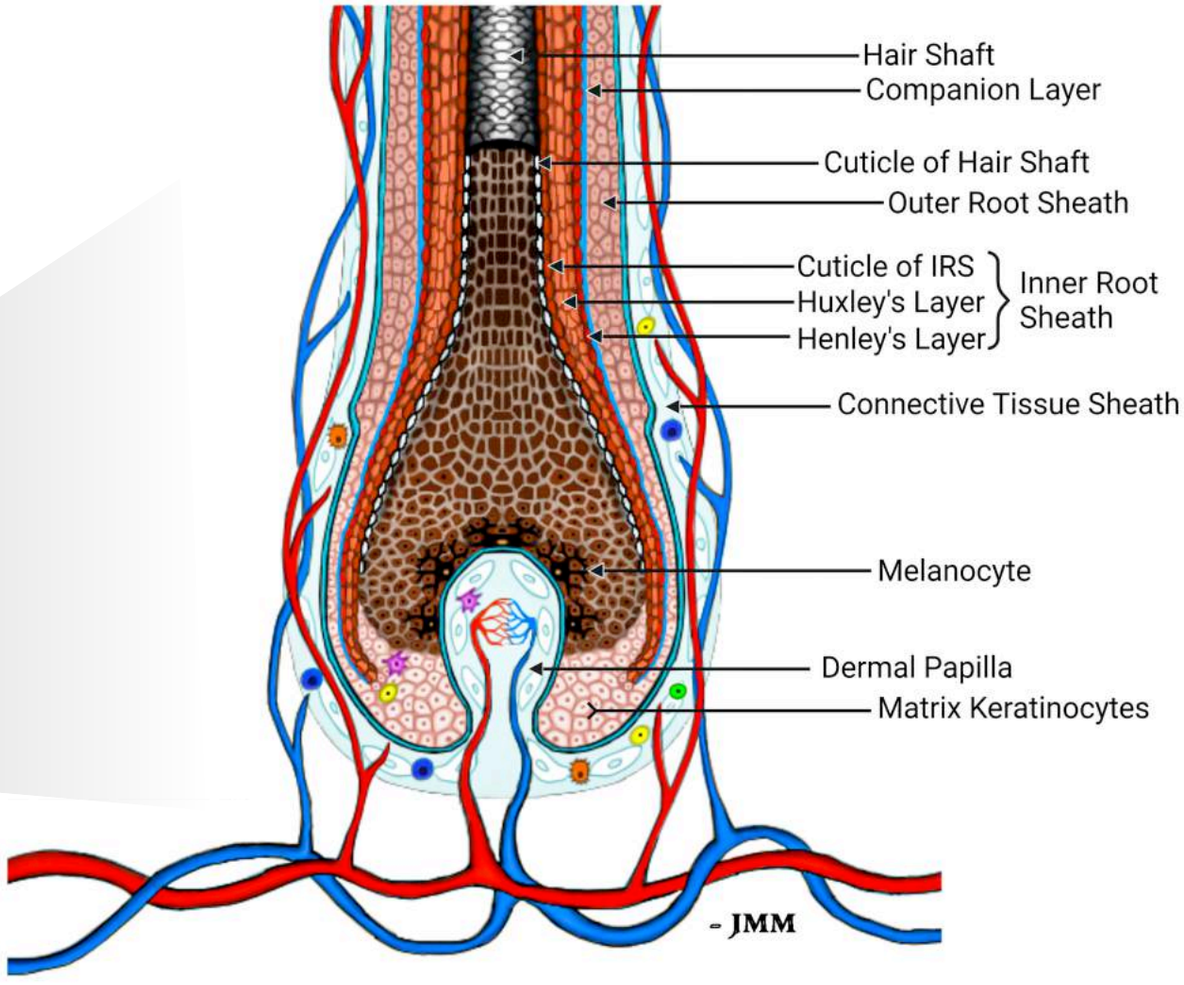

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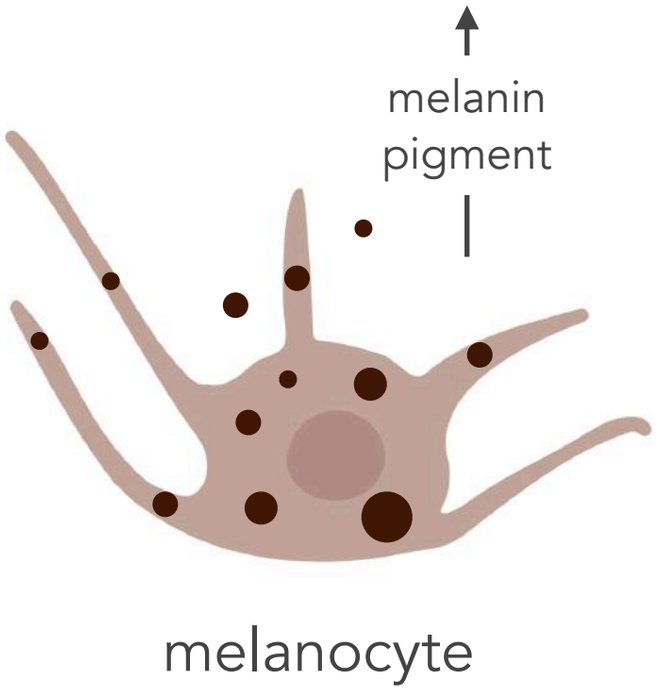
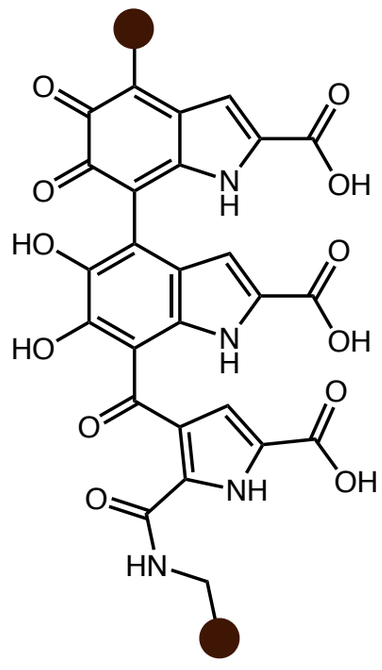
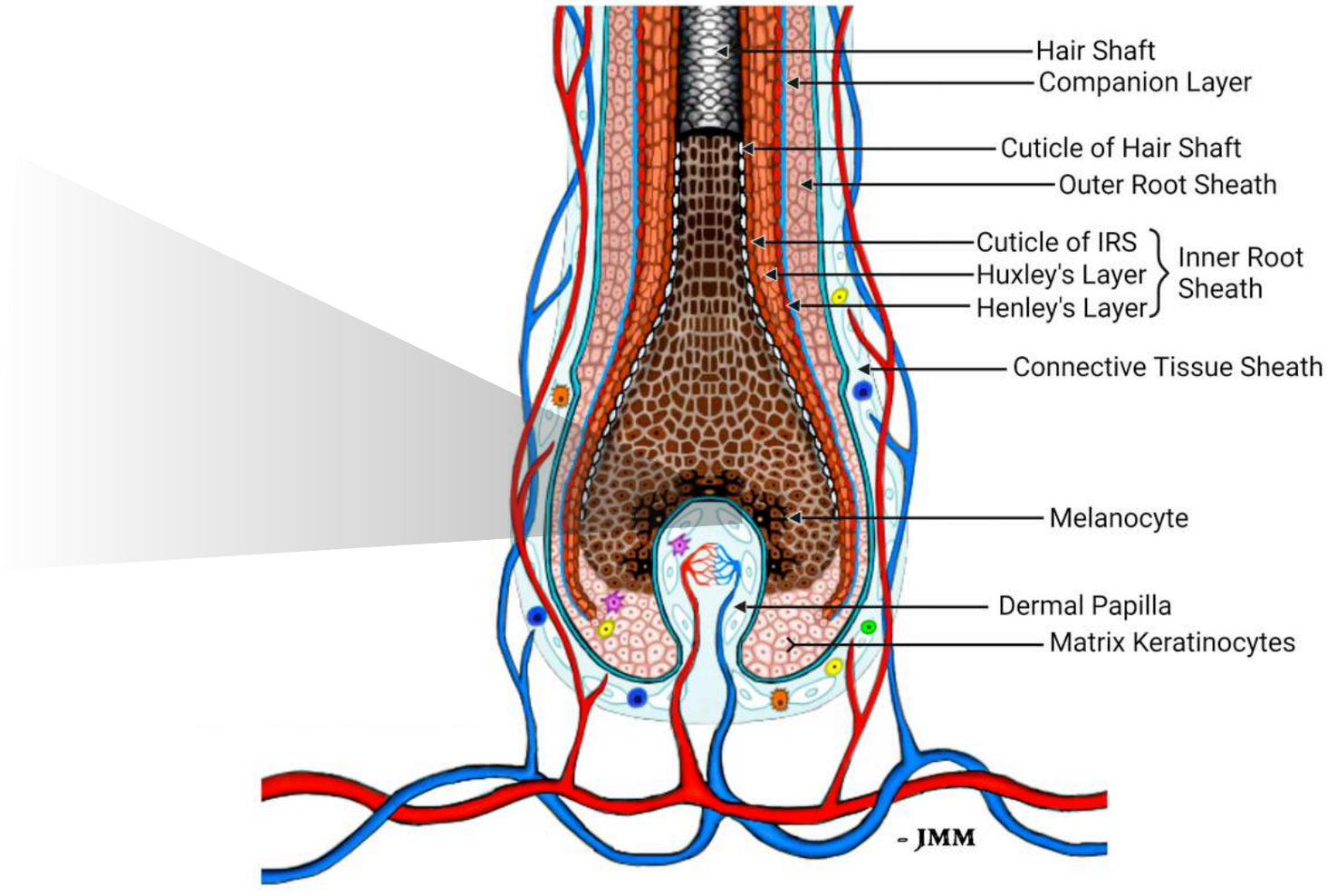


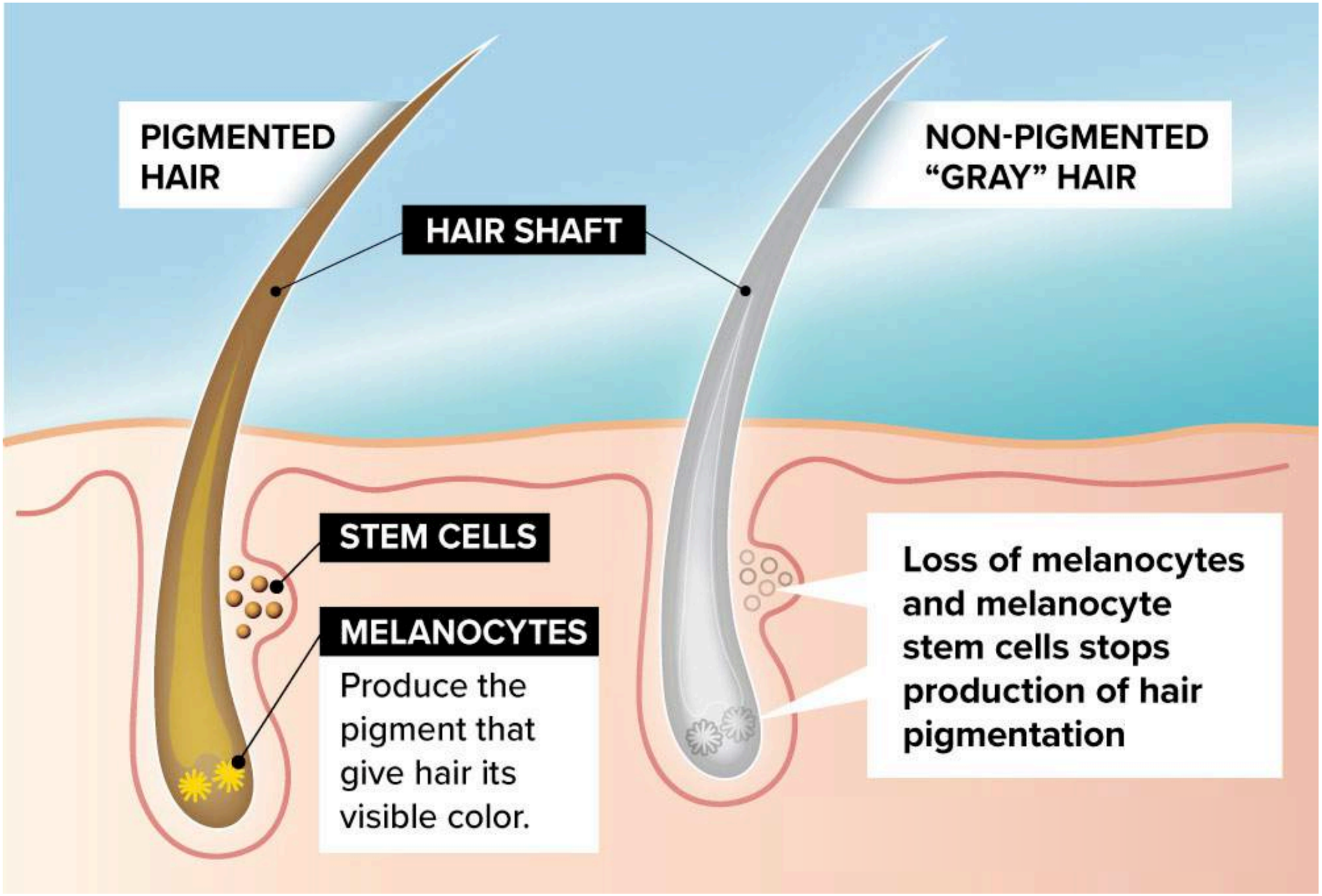
melanocyte

melanin

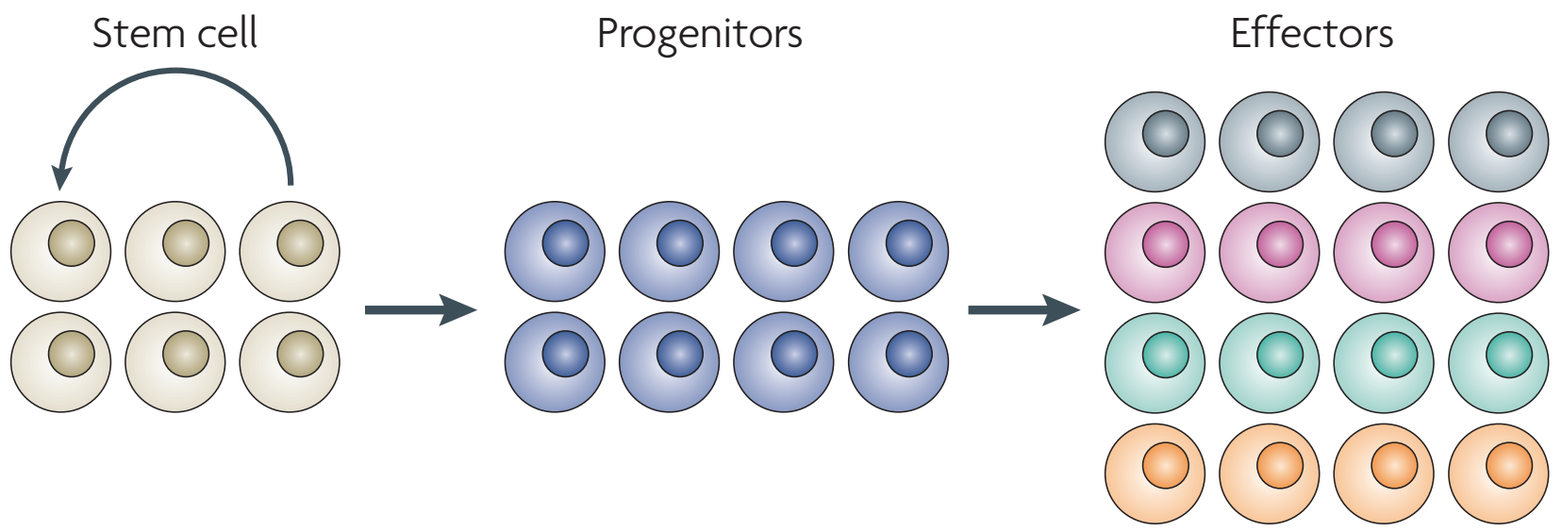




Cellular aging



Stem cells regenerate tissue



Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

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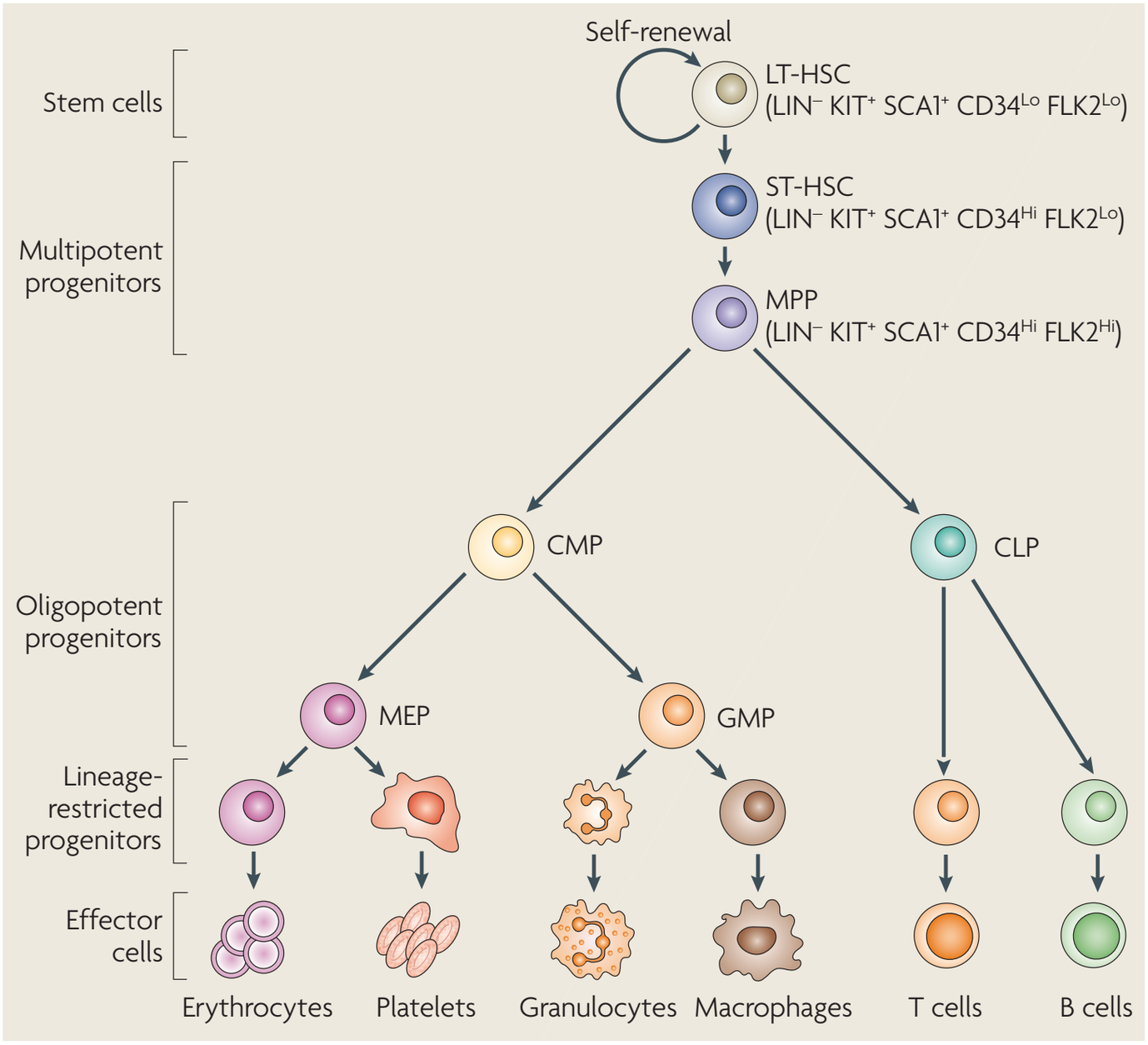

RBCs T cells platelets

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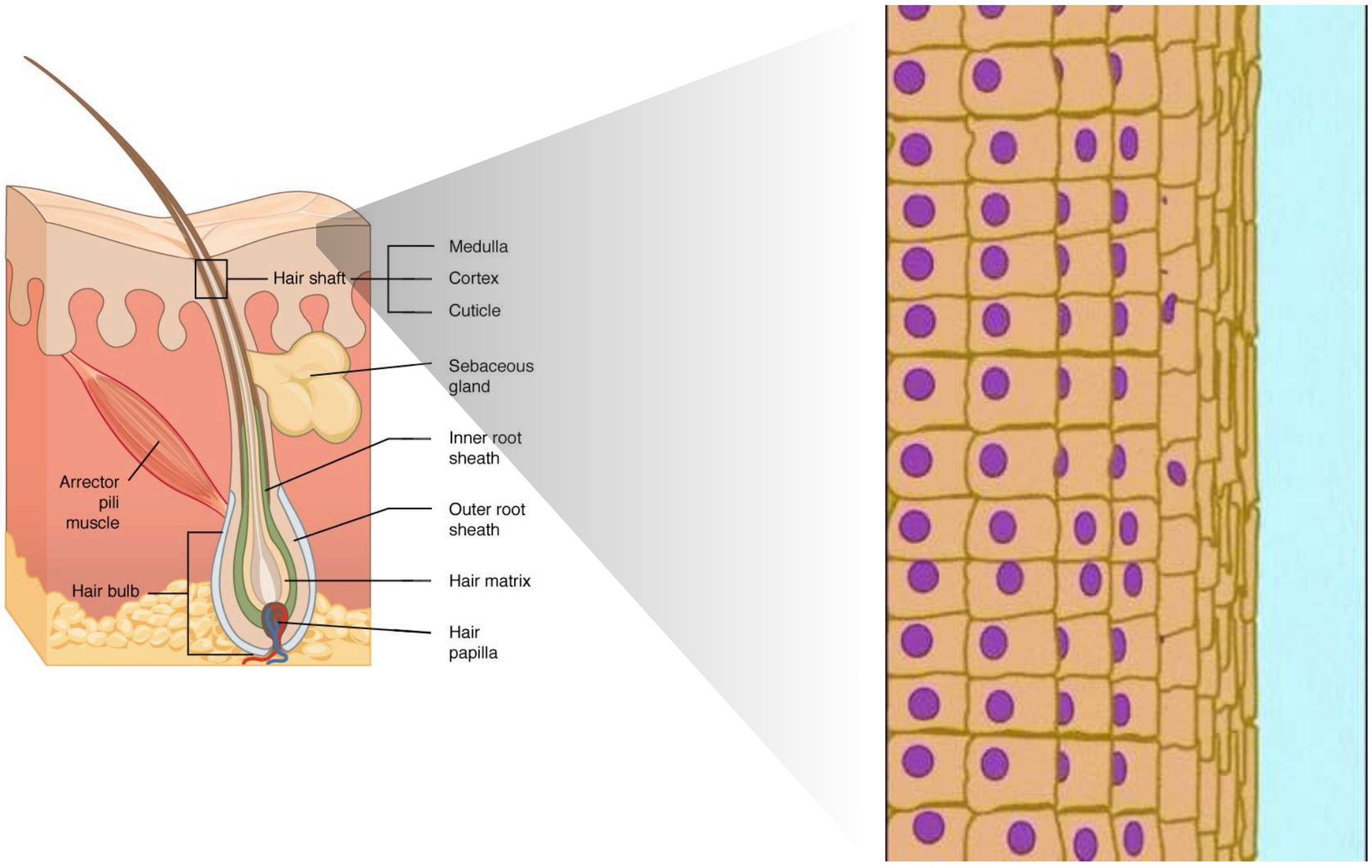

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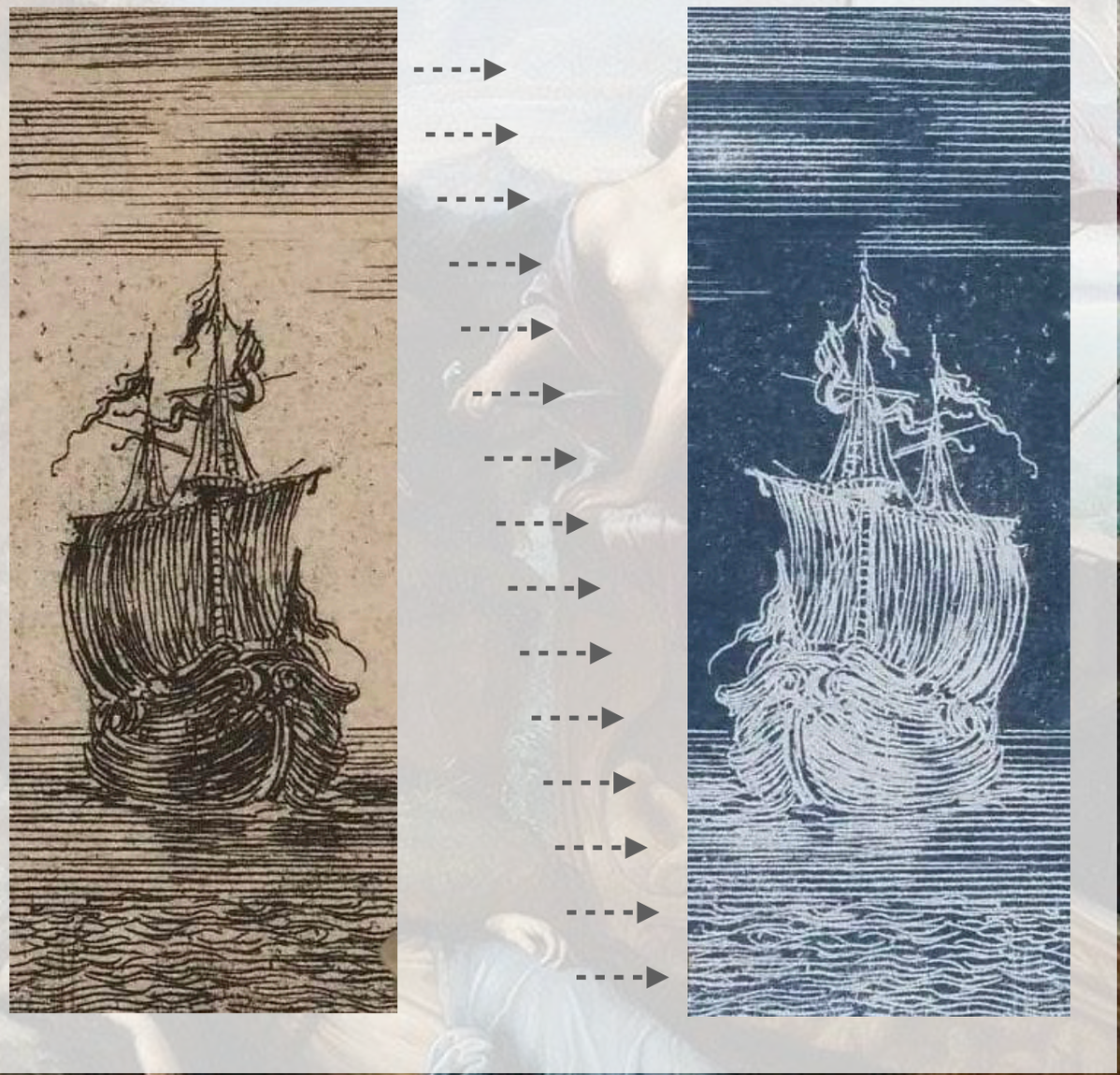
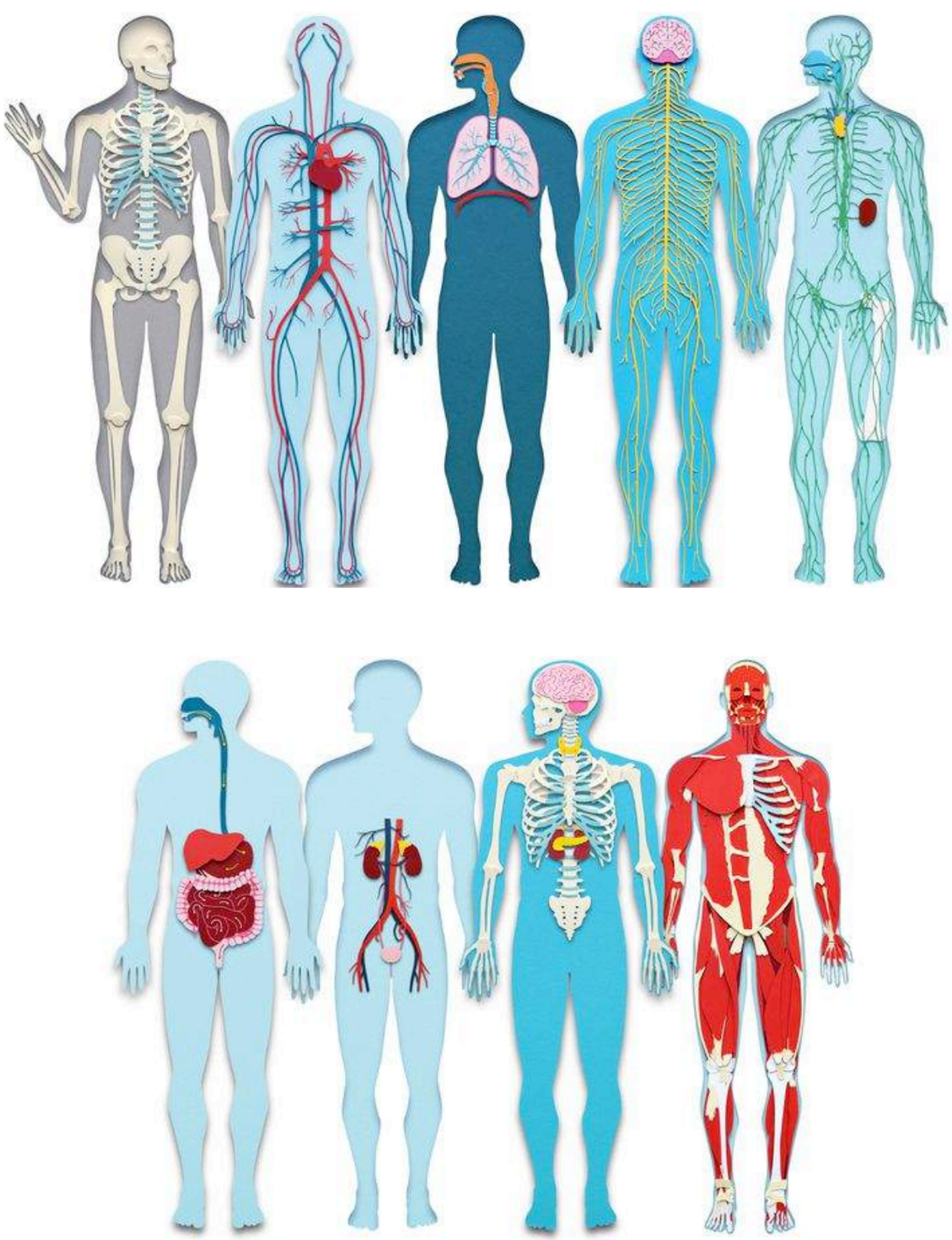
You are the ship of Theseus



cell type	turnover time
small intestine epithelium	2-4 days
stomach	2-9 days
blood Neutrophils	1-5 days
white blood cells Eosinophils	2-5 days
gastrointestinal colon crypt cells	3-4 days
cervix	6 days
lungs alveoli	8 days
tongue taste buds (rat)	10 days
platelets	10 days
bone osteoclasts	2 weeks
intestine Paneth cells	20 days
skin epidermis cells	10-30 days
pancreas beta cells (rat)	20-50 days
blood B cells (mouse)	4-7 weeks
trachea	1-2 months
hematopoietic stem cells	2 months
sperm (male gametes)	2 months
bone osteoblasts	3 months
red blood cells	4 months
liver hepatocyte cells	0.5-1 year
fat cells	8 years
cardiomyocytes	0.5-10% per year
central nervous system	life time
skeleton	10% per year

You are the ship of Theseus



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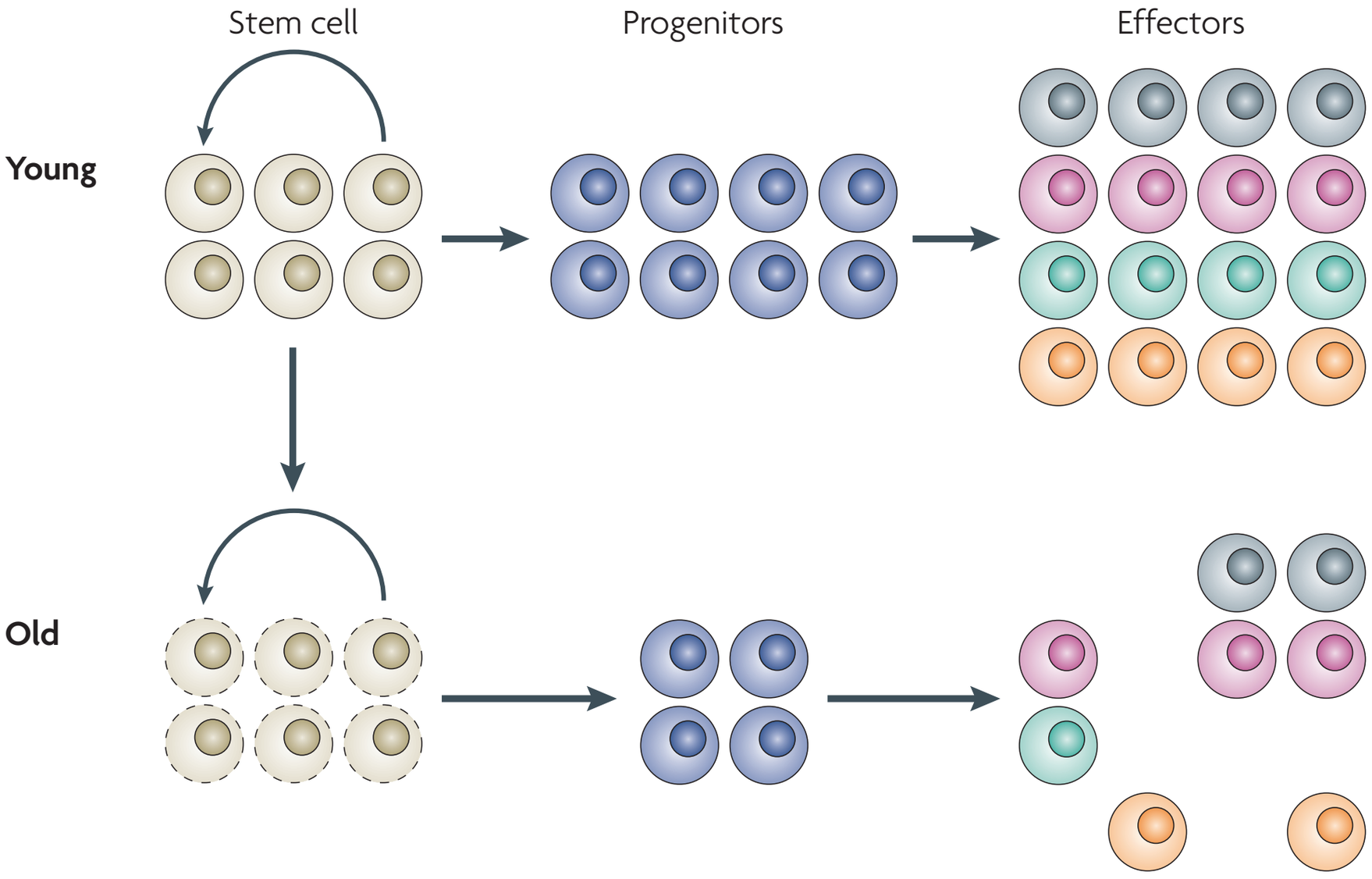
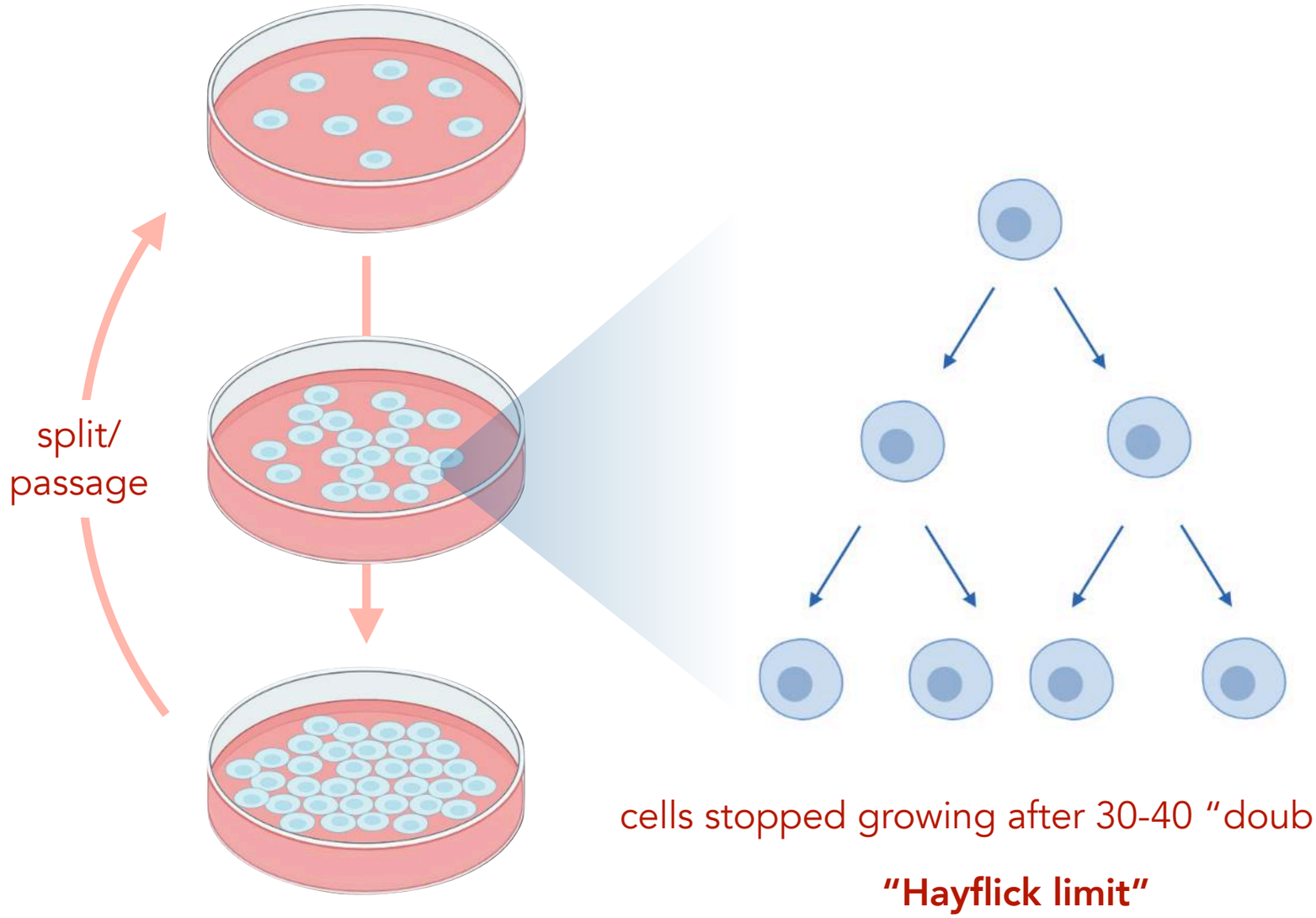


Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

Why do stem cells die as we age?

cell divisions are finite

Leonard Hayflick

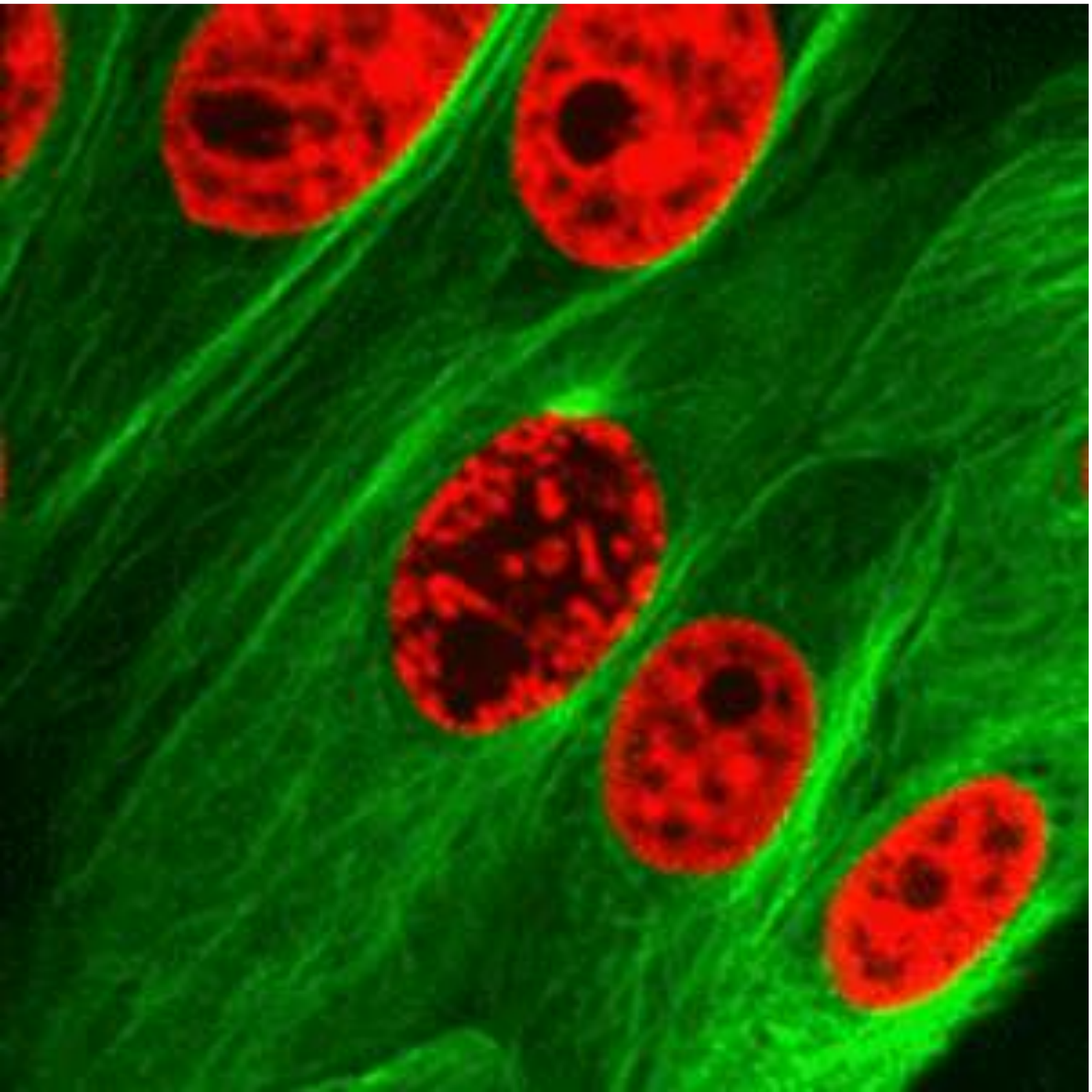


cells stopped growing after 30-40 “doublings”

“Hayflick limit”

Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

Why do stem cells die as we age?

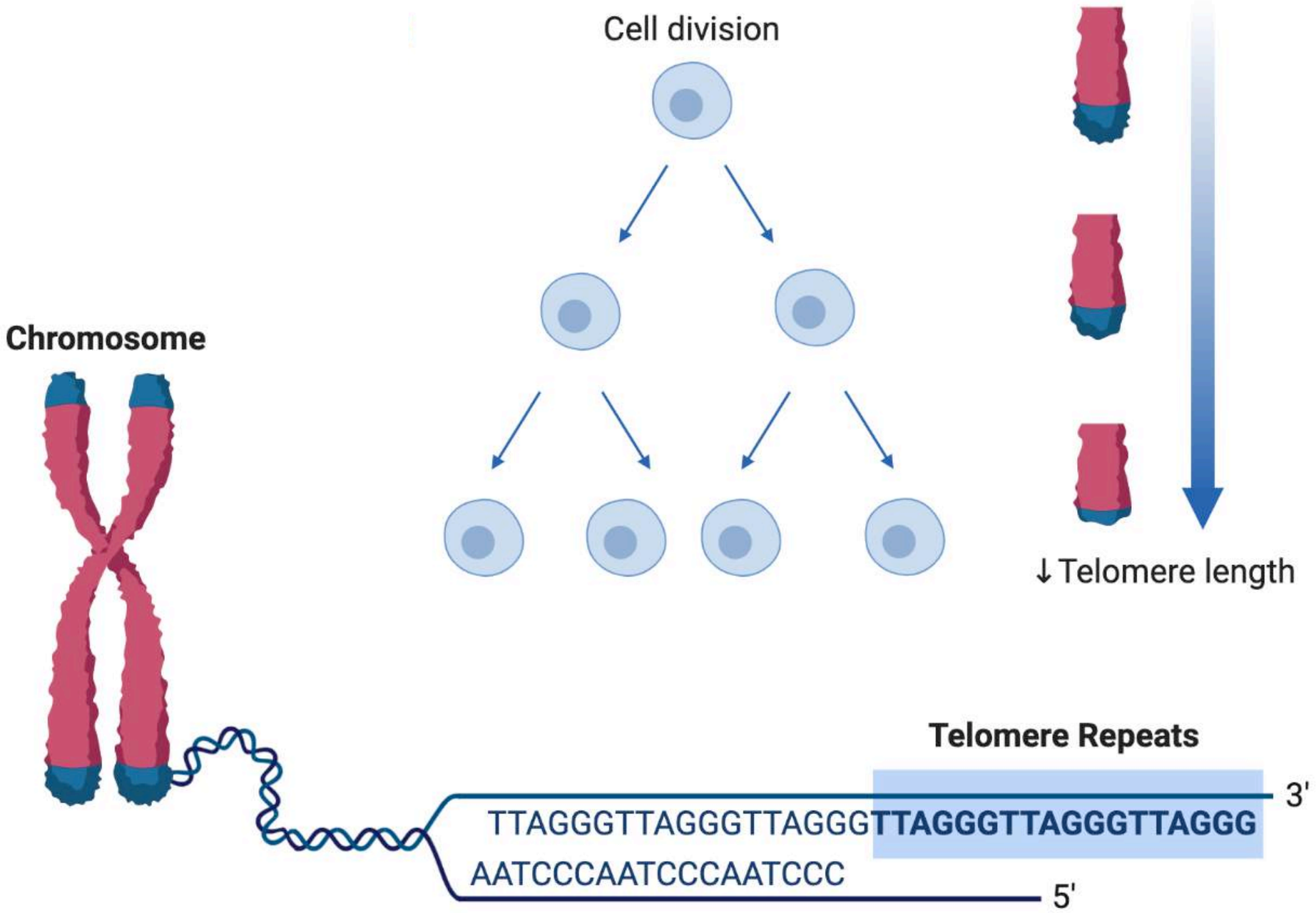


cell division

is a violent process

- chromosome condensation
- chromatid alignment
- mechanical separation

Telomere shortening



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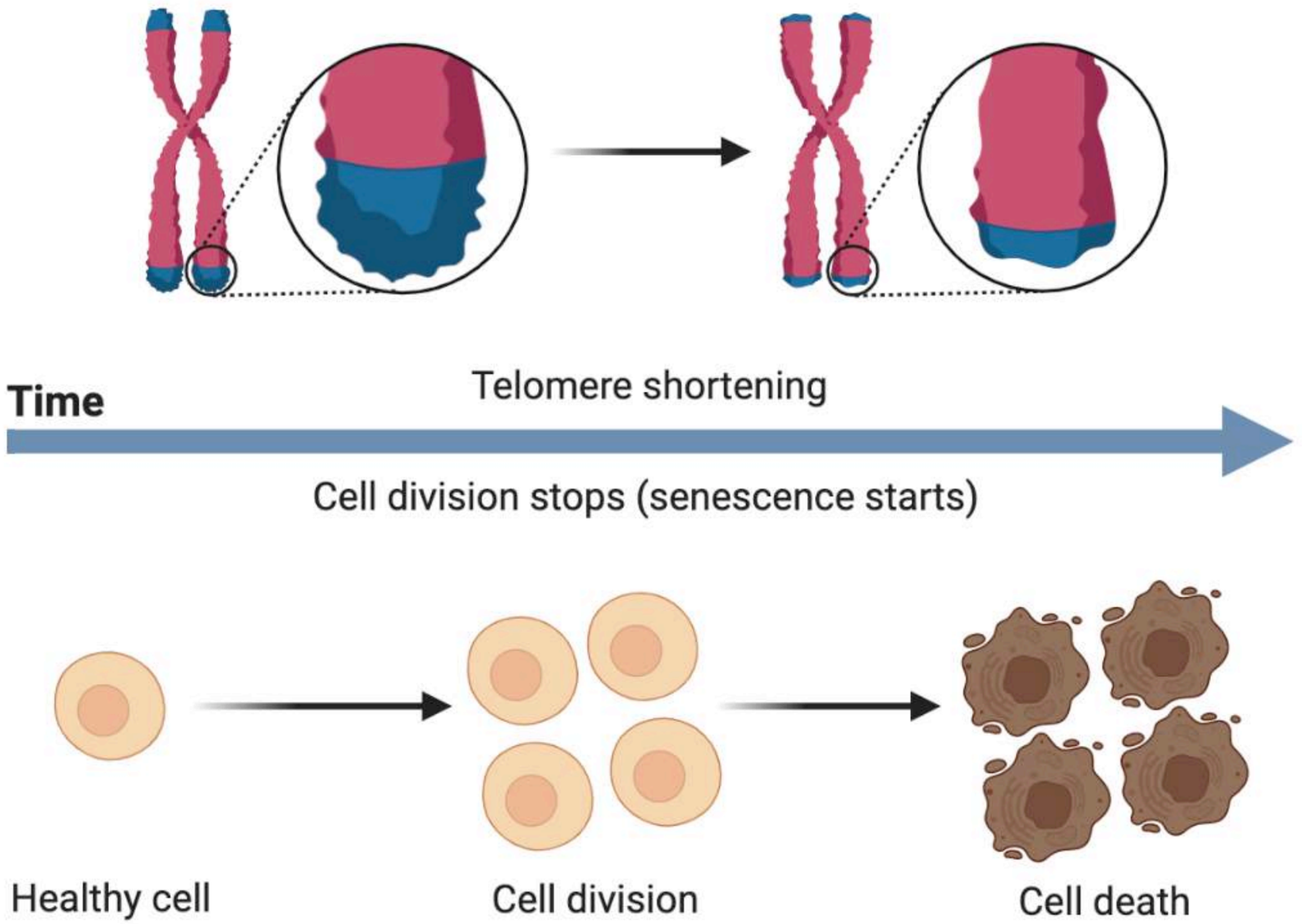
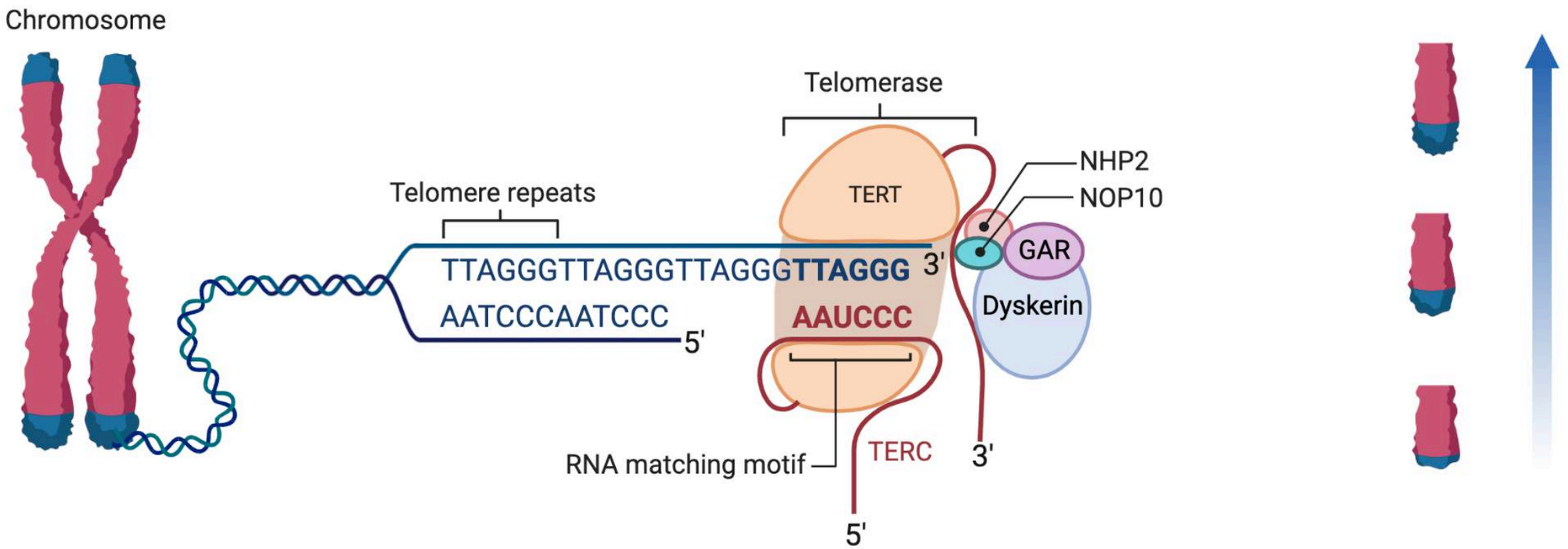
Telomere shortening

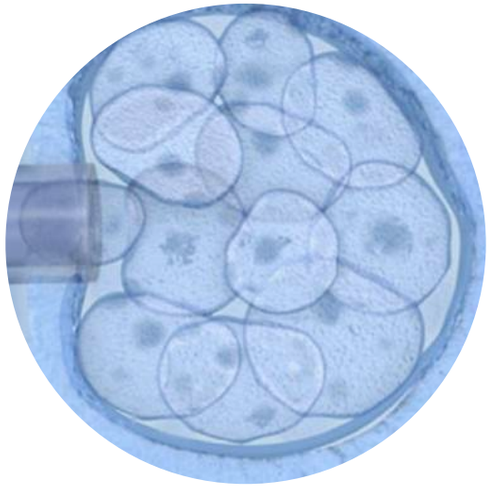


Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

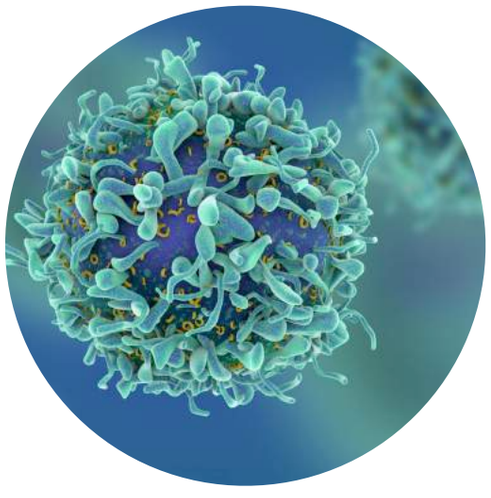
Telomere lengthening



sperm



egg/embryos

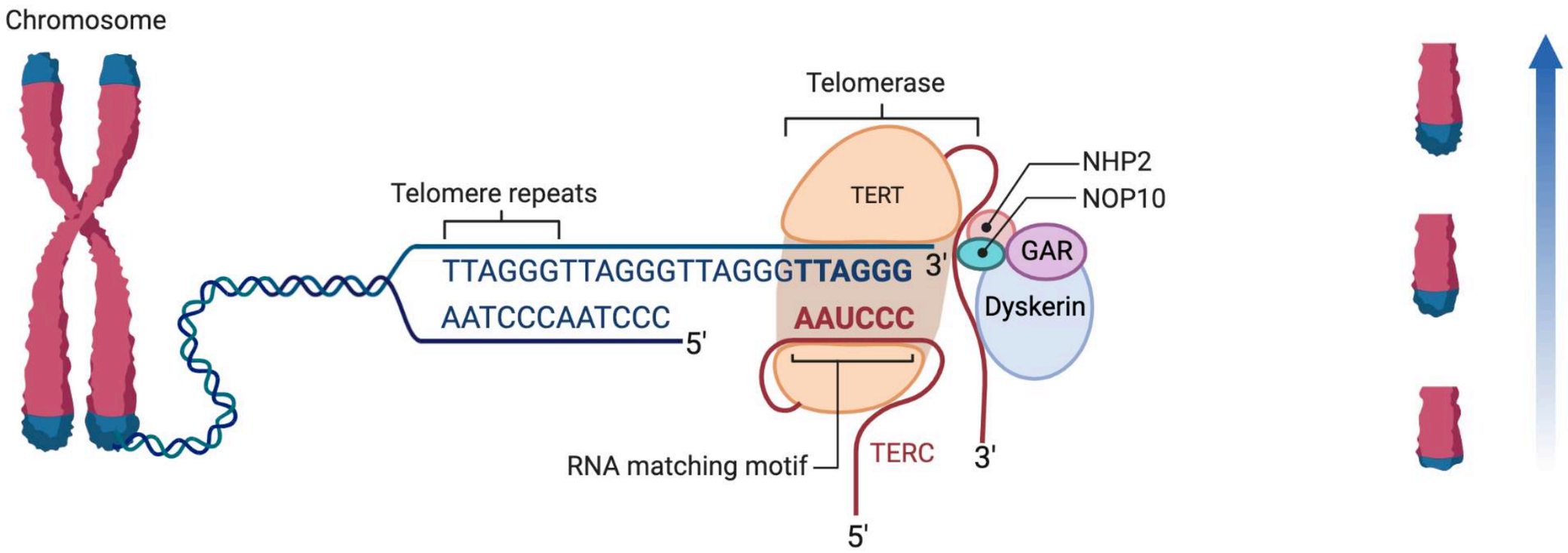


T and B cells

skin cells

Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

Telomere lengthening



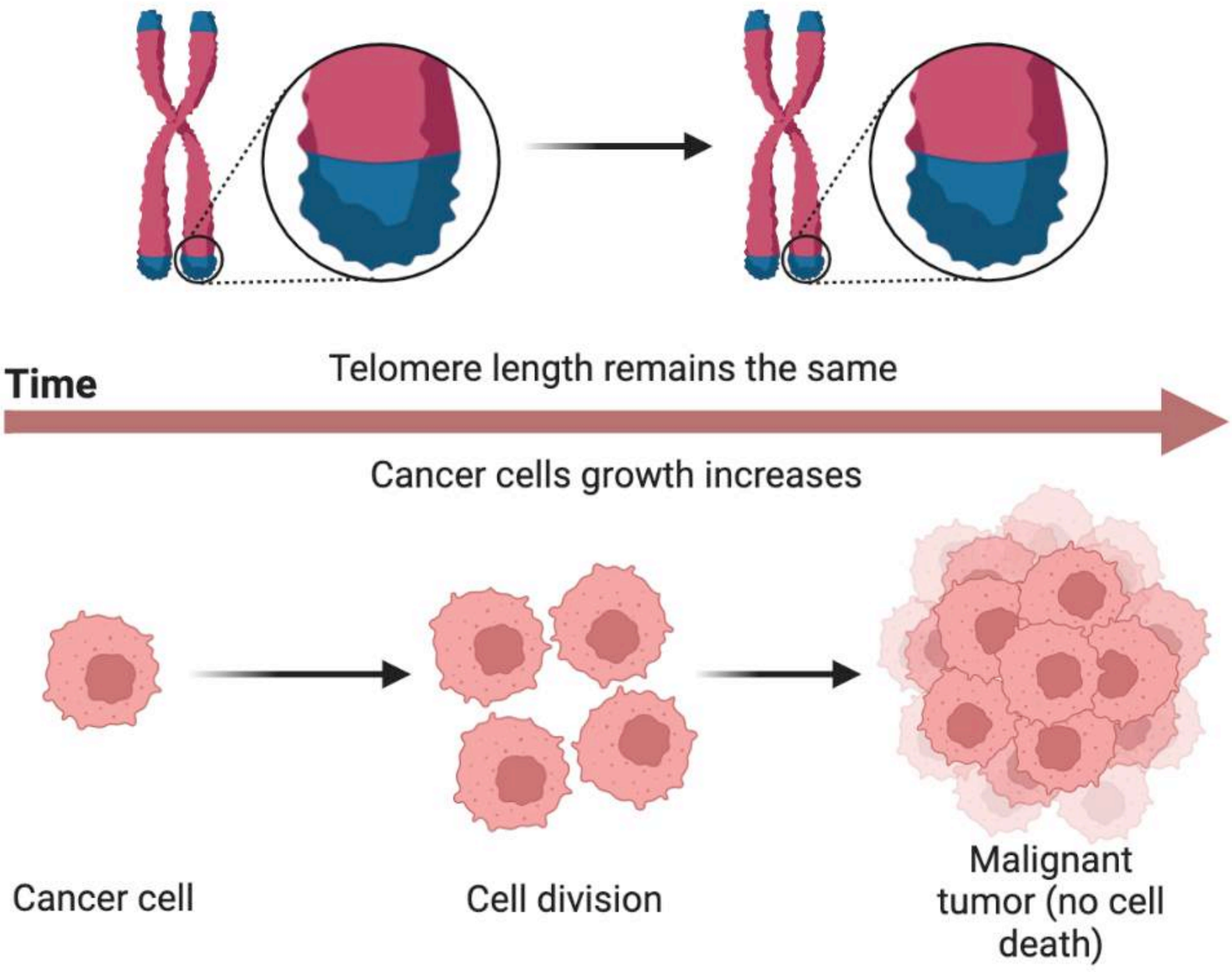
Carol Greider

Elizabeth Blackburn

Jack Szostak

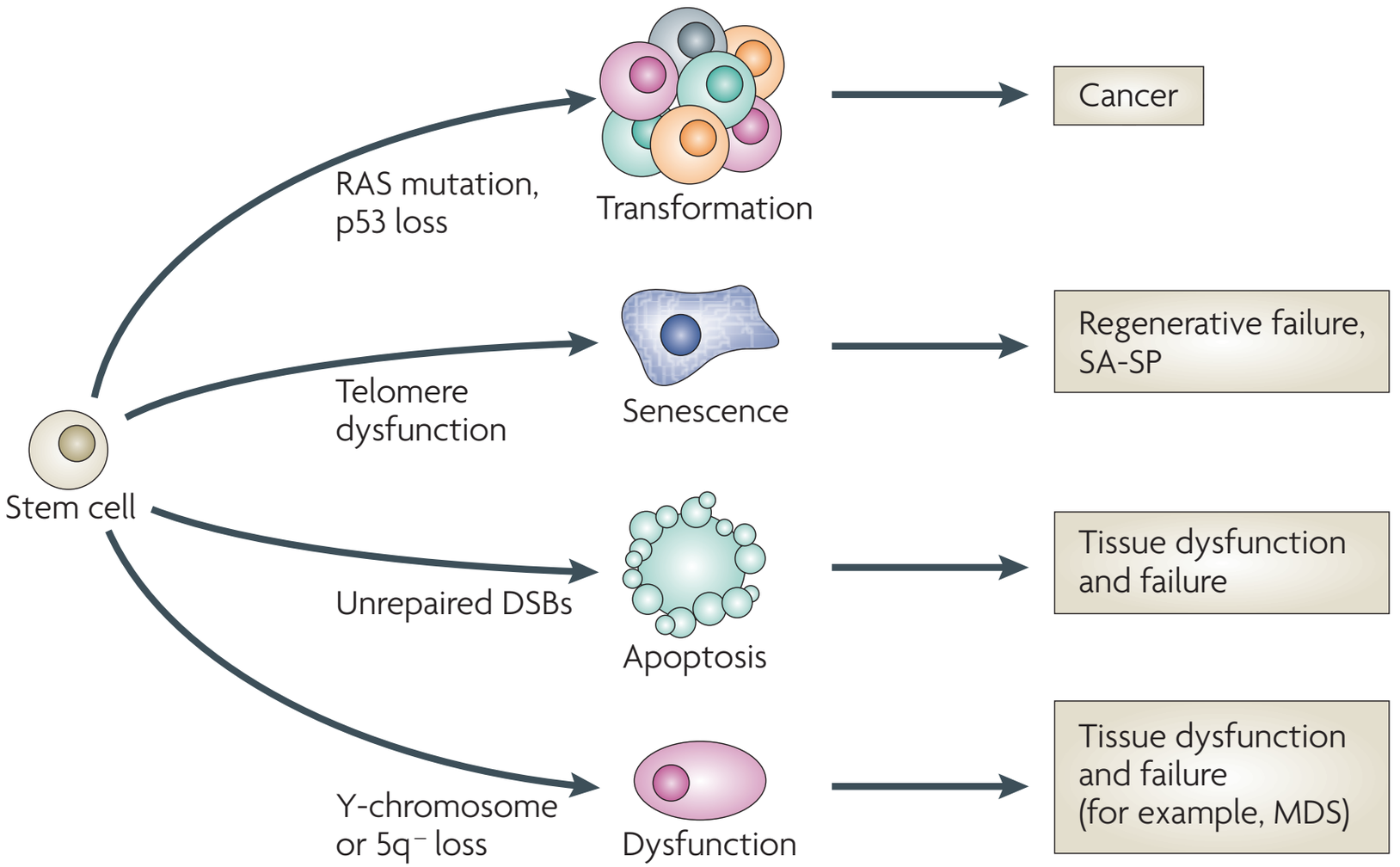
Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

Telomere lengthening = not always good



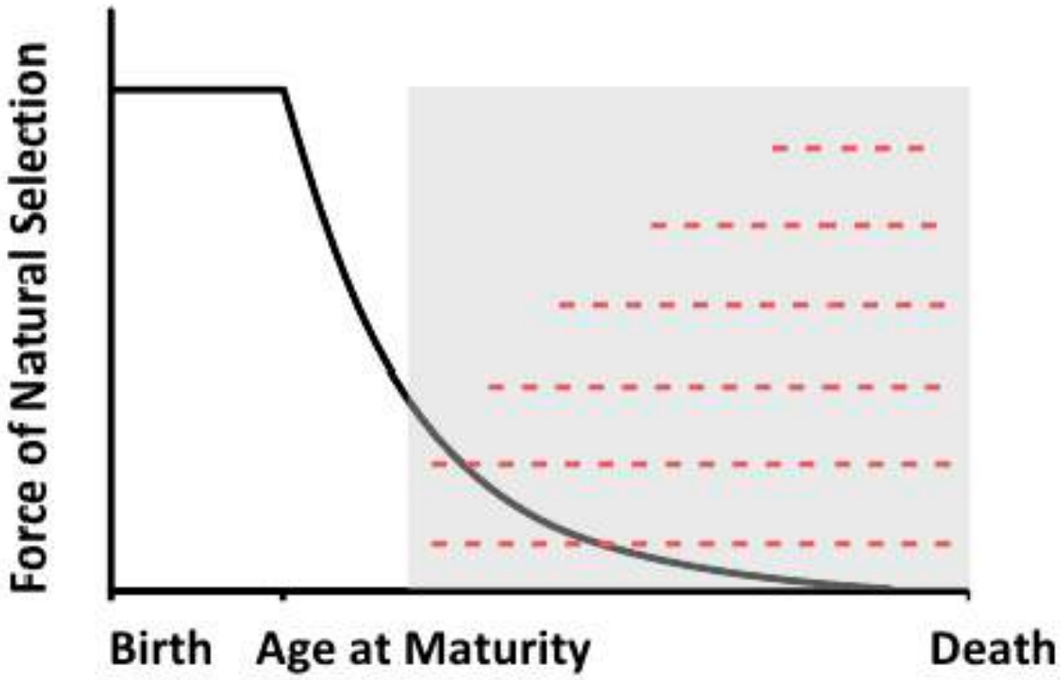
Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

Stem cell damage and dysfunction



Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

Damage accumulation



- DNA damage accumulation throughout life causes aging (wear and tear?)
- again, this is “invisible” to natural selection
- aging evolves because selection cannot eliminate “bad” mutations that only occur late in life

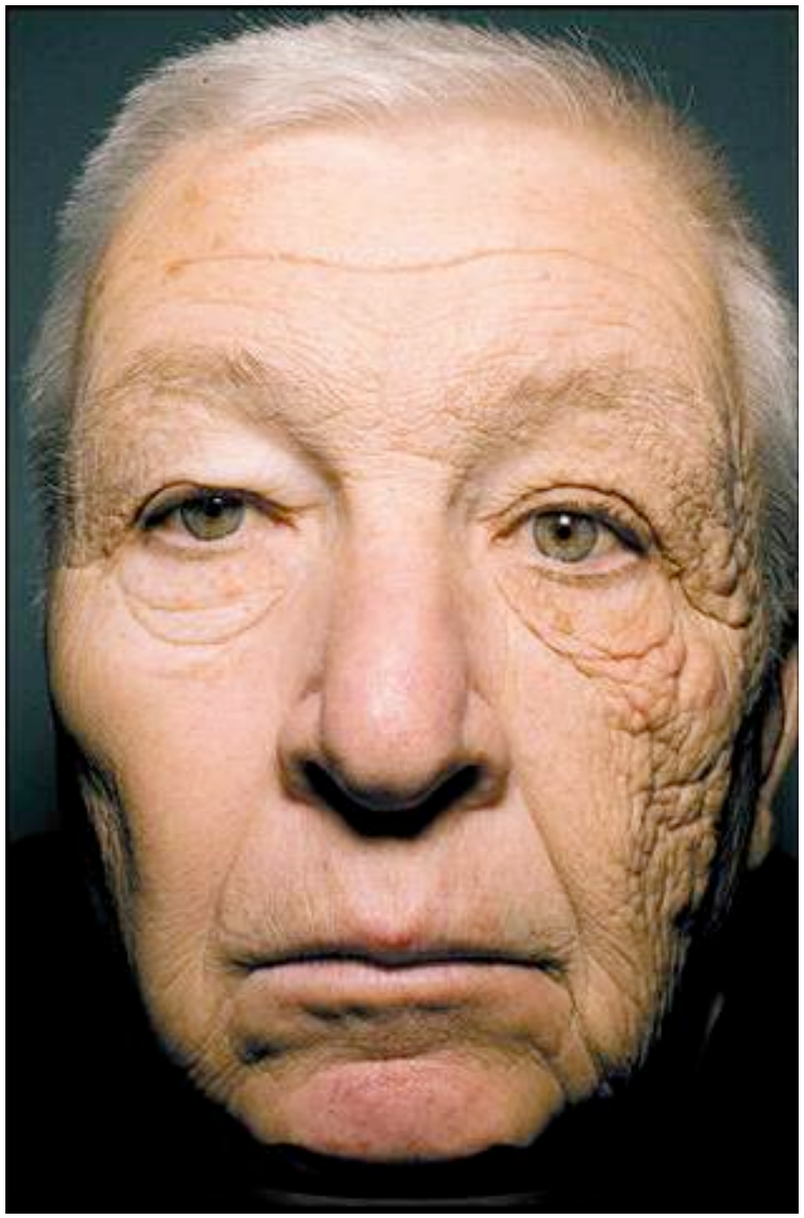
Damage accumulation

- non-smoker
- <10 drinks per week
- ~5 h sun exposure per week

- smoker
- ~20 drinks per week
- ~30 h sun exposure per week (job outside)

Bahman, G. et al., *Plastic and Recon. Surg.*, **2009,** *123*, 1321-1331

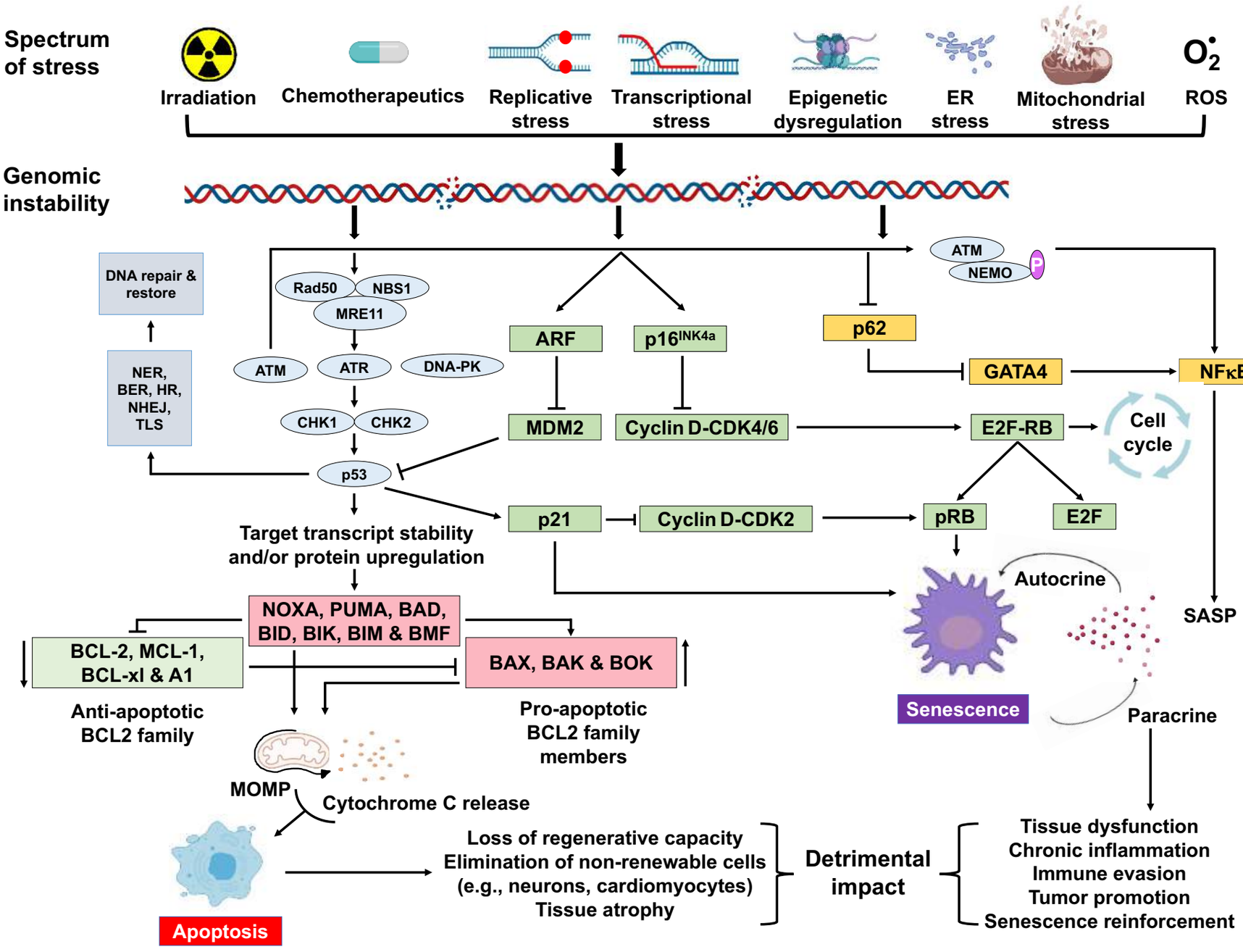
Damage accumulation



"truck driver facial syndrome"

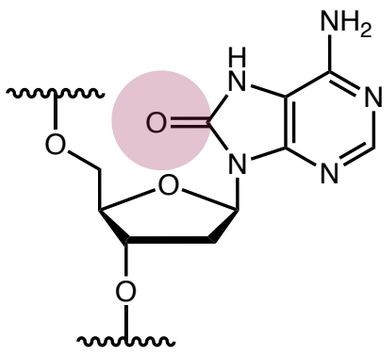
Bahman, G. et al., *Plastic and Recon. Surg.*, **2009,** *123*, 1321-1331

Damage accumulation

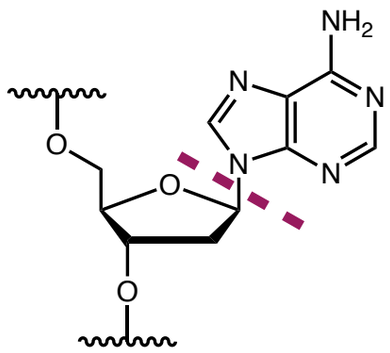


Yousefzadeh, M. et al., *Elife*, **2021,** e62852

Damage accumulation



oxidation



depurination

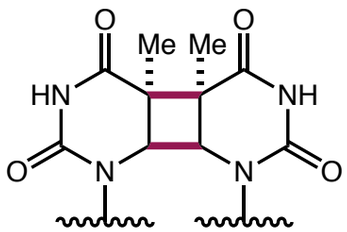
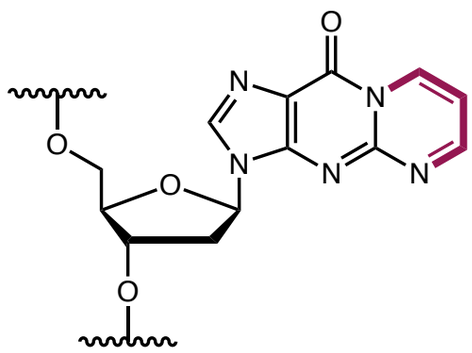
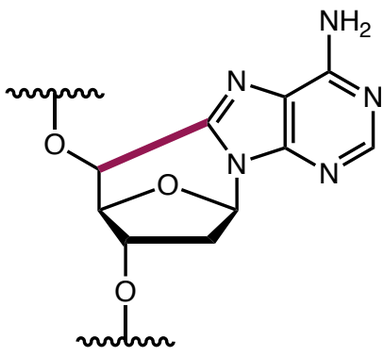


photo-dimerization



alkylation



cyclopurination

Endogenous DNA adducts

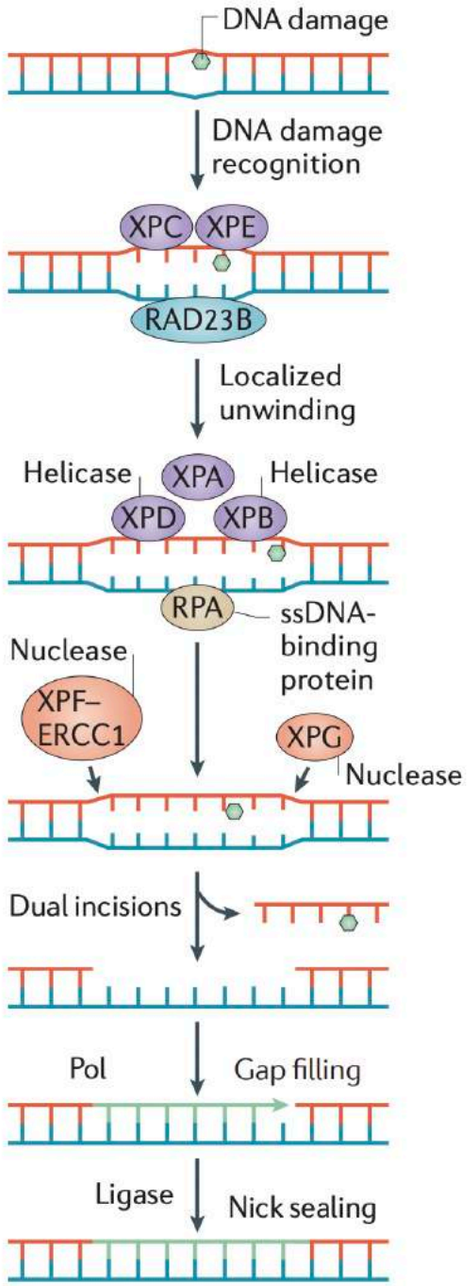
DNA lesion	DSB	Cytosine deamination	Cyclopurine adducts	Depyrimidination	8-oxoG	Malondialdehyde adducts	Alkylation adducts	Depurination	SSB
Frequency per cell per day	10^1	10^2	10^2	10^2	10^3	10^3	10^3	10^4	10^4

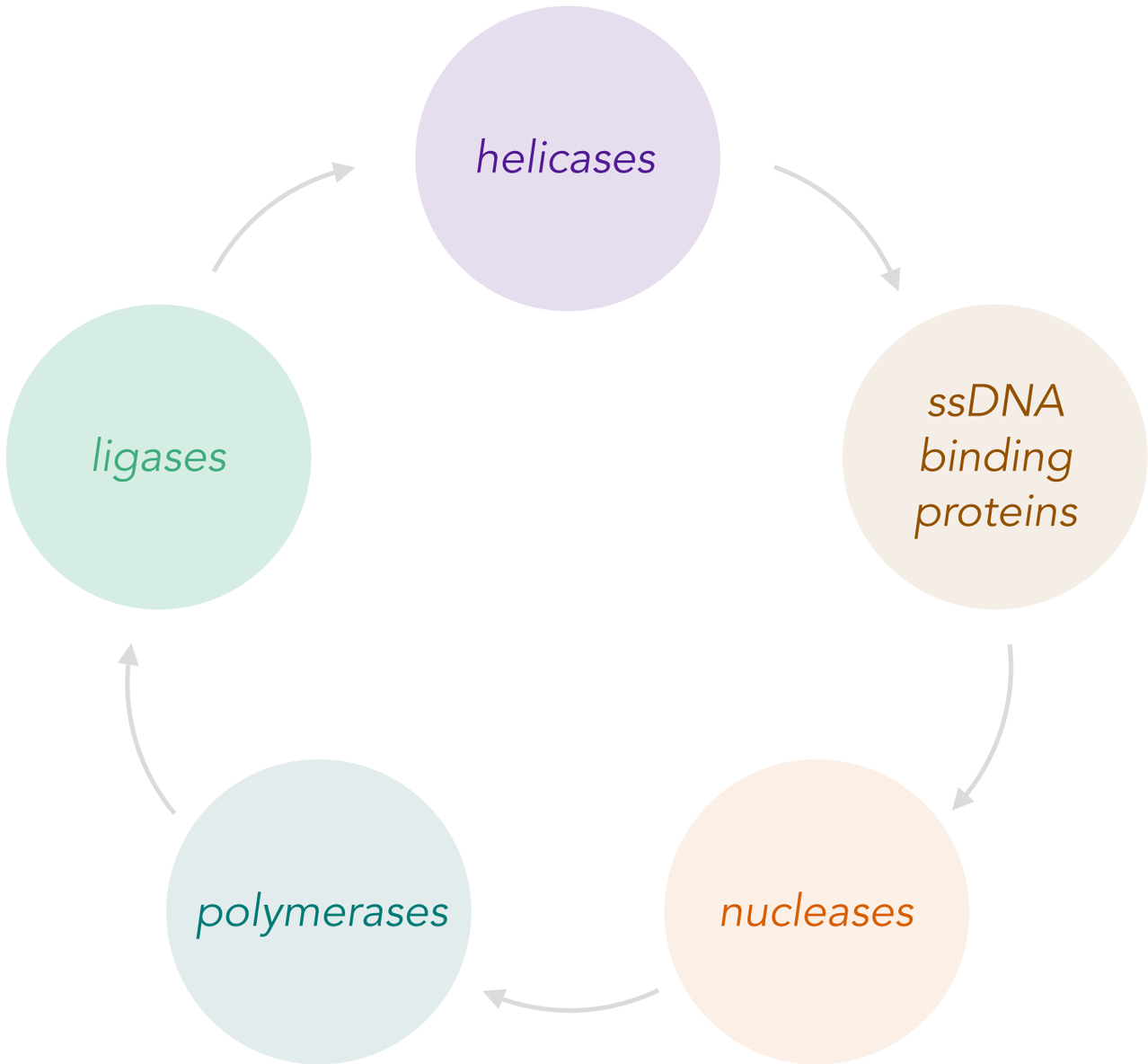
DNA adducts caused by environmental exposures

Genotoxin	Sunlight	Background radiation			Ionizing radiation therapy		Oxaliplatin cancer therapy
Lesion	Photodimers	Damaged bases	SSB	DSB	Damaged bases	SSB	Intra- and interstrand crosslinks
Frequency per cell per day	10^2 in skin cells only	10	2–5	0.25	10^3	10^3	10^3

Yousefzadeh, M. et al., *Elife*, **2021,** e62852

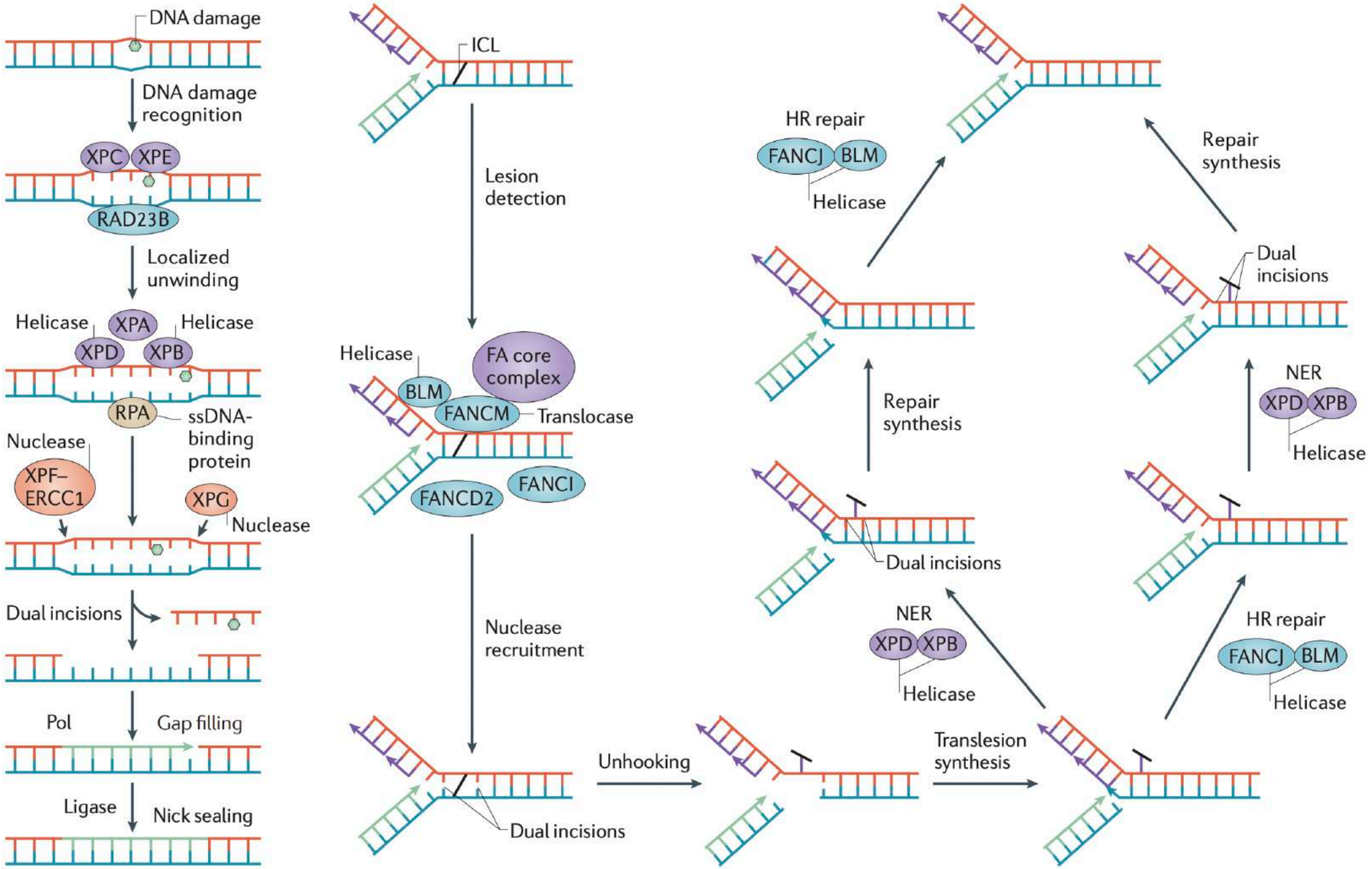
Unrepaired DNA damage accelerates aging





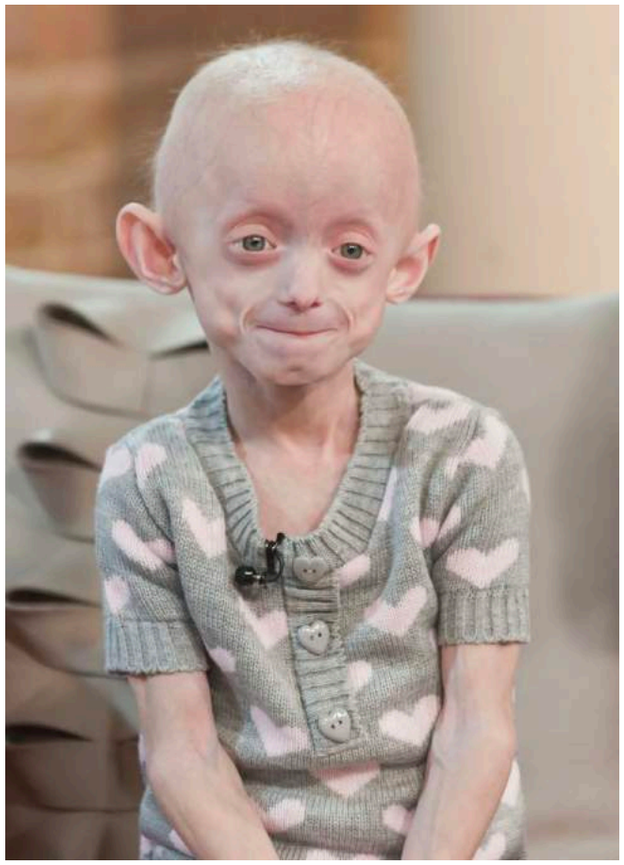
Brosh. R. M. et al., *Nat. Rev. Cancer*, **2013**, *13*, 542-558

Unrepaired DNA damage accelerates aging



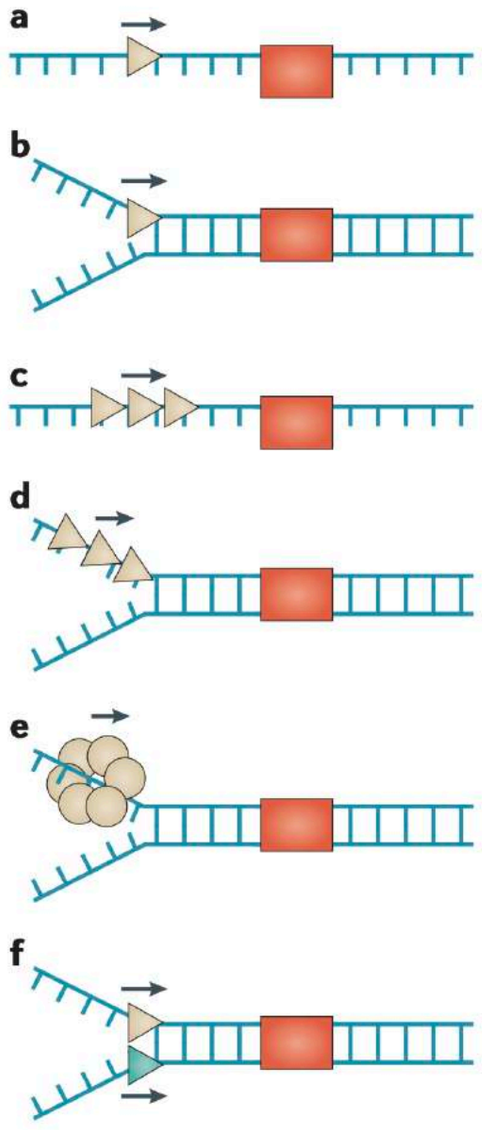
Brosh. R. M. et al., *Nat. Rev. Cancer*, **2013**, *13*, 542-558

Helicases are critical for damage repair



Werner Syndrome

defective RecQ helicase



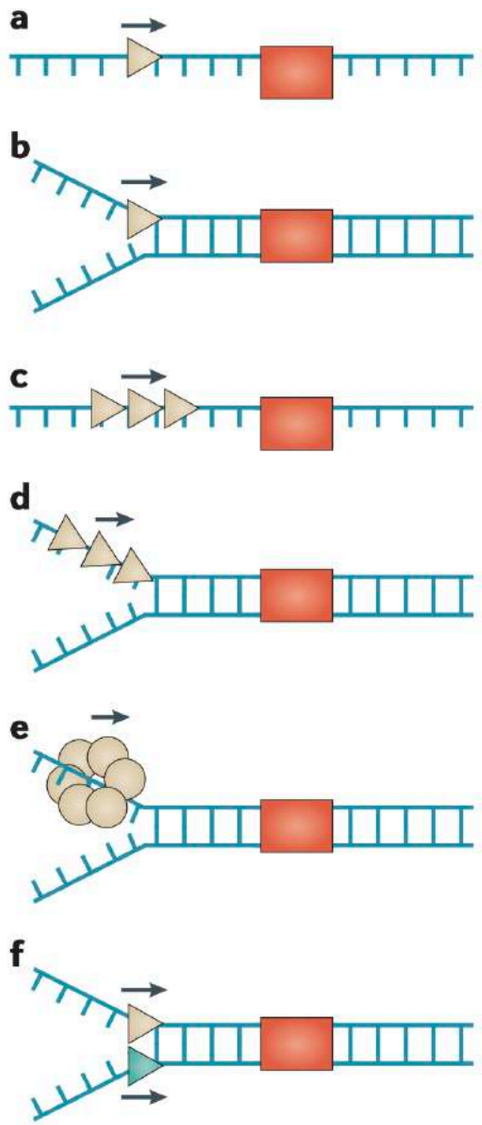
key helicase modes of action

Brosh. R. M. et al., *Nat. Rev. Cancer*, **2013**, *13*, 542-558

Helicases are critical for damage repair

wildtype mouse
(2 mo old)

XPR helicase double KO
(2 mo old)

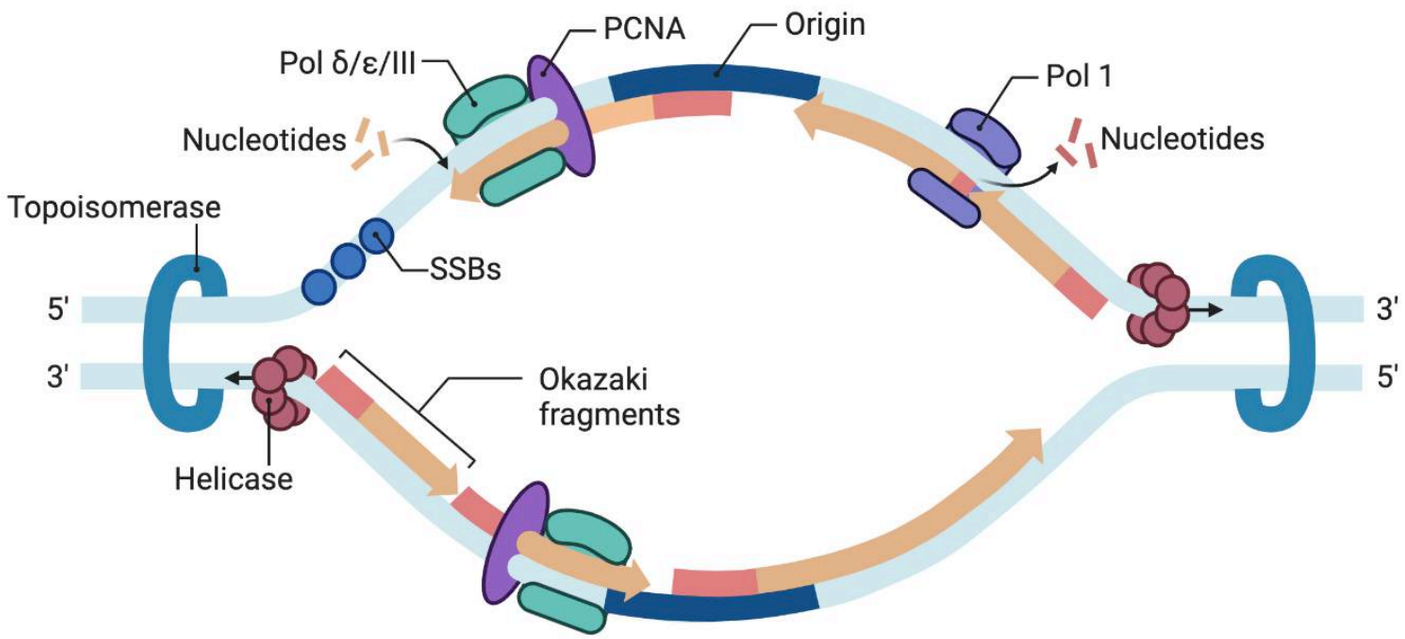


key helicase modes of action

De Boer, J. et al., *Science*, **2002**, *296*(5571), 1276-1279

Mutational damage alone does not cause aging

Michael Stratton



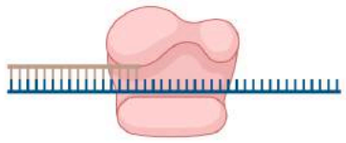
Robinson et al., *Nat. Genetics*, **2021,** *53*, 1434-1442

Mutational damage alone does not cause aging

Michael Stratton

normal polymerase

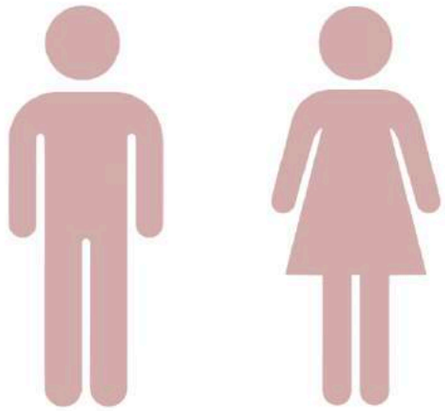
normal amount of mutations



mutant polymerase

abnormally more mutations

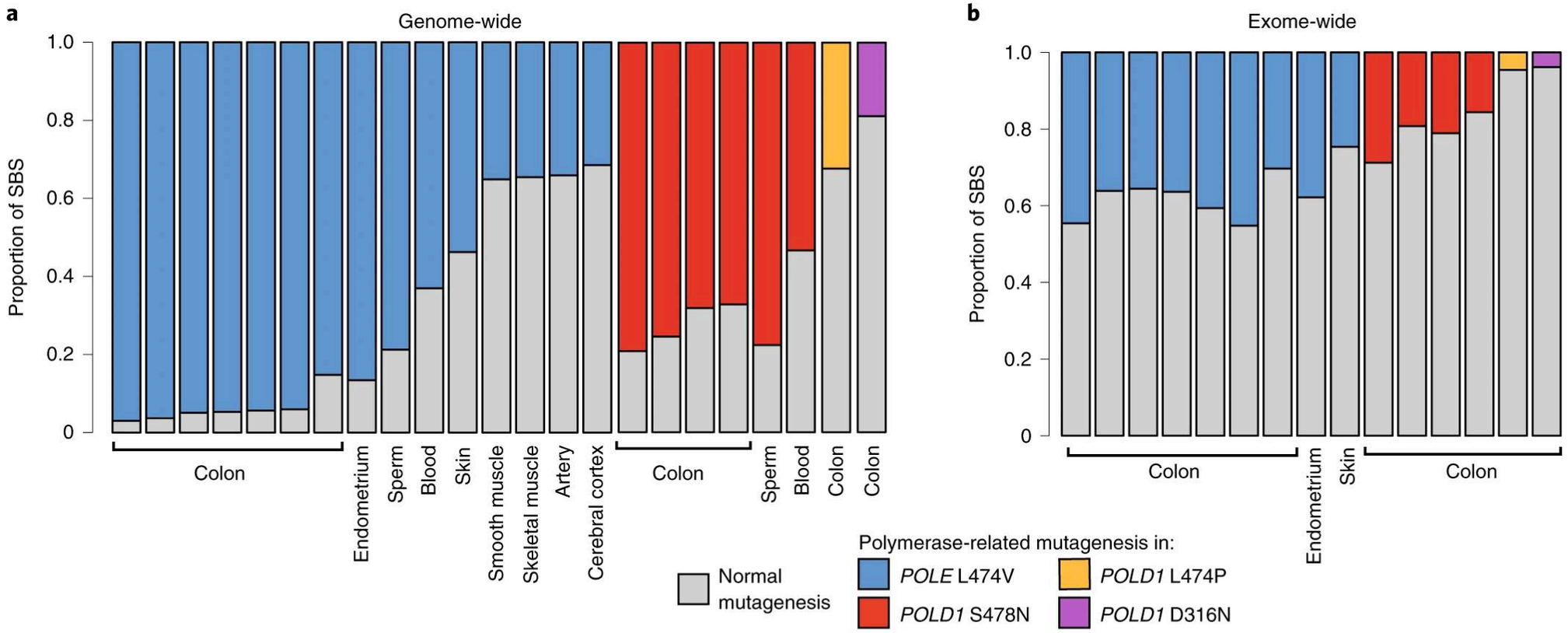
individuals with
normal polymerase



individuals with
mutant polymerase

Robinson et al., *Nat. Genetics*, **2021,** *53*, 1434-1442

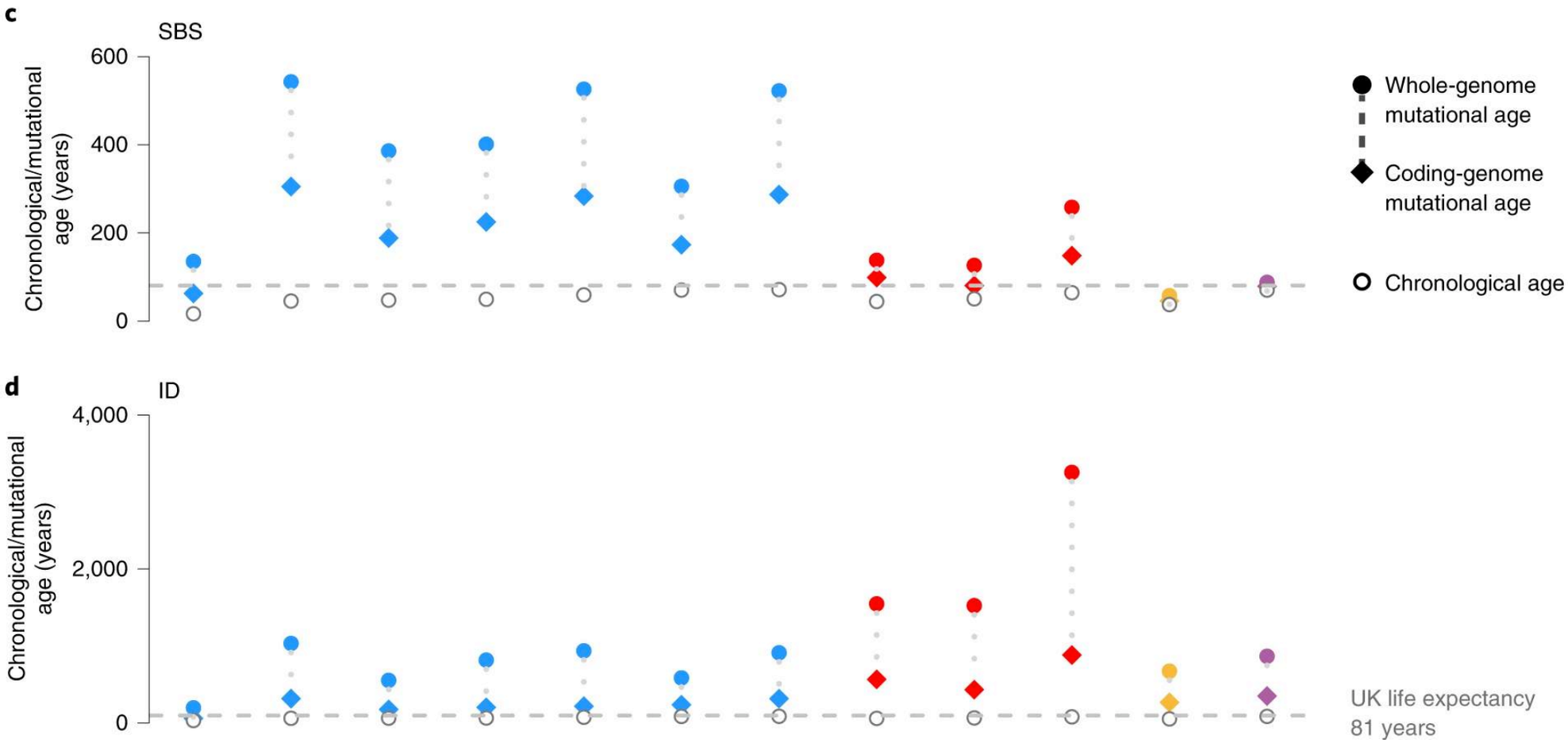
Mutational damage alone does not cause aging



individuals with mutant polymerase aquire massive amounts of mutations throughout lifetime

Robinson et al., *Nat. Genetics*, **2021,** *53*, 1434-1442

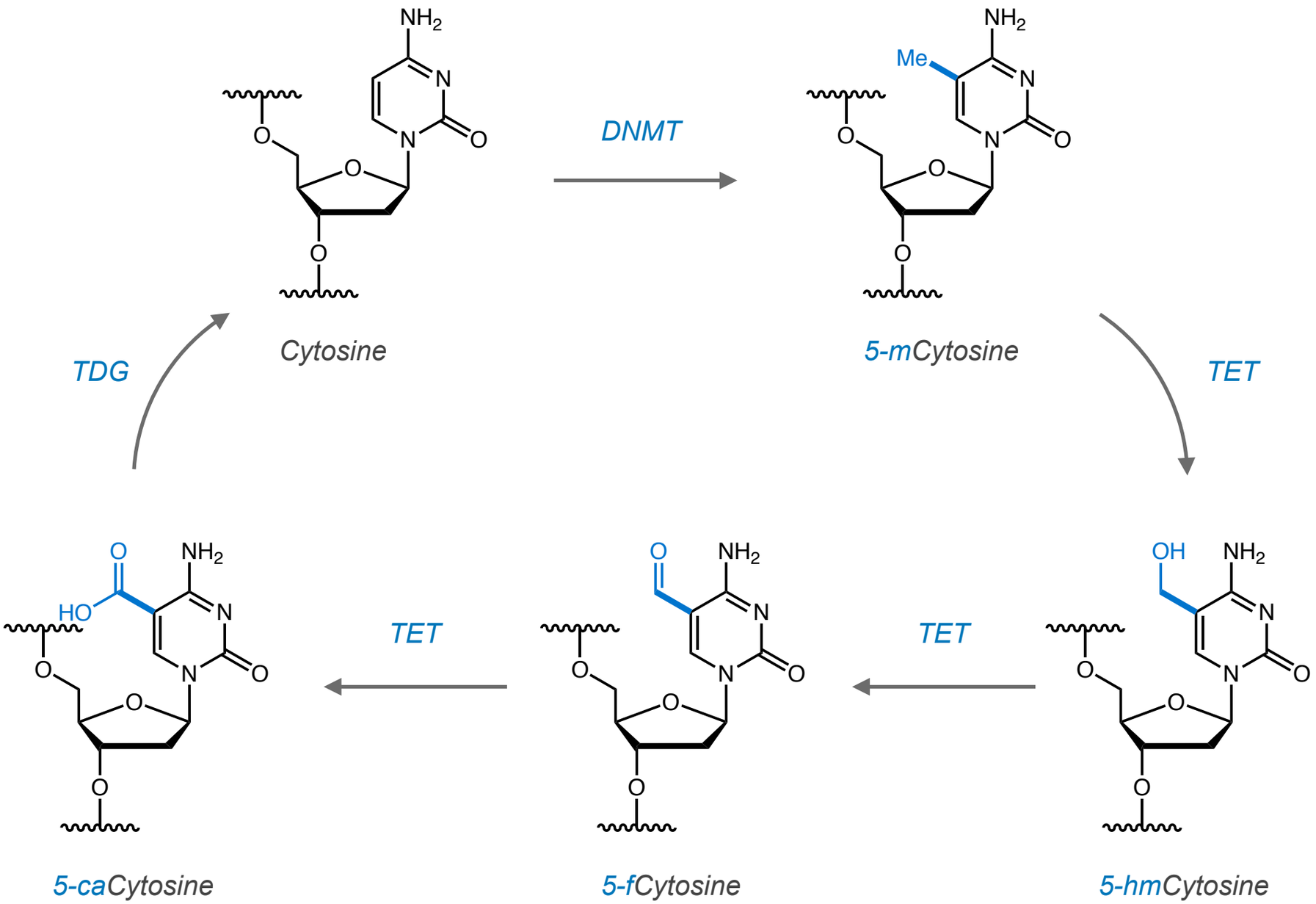
Mutational damage alone does not cause aging



almost no correlation between mutational rate and lifespan and overall aging phenotype

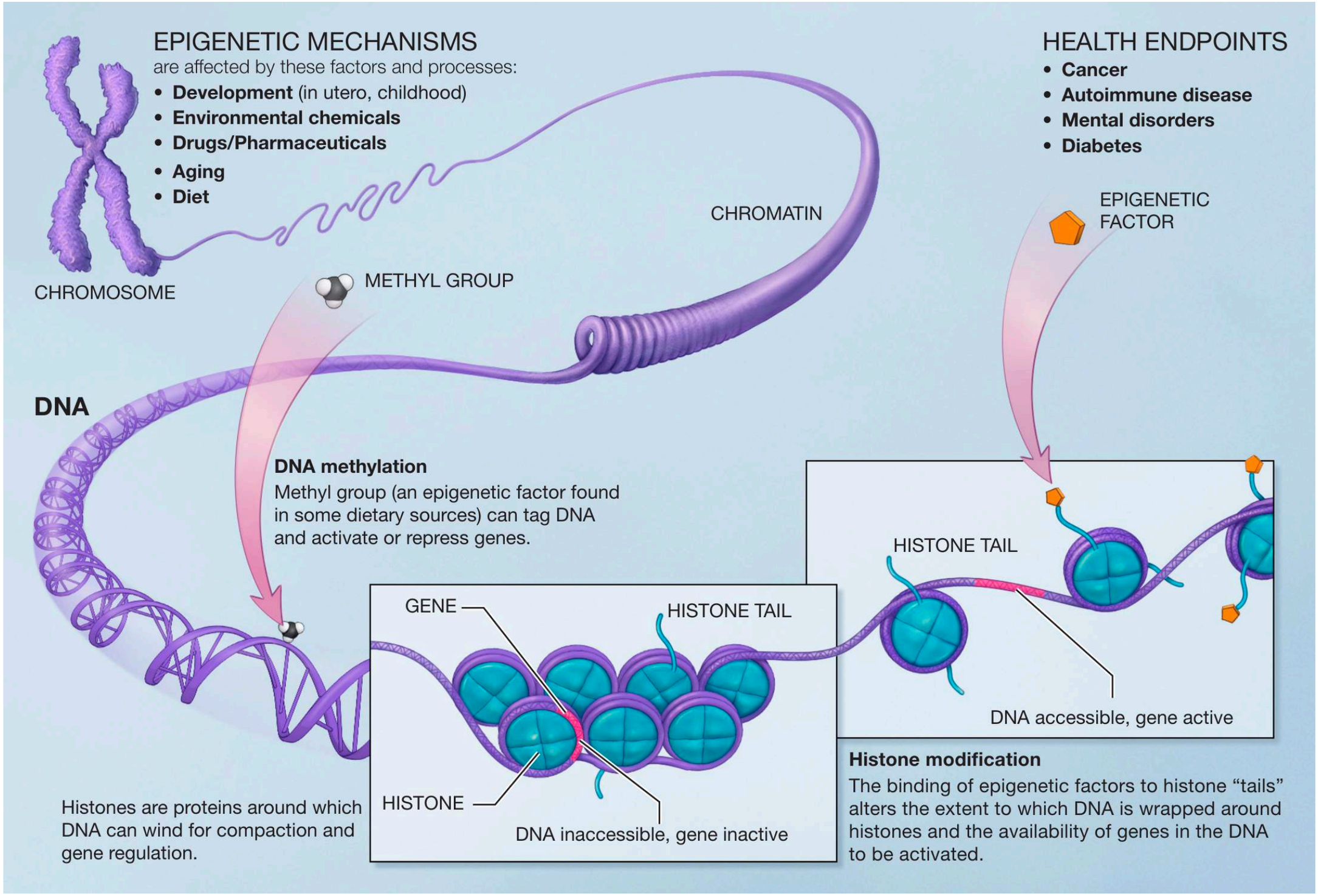
Robinson et al., *Nat. Genetics*, **2021,** *53*, 1434-1442

Epigenetic dysregulation



Cavalli et al., *Nature*, **2019,** *571*, 489-499

Epigenetic dysregulation

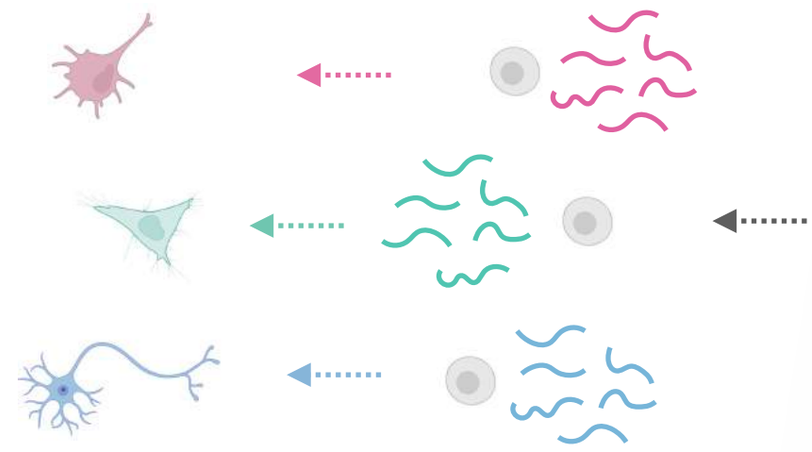


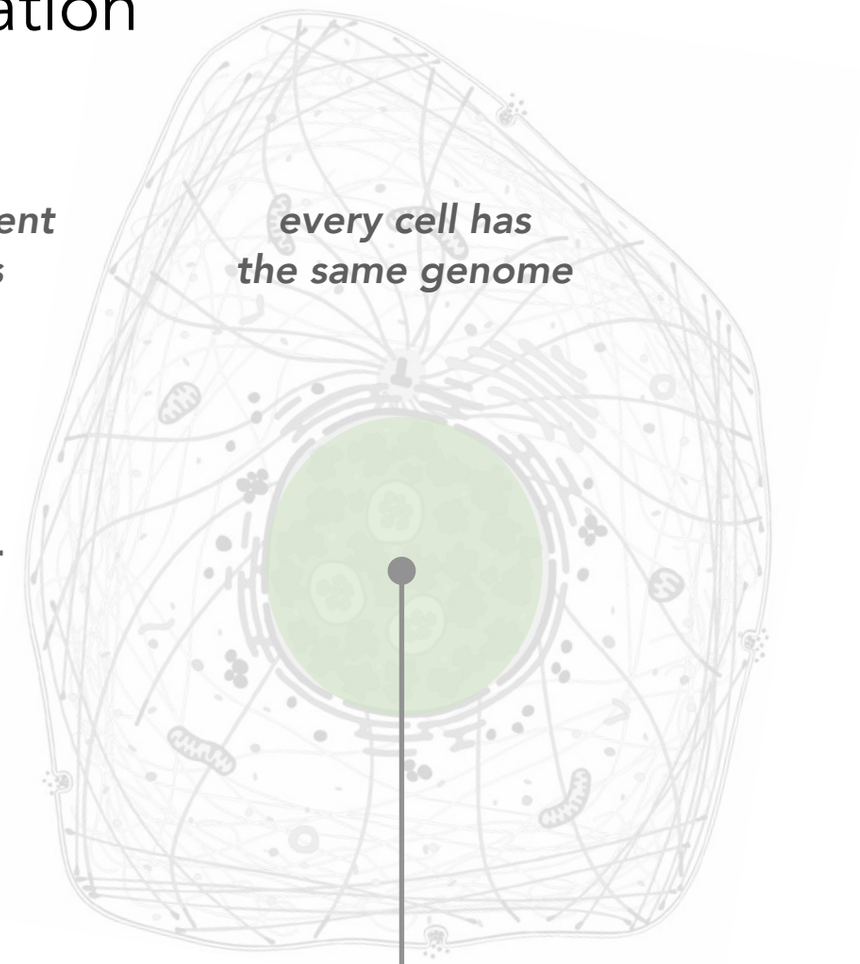
Cavalli et al., *Nature*, **2019,** *571*, 489-499

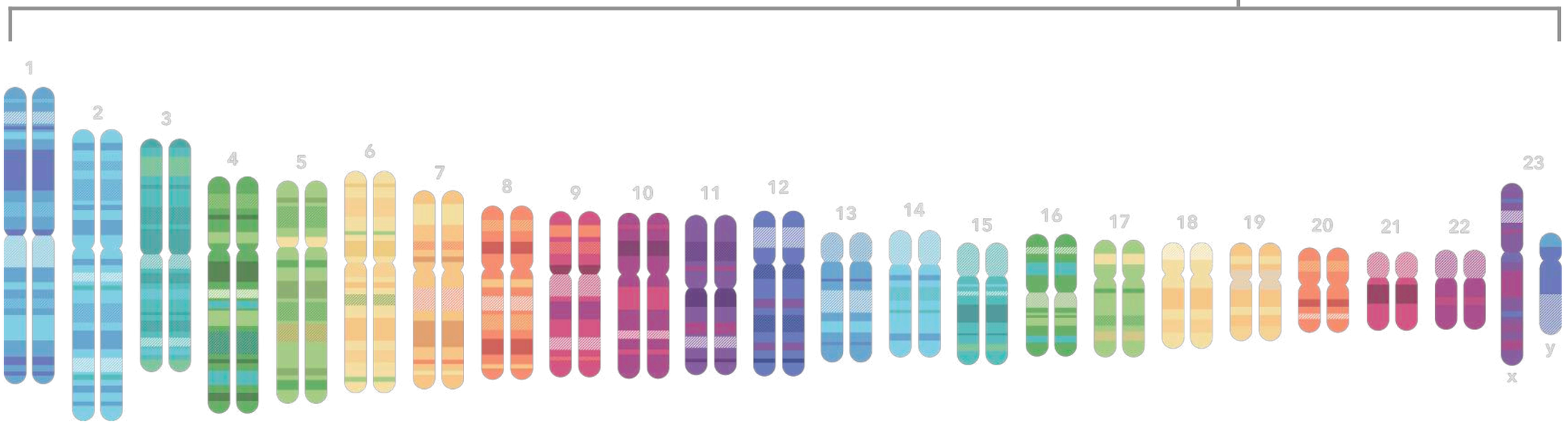
Epigenetic dysregulation

different cell types run different gene expression programs

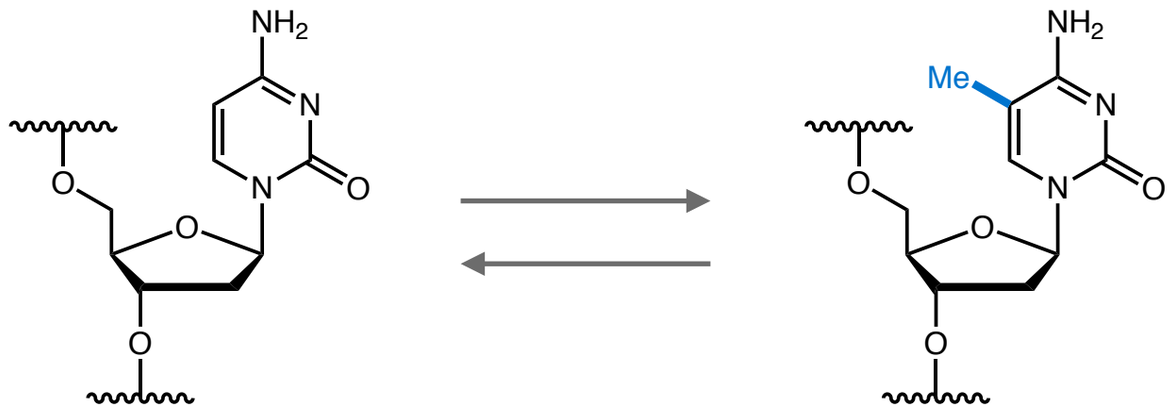
every cell has the same genome



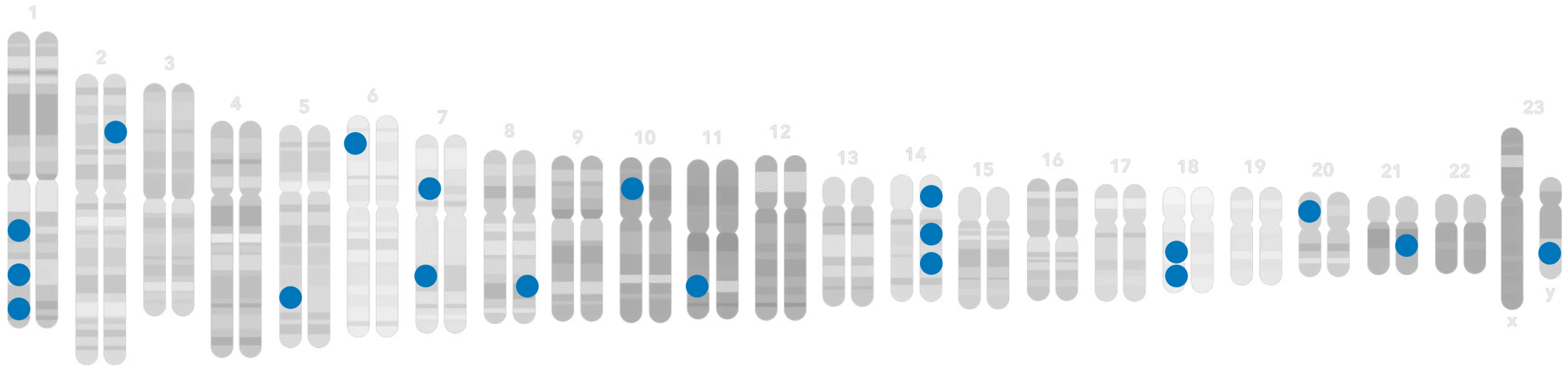




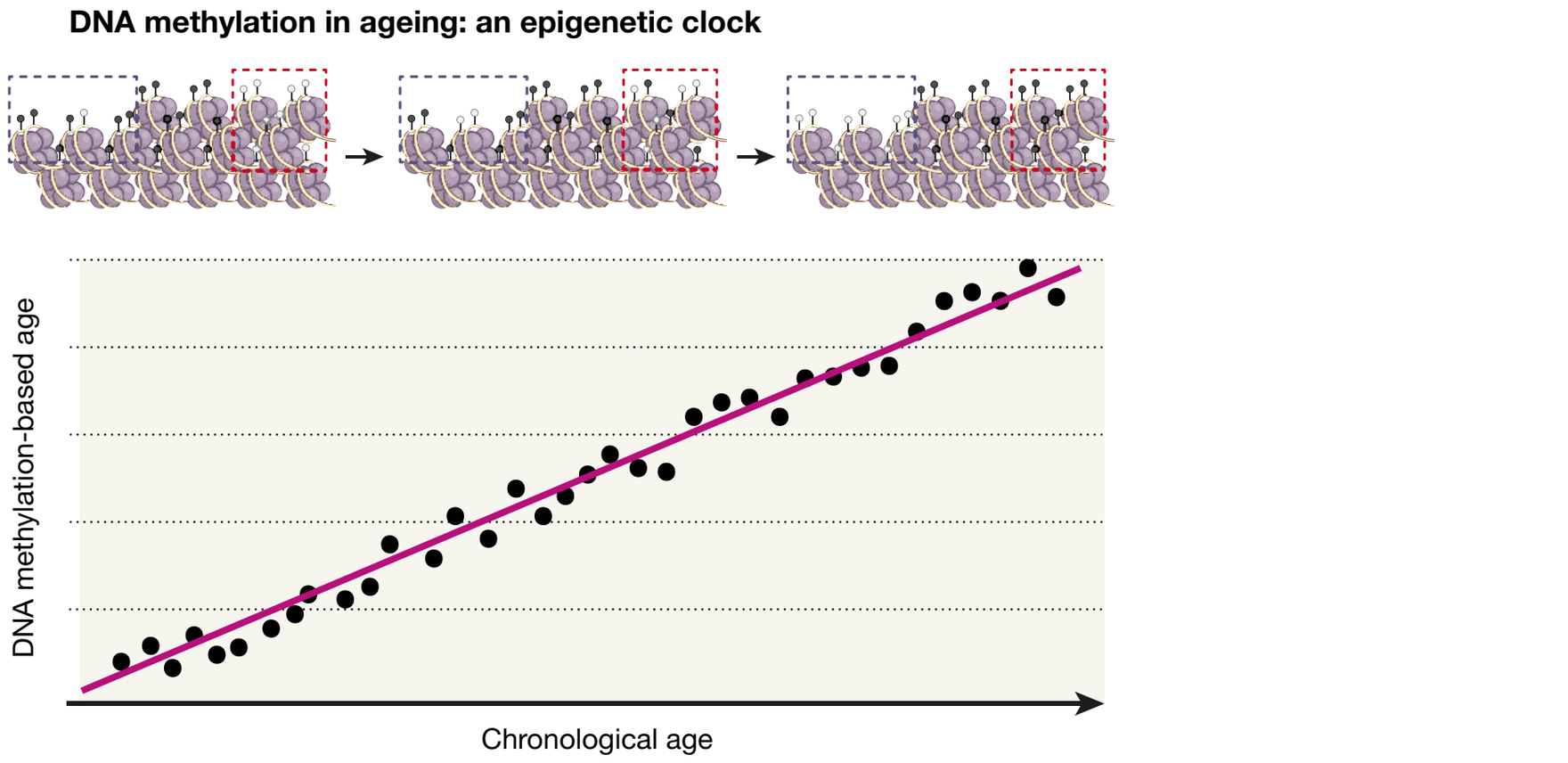
Epigenetic dysregulation

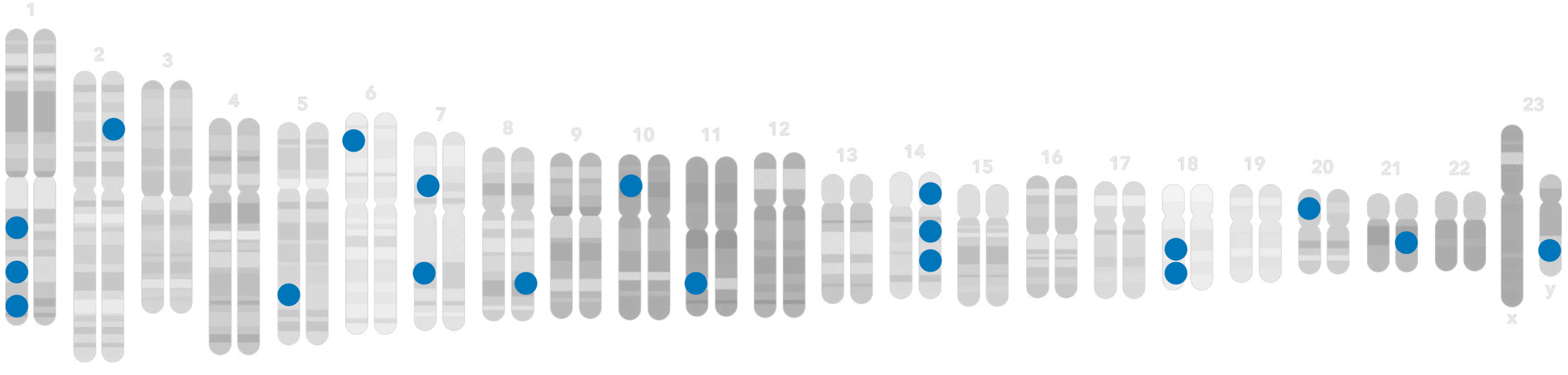


Cytosine *5-mCytosine*



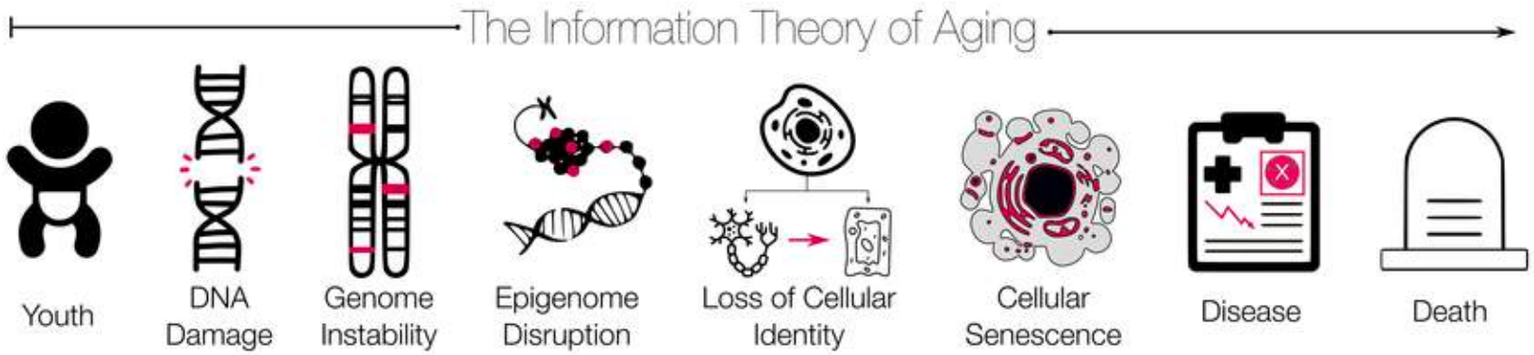
Epigenetic dysregulation





Cavalli et al., *Nature*, **2019,** *571*, 489-499

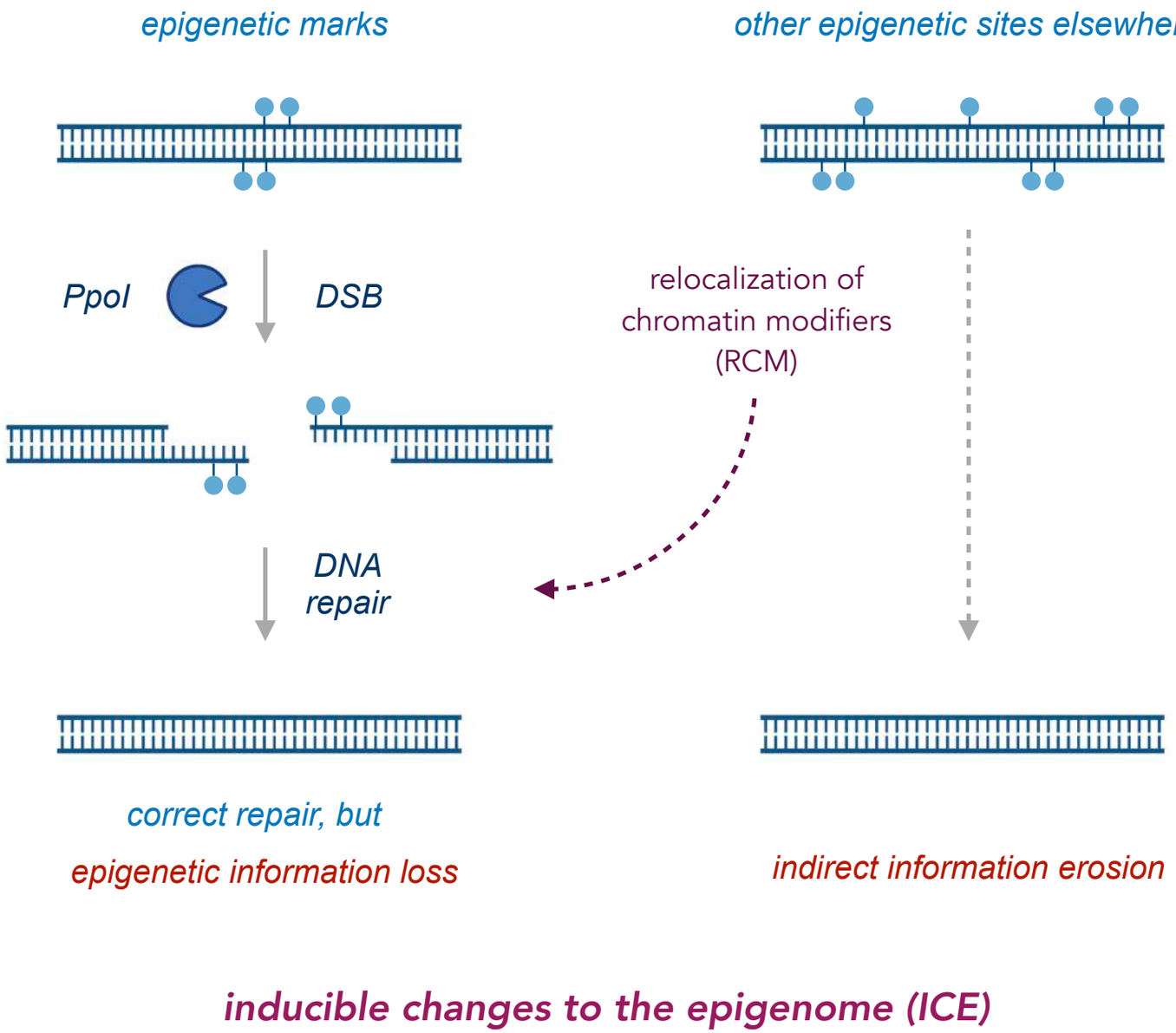
Epigenetic damage and information loss



David Sinclair

Yang. J. et al., *Cell*, **2023,** *186*, 305-326

Epigenetic damage and information loss



David Sinclair

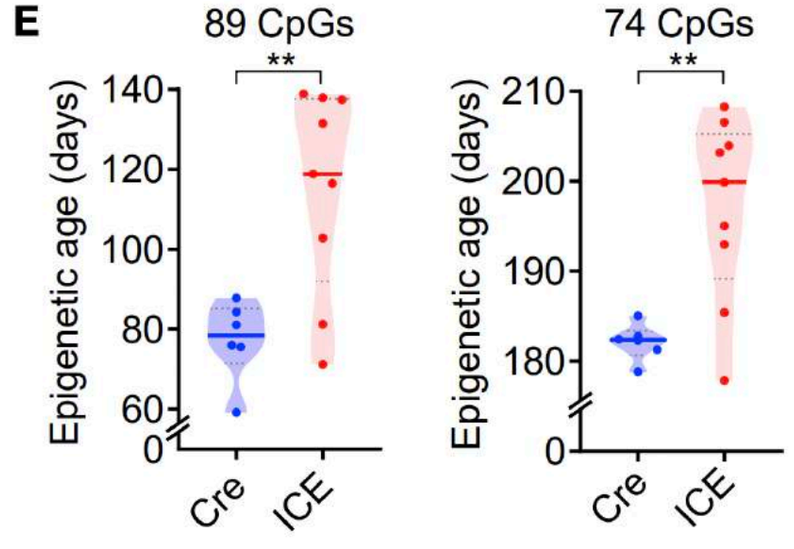
inducible changes to the epigenome (ICE)

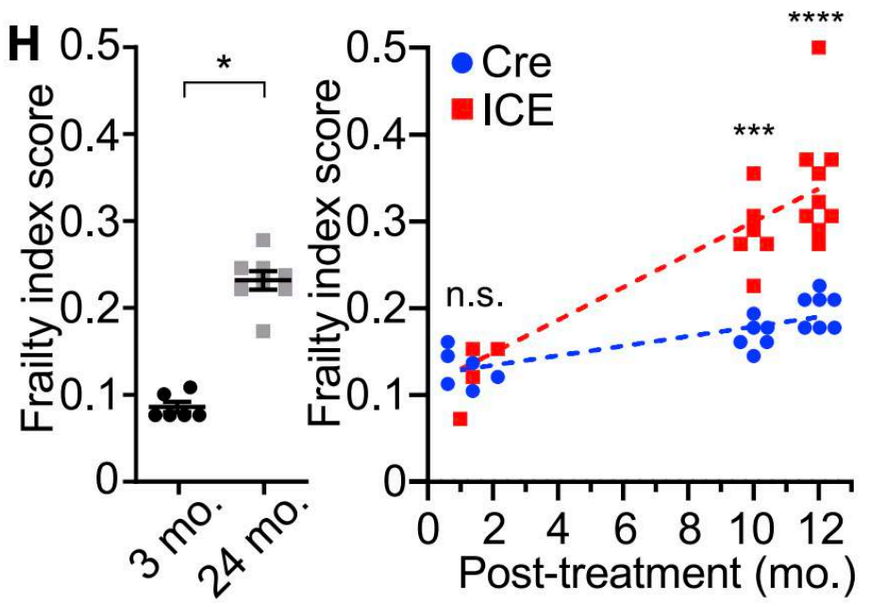
Yang. J. et al., *Cell*, **2023,** *186*, 305-326

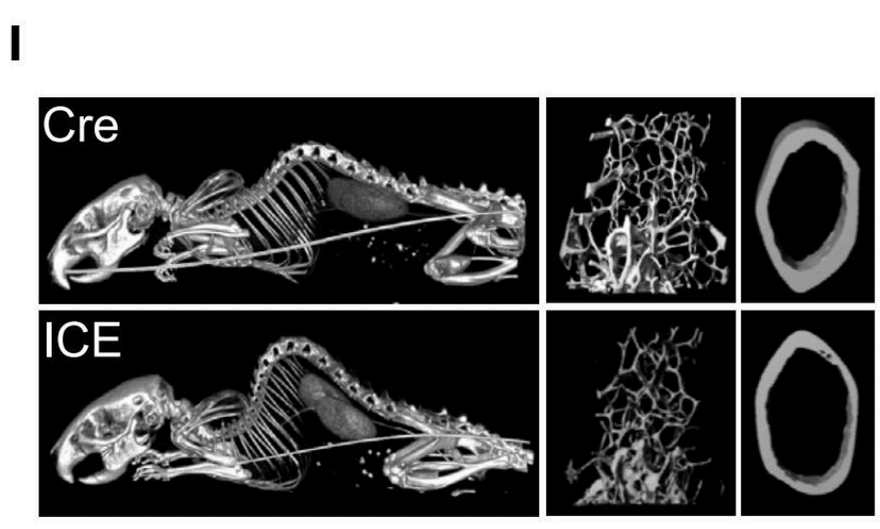
Epigenetic damage and information loss

3 mo old

3 mo old

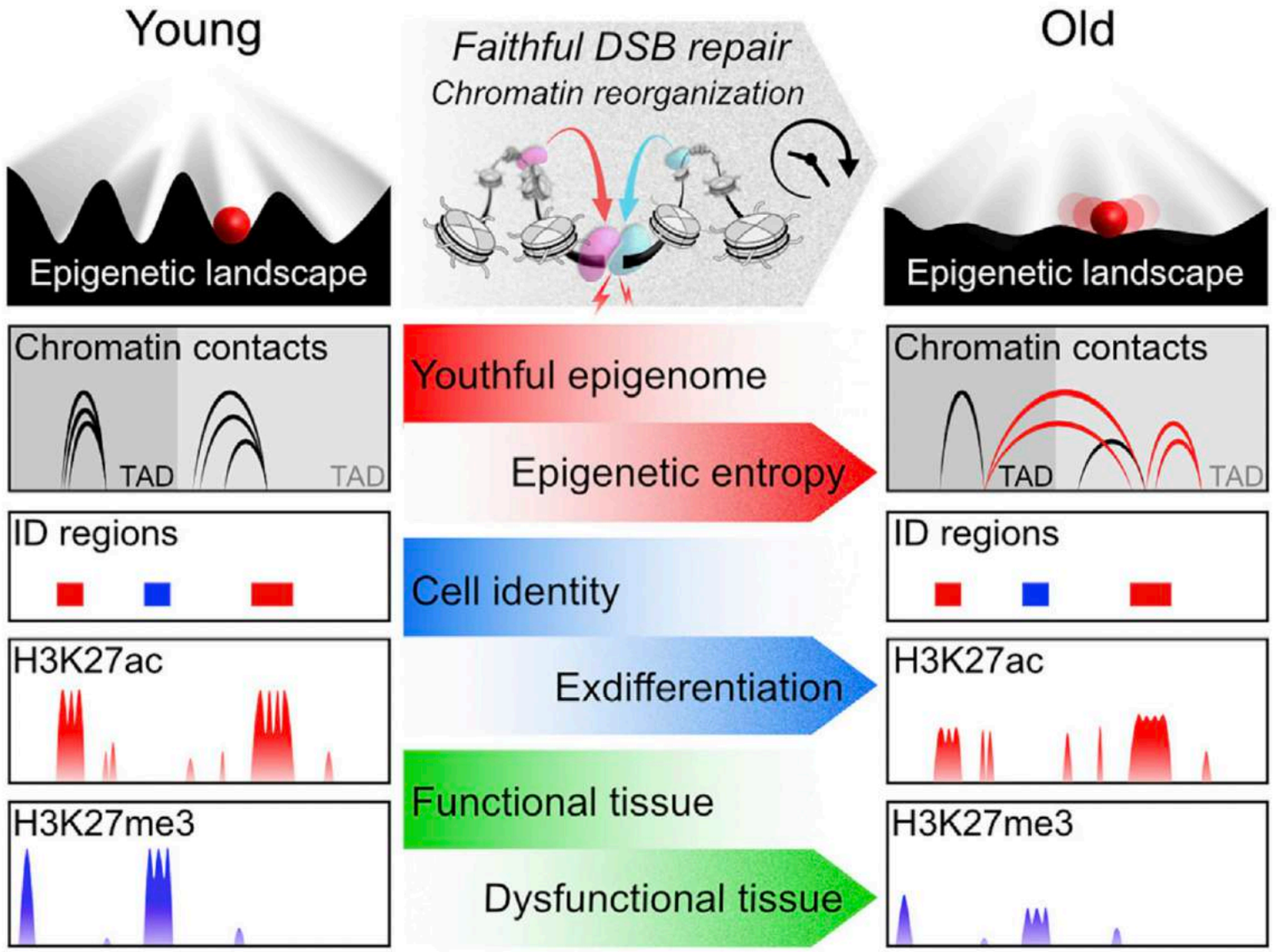






Yang. J. et al., *Cell*, **2023,** *186*, 305-326

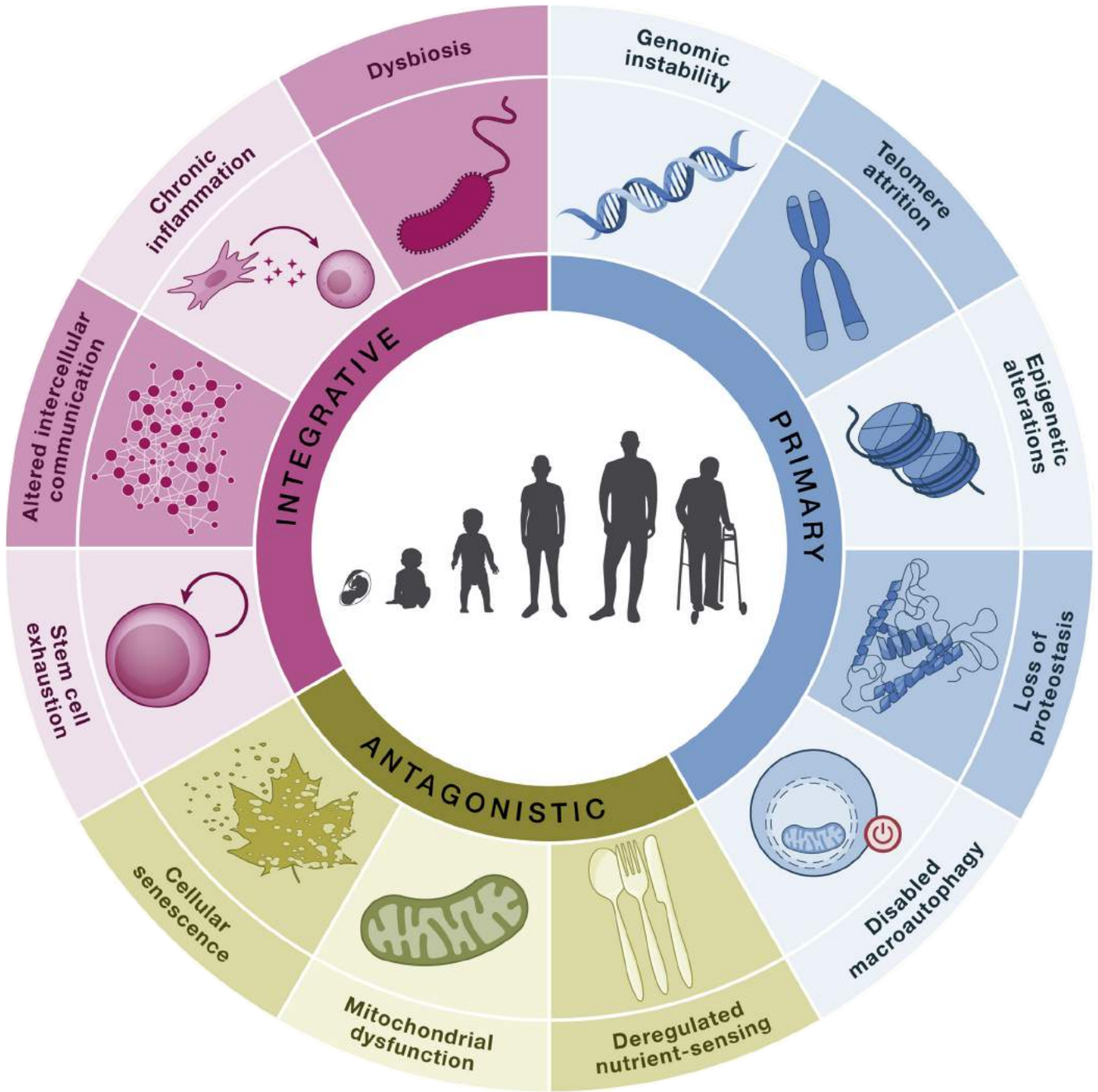
Epigenetic damage and information loss



David Sinclair

Yang. J. et al., *Cell*, **2023,** *186*, 305-326

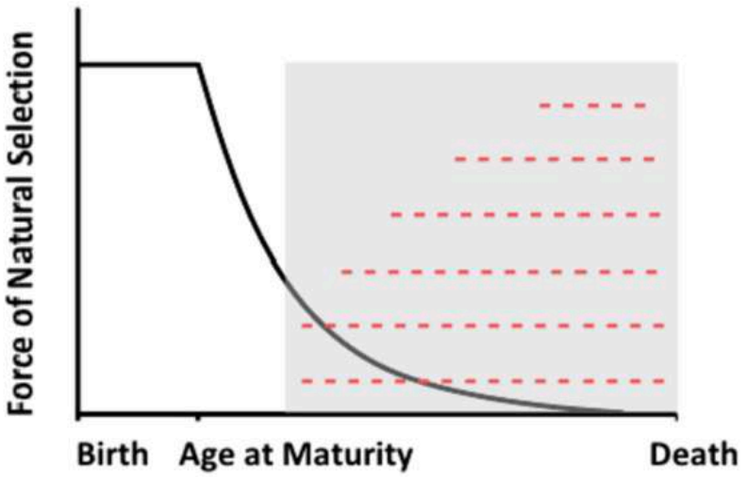
The current best aging model



Lopez, Otin, C. et al., *Cell*, **2023,** in press

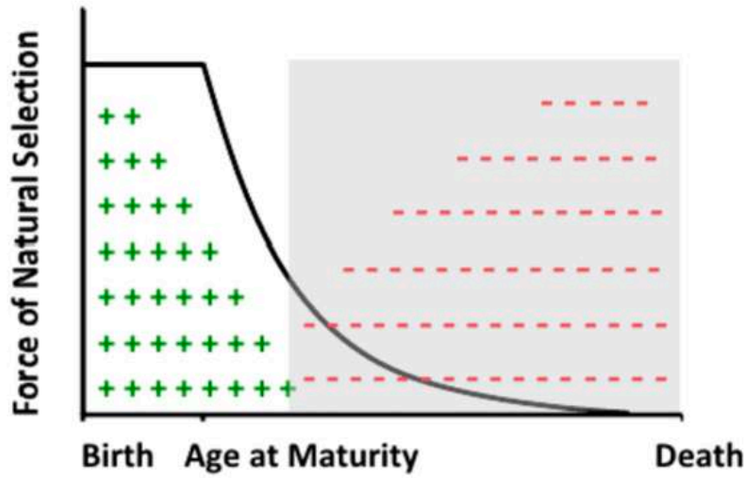
The current best aging model

damage accumulation



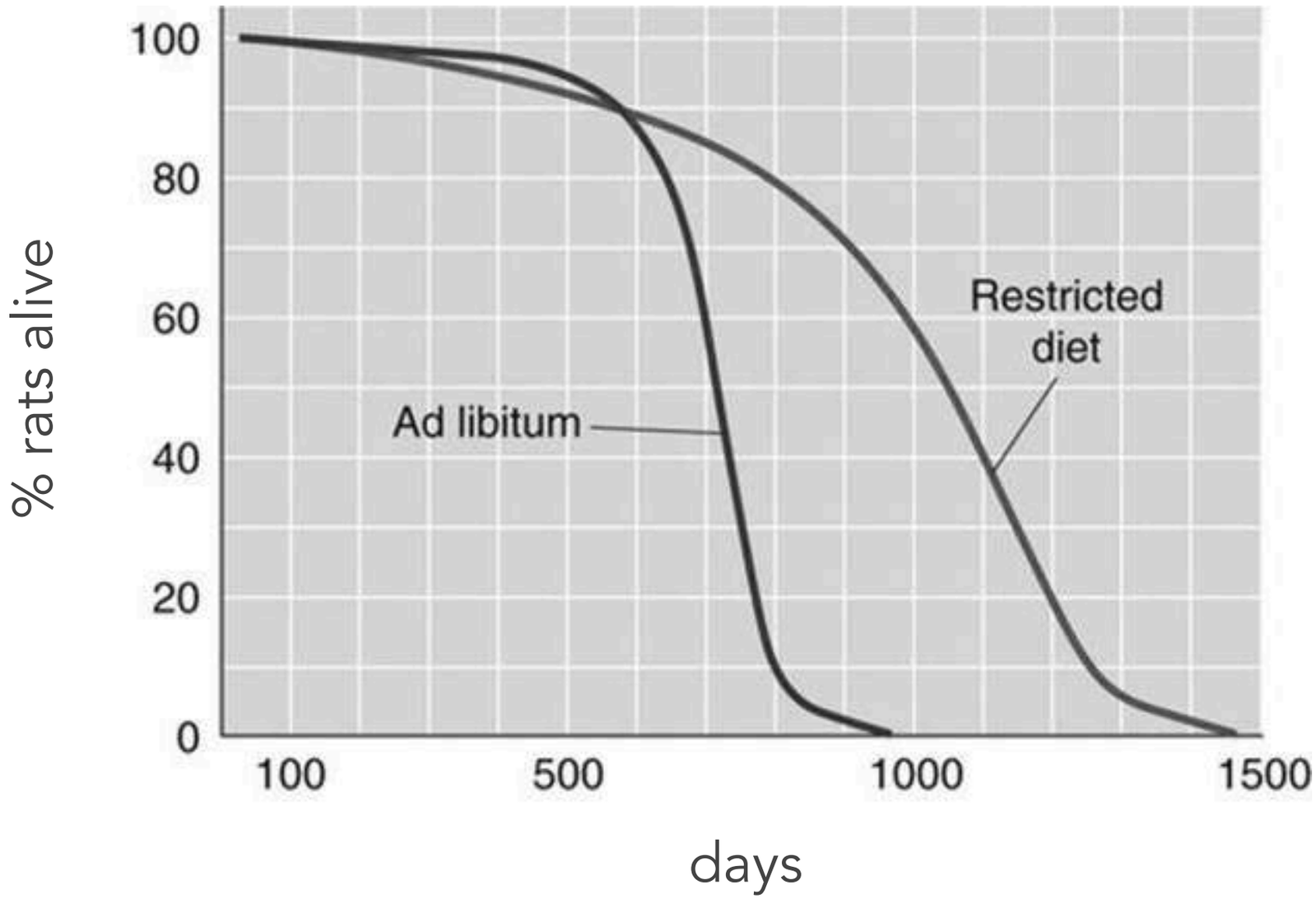
- DNA, organelle, and cell damage throughout life causes aging
- repair mechanisms cannot fully keep up
- **net degeneration of cells/tissue/body**

antagonistic pleiotropy



- genes that beneficial early in life become detrimental later and **cause aging**
- DNA repair good, then bad
- **net degeneration and loss of information**

Caloric restriction works… but **why?**



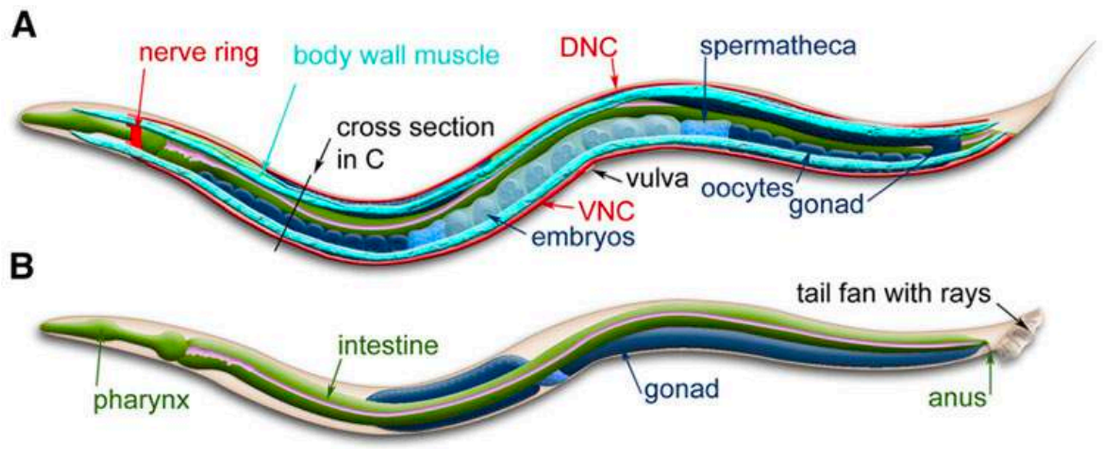
Klass, M. et al., *Nature*, **1976**, *260*(1), 523-525.

Caloric restriction works… but **why?**

Cynthia Kenyon

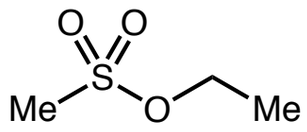
Caenorhabditis elegans (C. elegans)

lifespan ~ 2 weeks

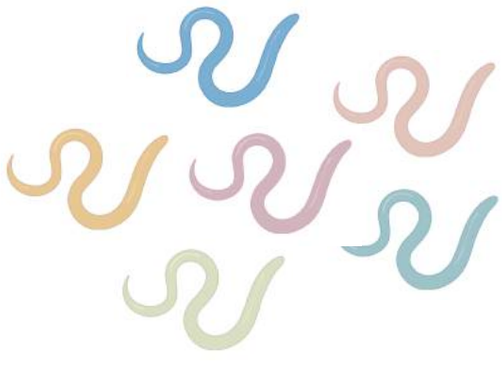


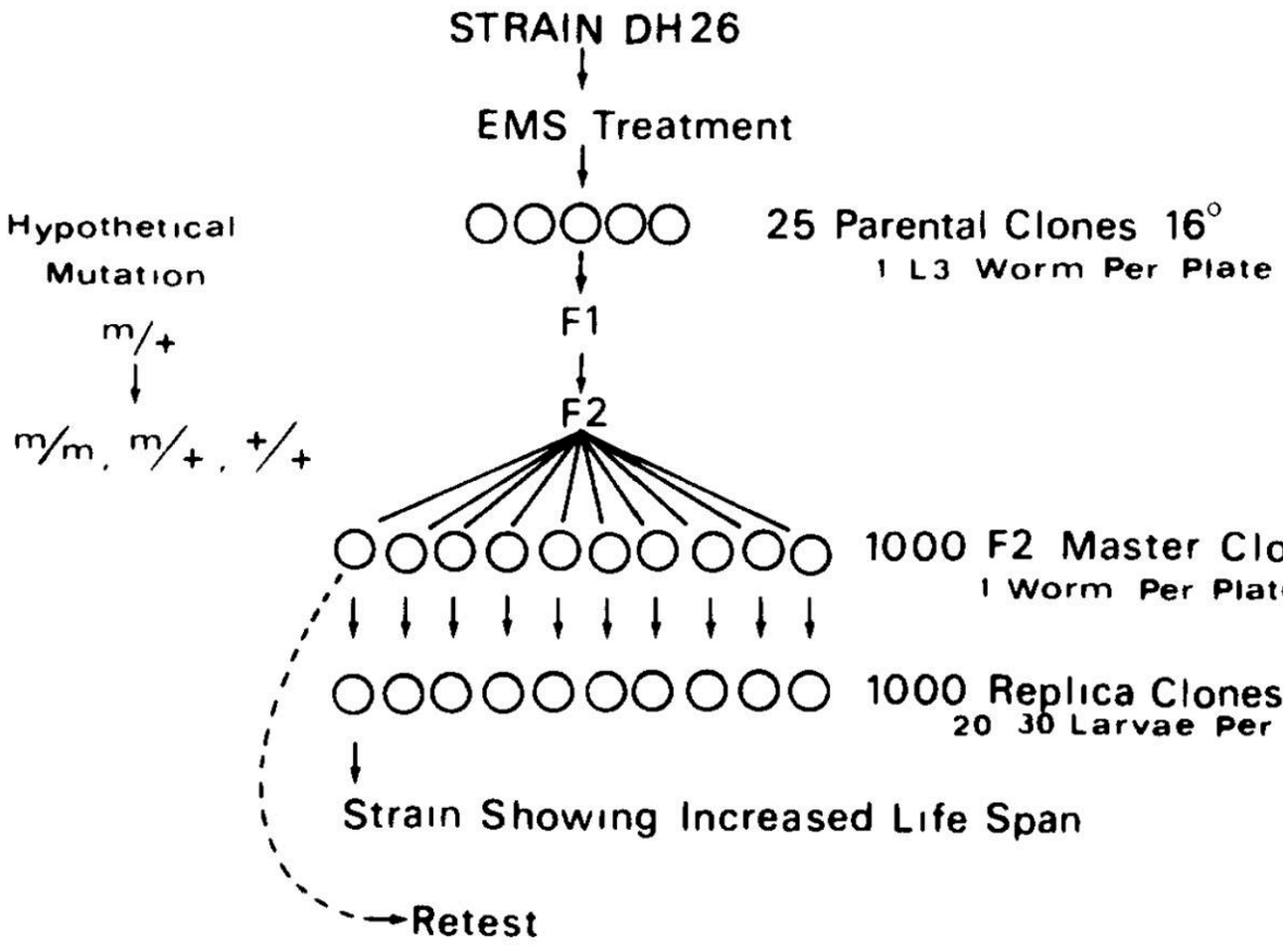
Klass, M. et al., *Nature*, **1976**, *260*(1), 523-525.

Caloric restriction works… but **why?**



ethyl methanesulfonate

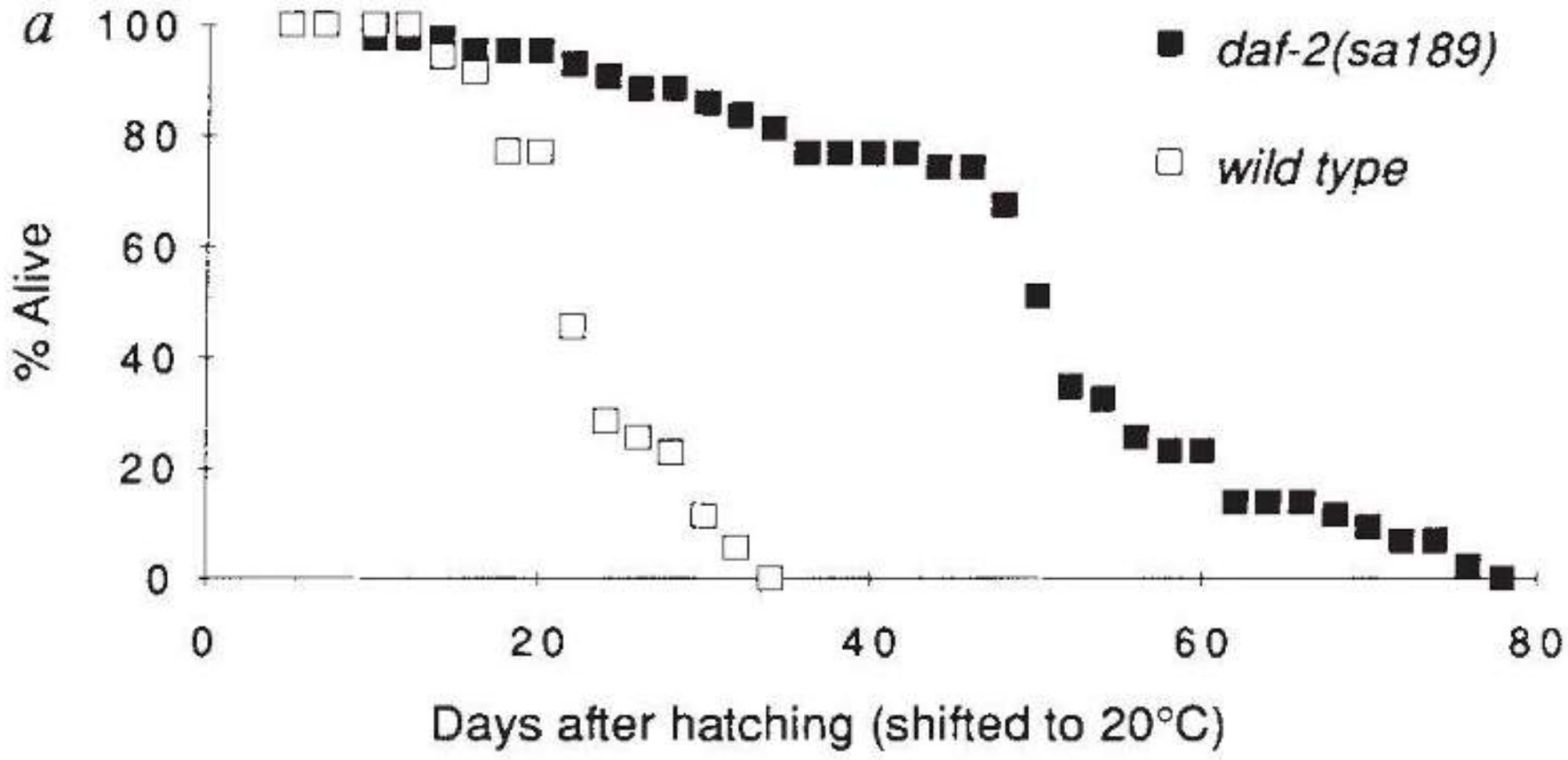




Klass, M. et al., *Nature*, **1976**, *260*(1), 523-525.

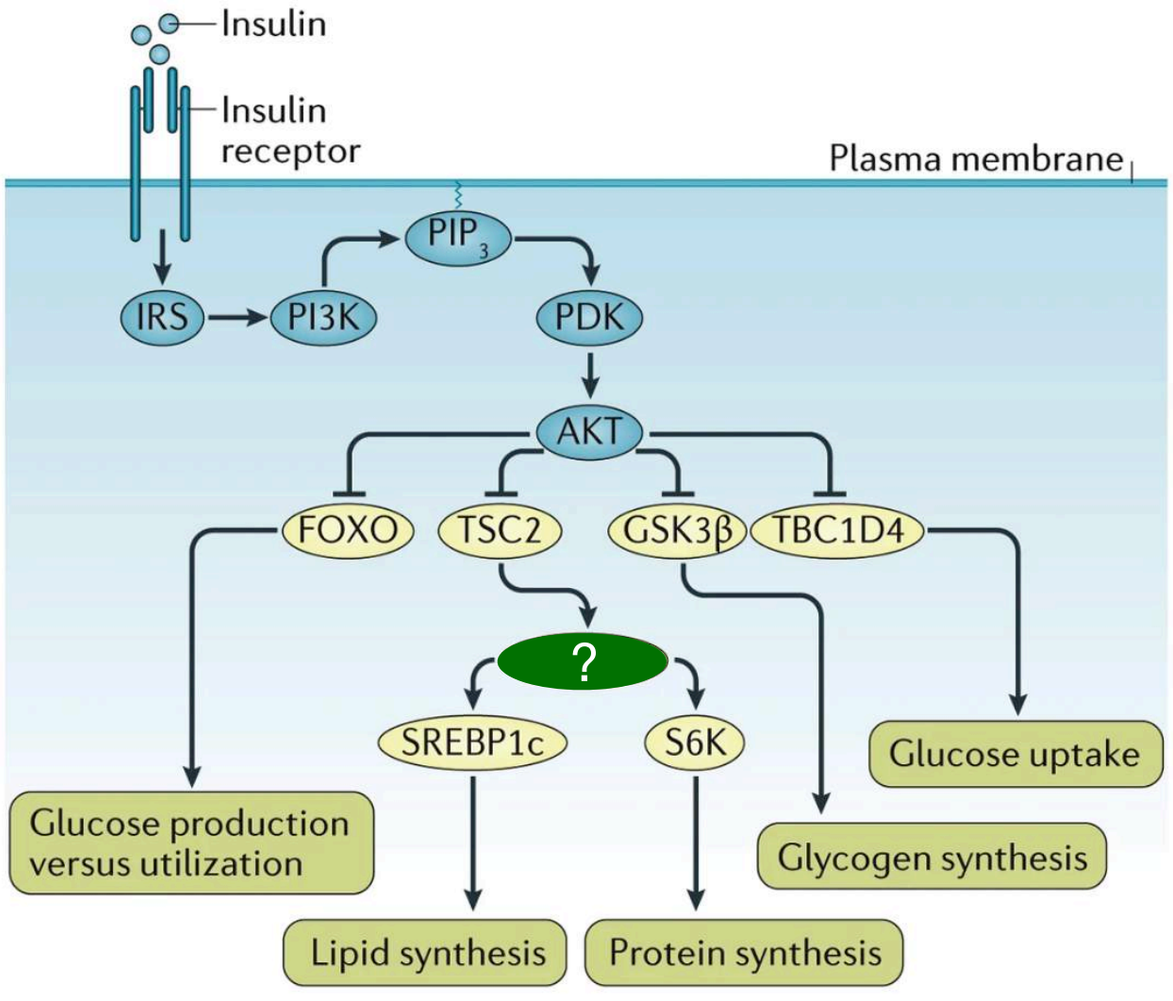
Caloric restriction works… but **why?**

daf-2 mutants lived 2X as long



Kenyon, C. et al., *Nature*, **1993**, *366*(1), 461-464.

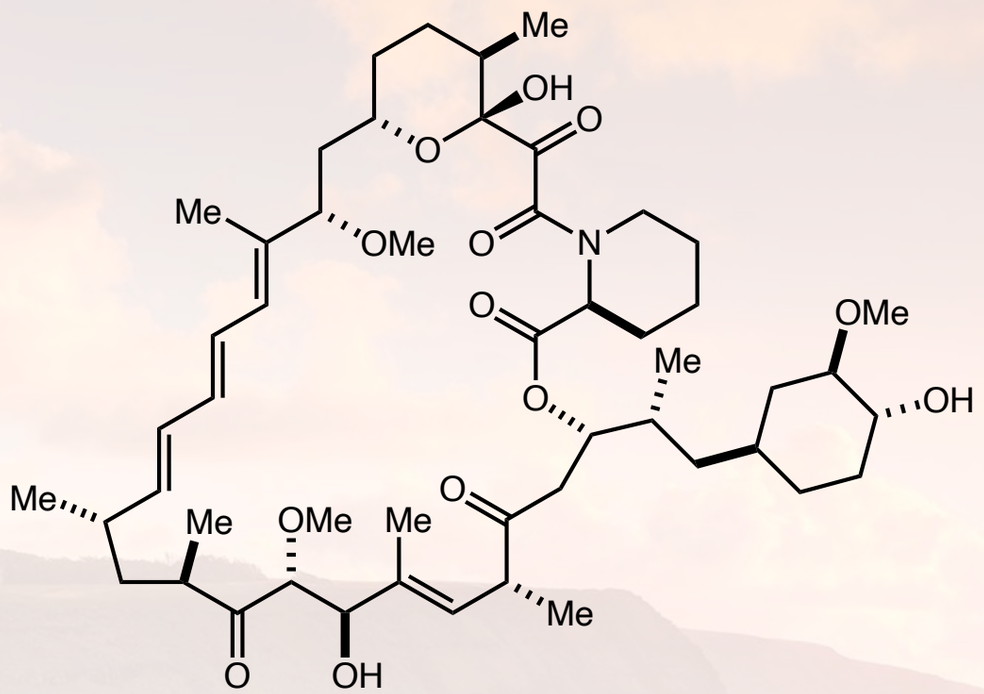
Daf2 is the insulin receptor



↑ *growth* ↑ *cell division* ↑ *metabolism*

Kenyon, C. et al., *Nature*, **1993**, *366*(1), 461-464.

Meanwhile, on Easter Island



rapamycin

high doses

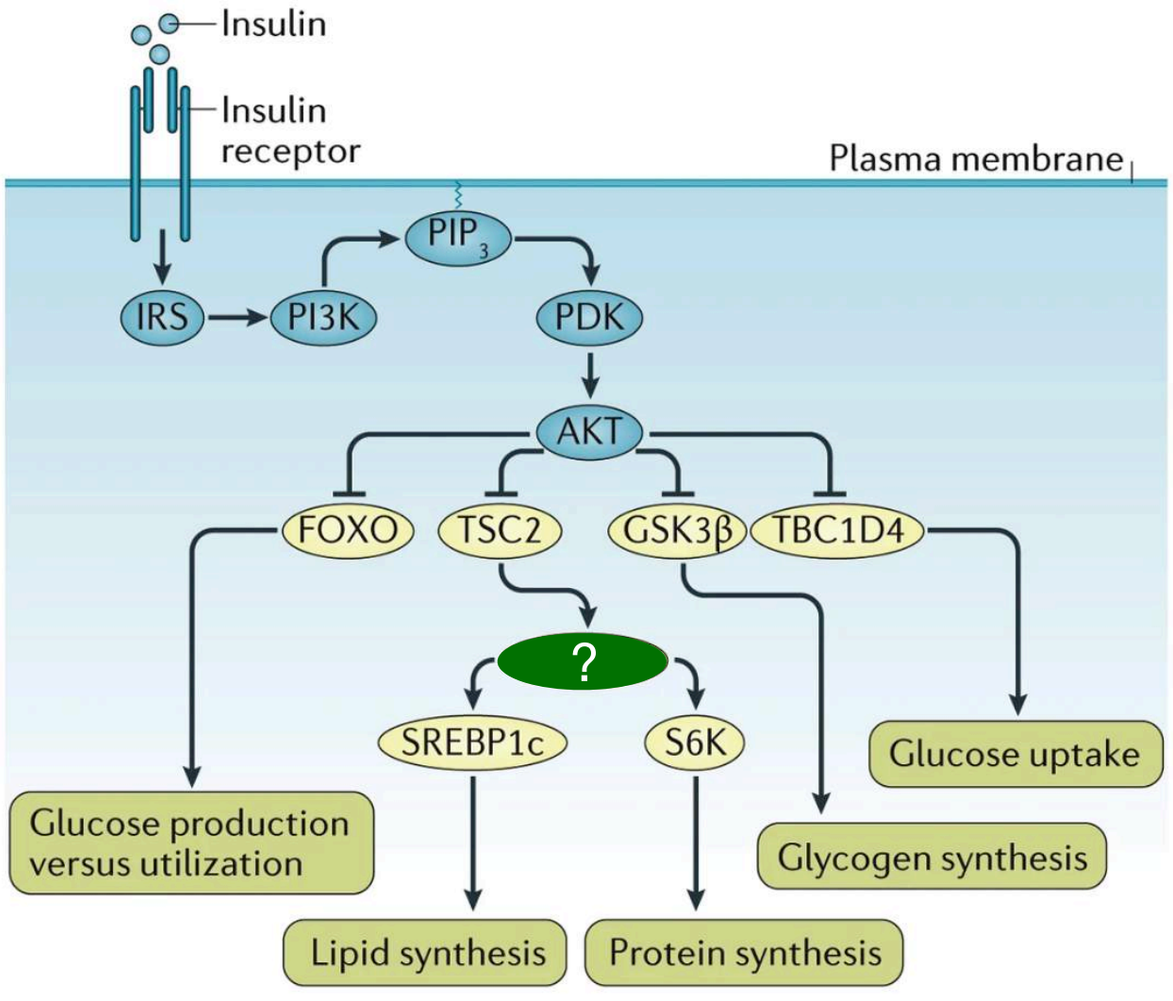
cytotoxic

low doses

cytostatic

slowed growth

Rapamycin inhibits insulin signaling



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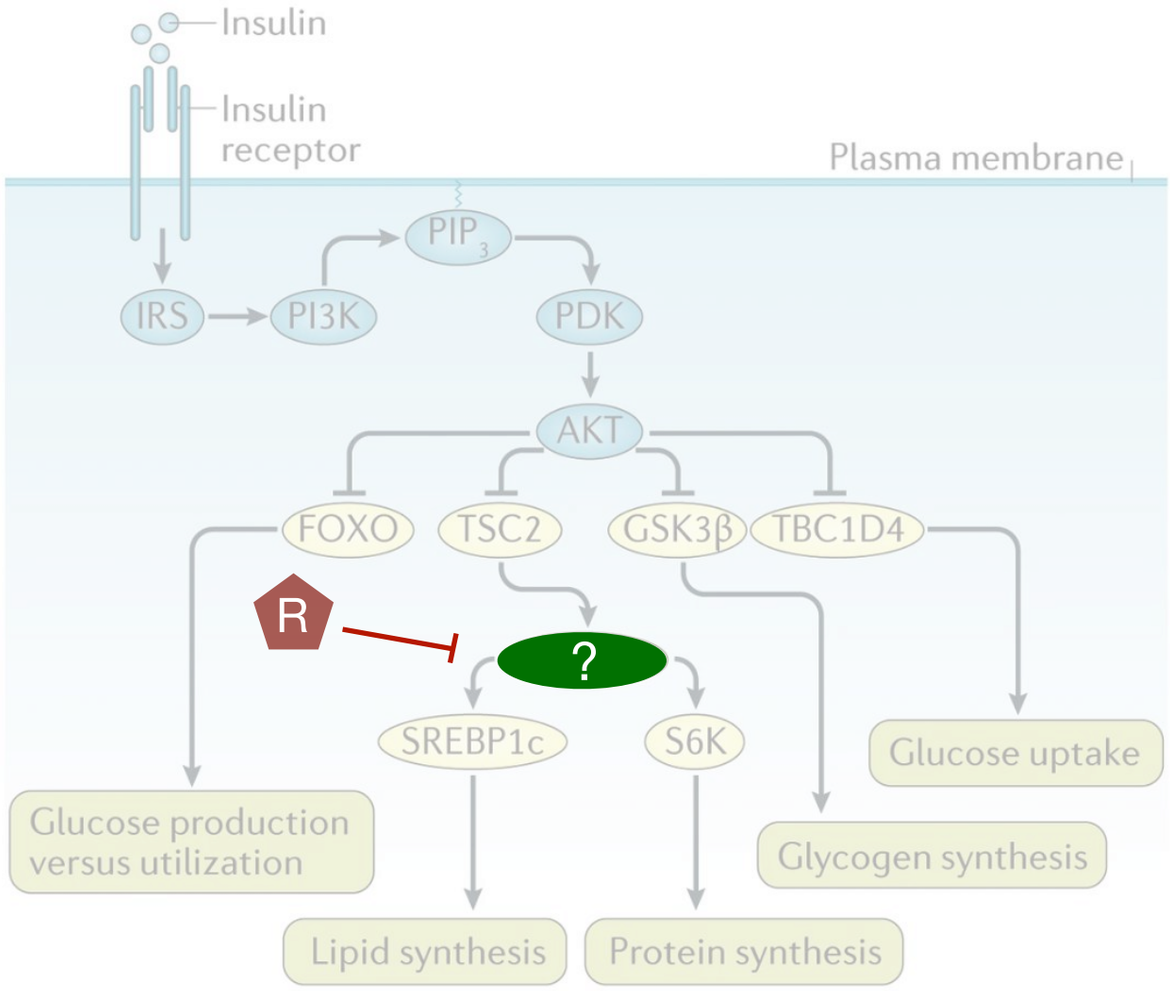

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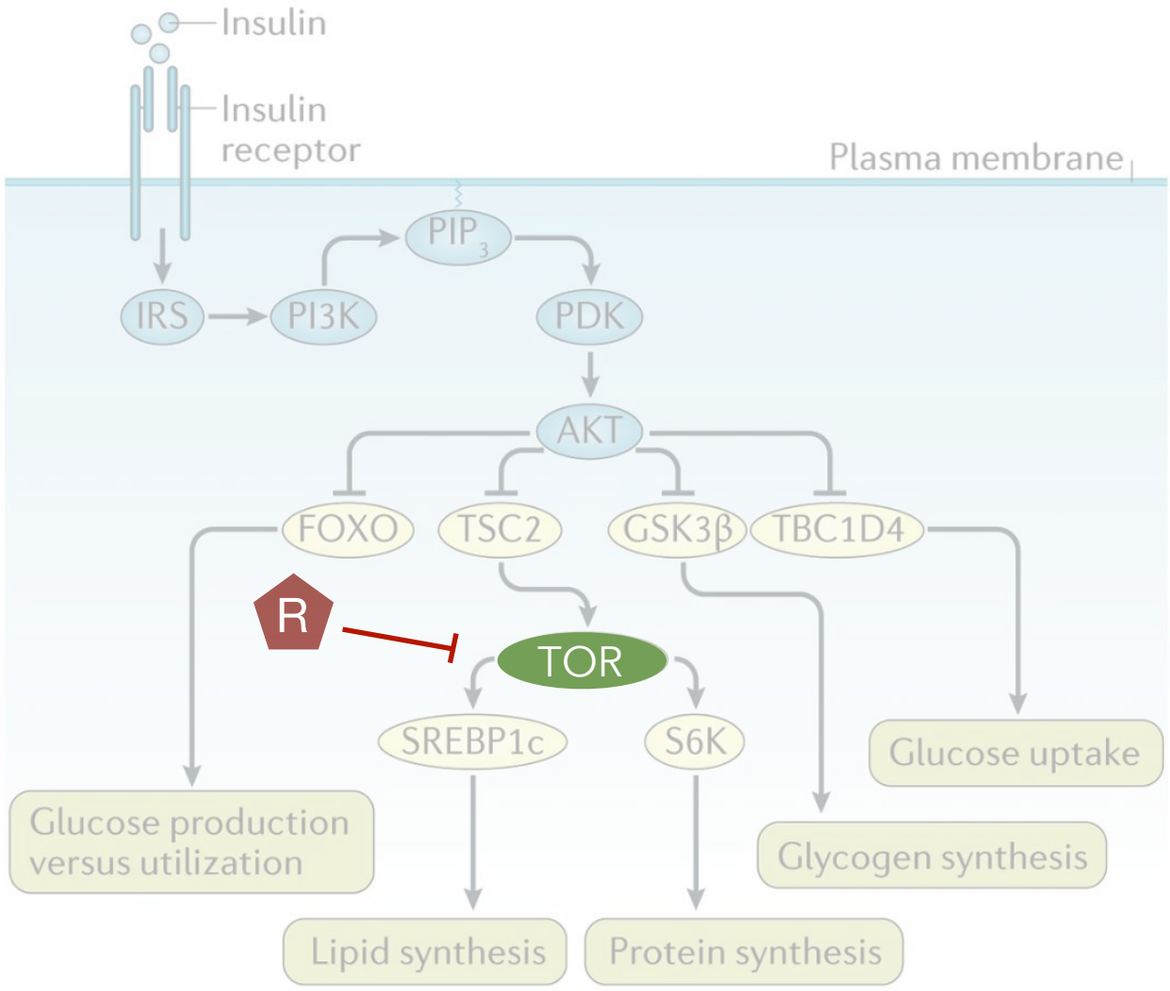
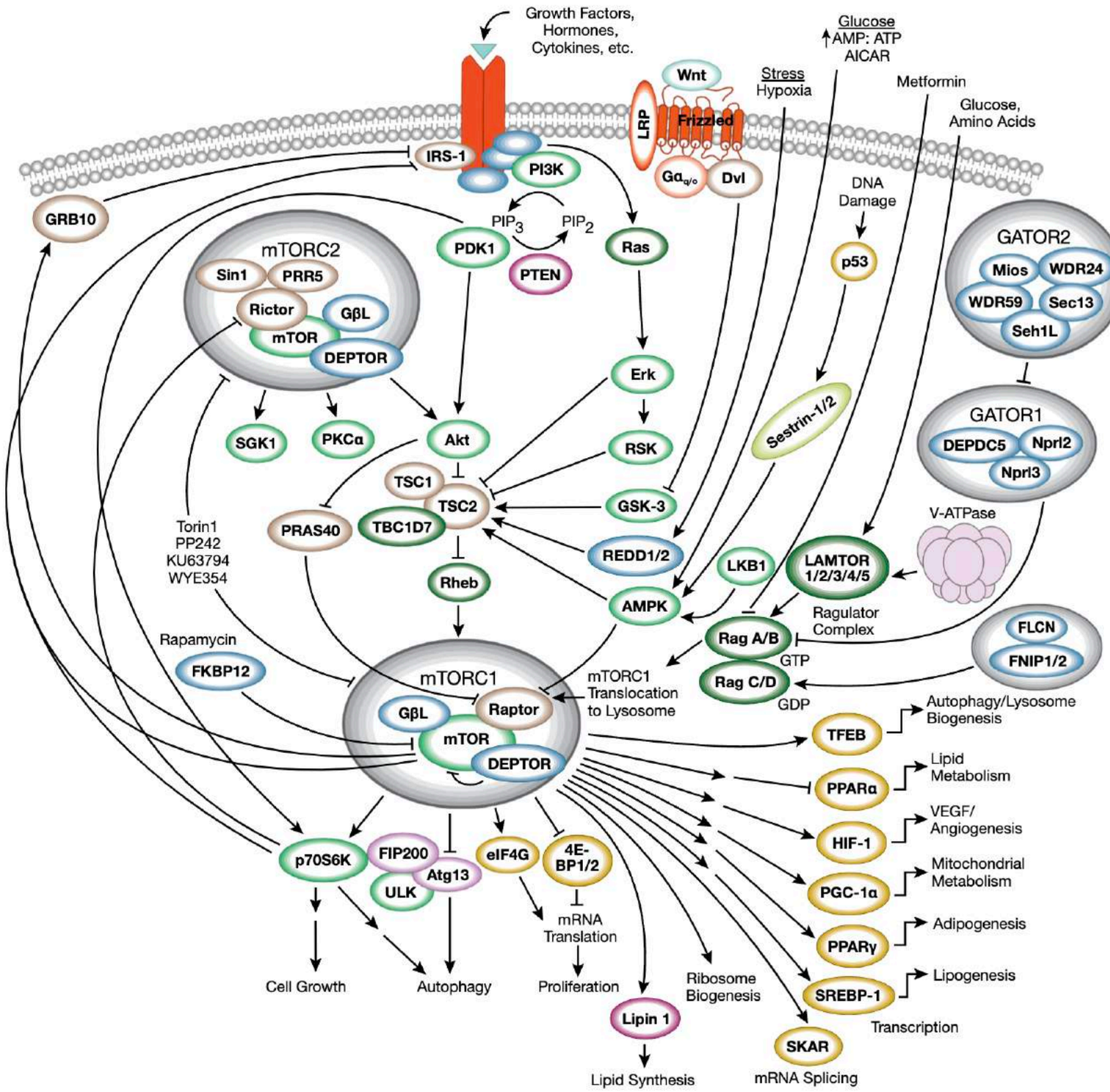
Rapamycin inhibits insulin signaling



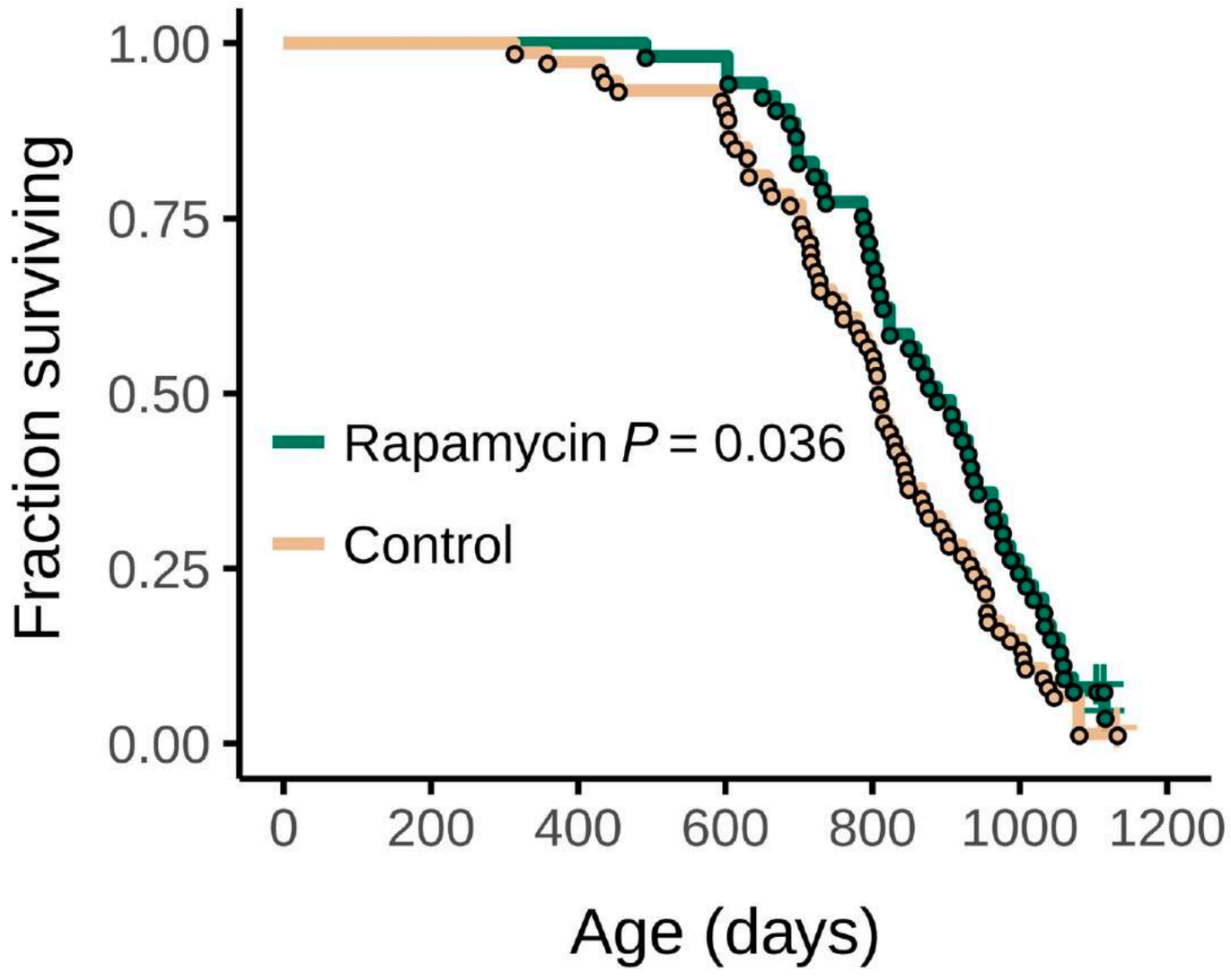
↓ *growth* ↓ *cell division* ↓ *metabolism*

Kenyon, C. et al., *Nature*, **1993**, *366*(1), 461-464.

mTOR is **the** growth signaling hub



Low dose rapamycin extends lifespan in mice



Shindyapina. A. et al., *Science*, **2022**, *8*(37), eabo5482.

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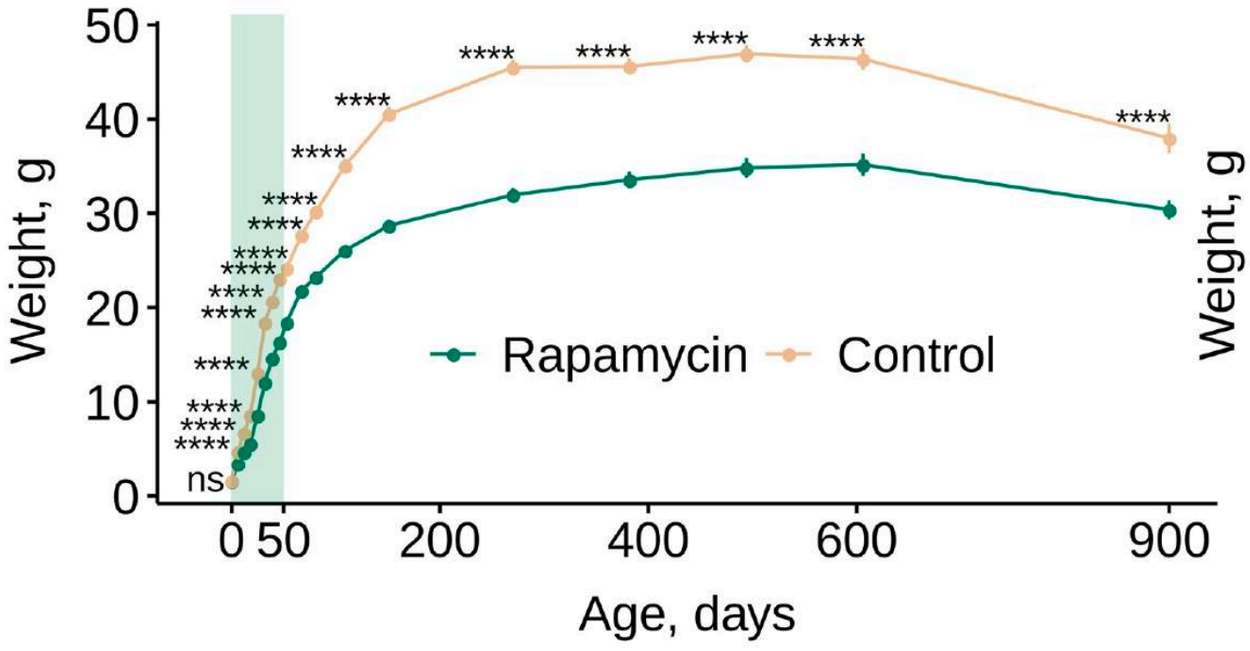

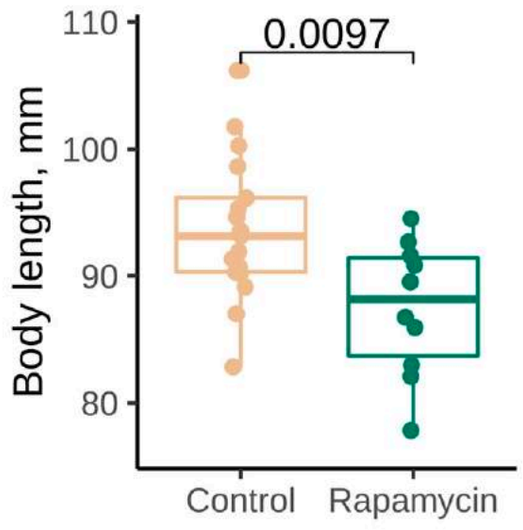

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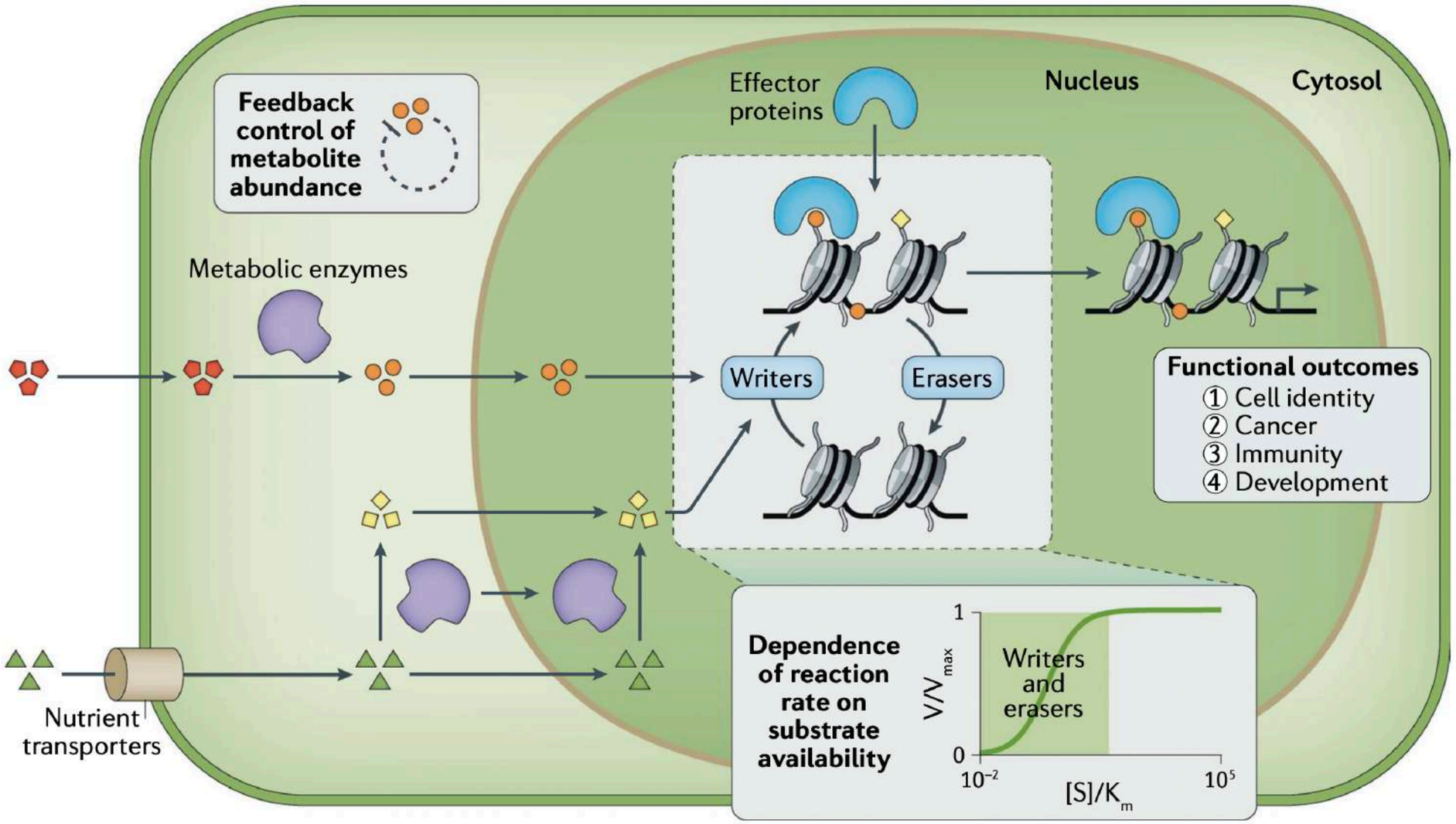
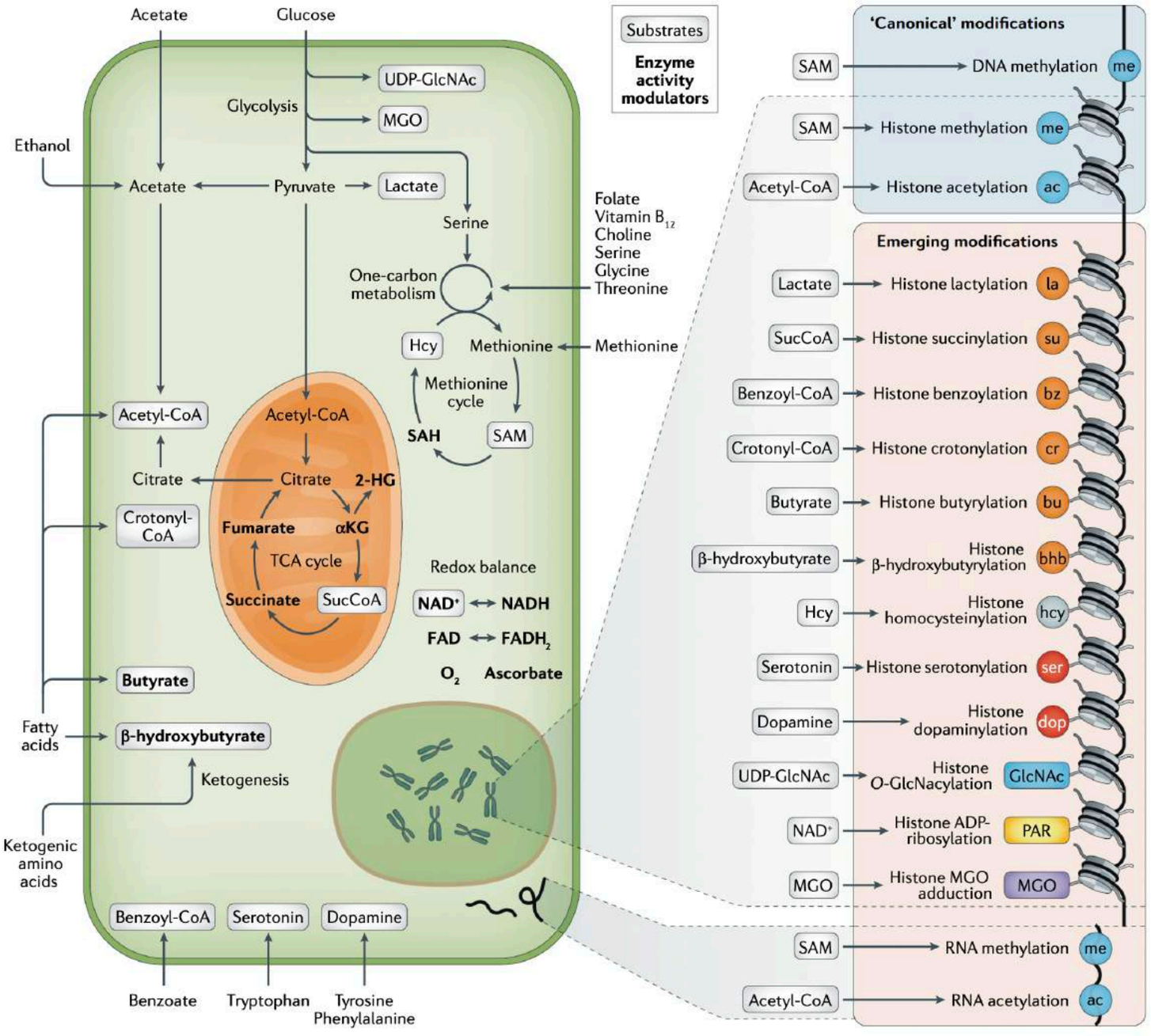
The missing link: **metabolism** and **epigenetics**



Dai, Z. et al., *Nat. Rev. Genet.*, **2020**, *21*, 737-753.

The missing link: **metabolism** and **epigenetics**



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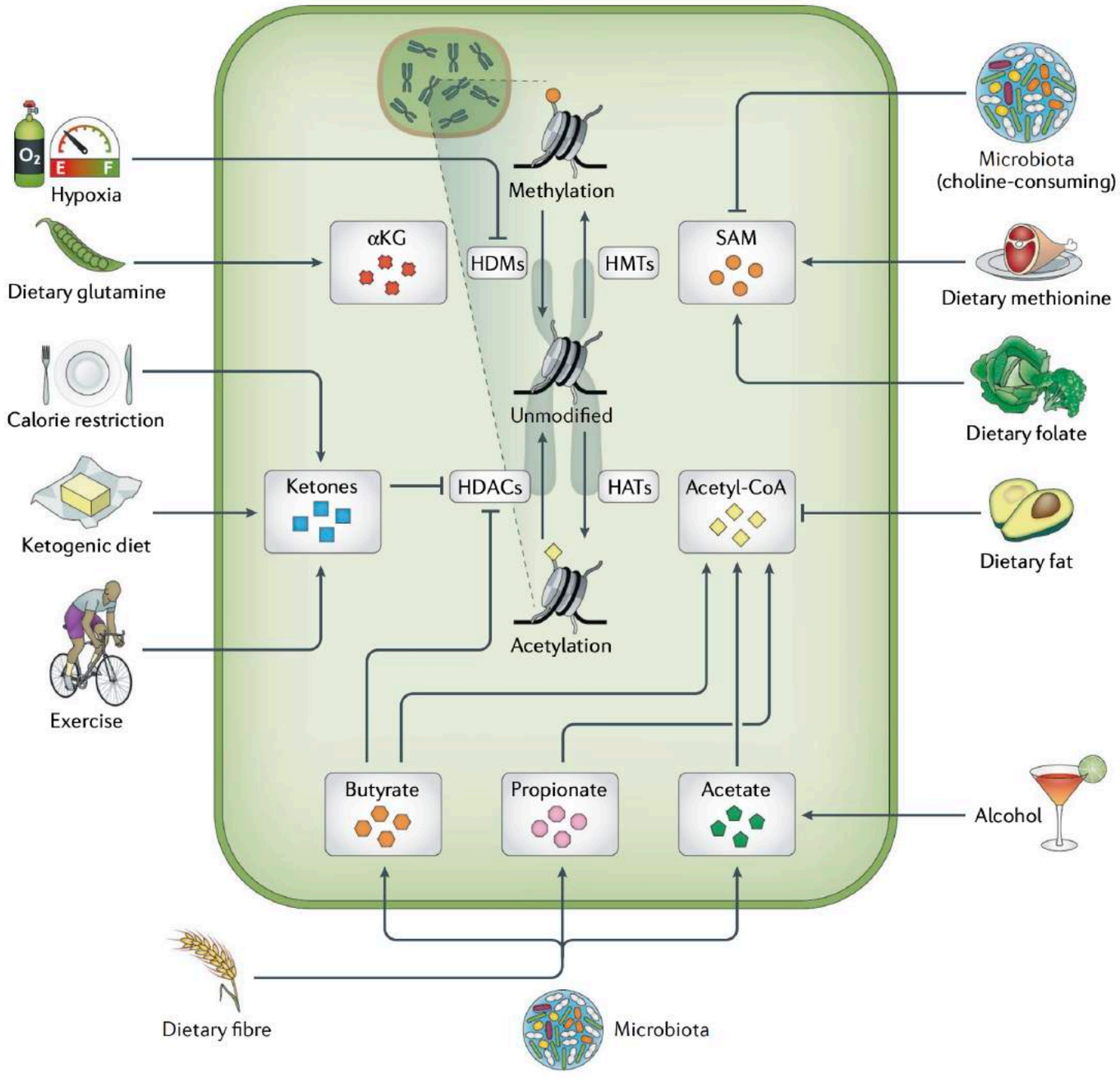

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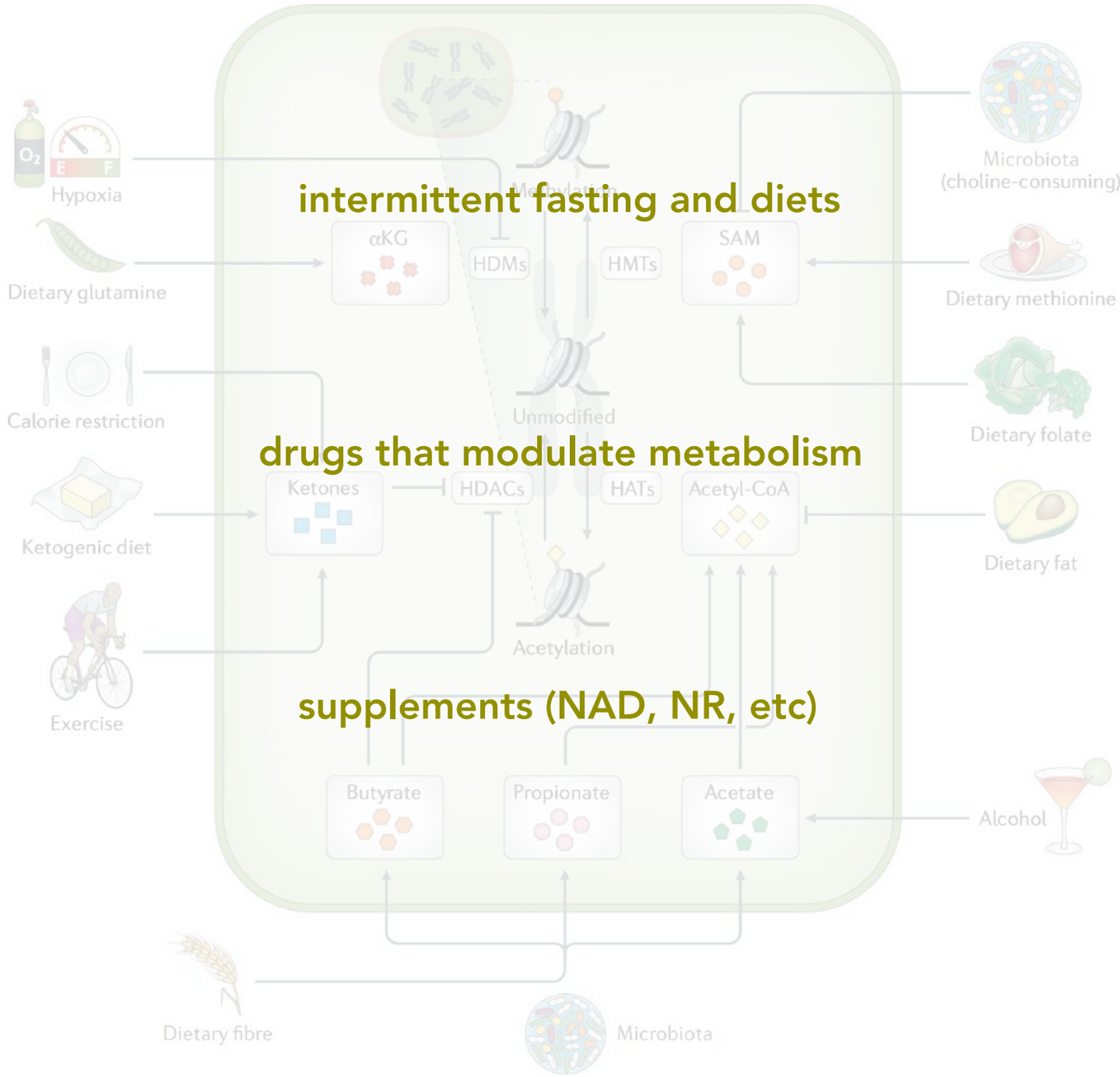
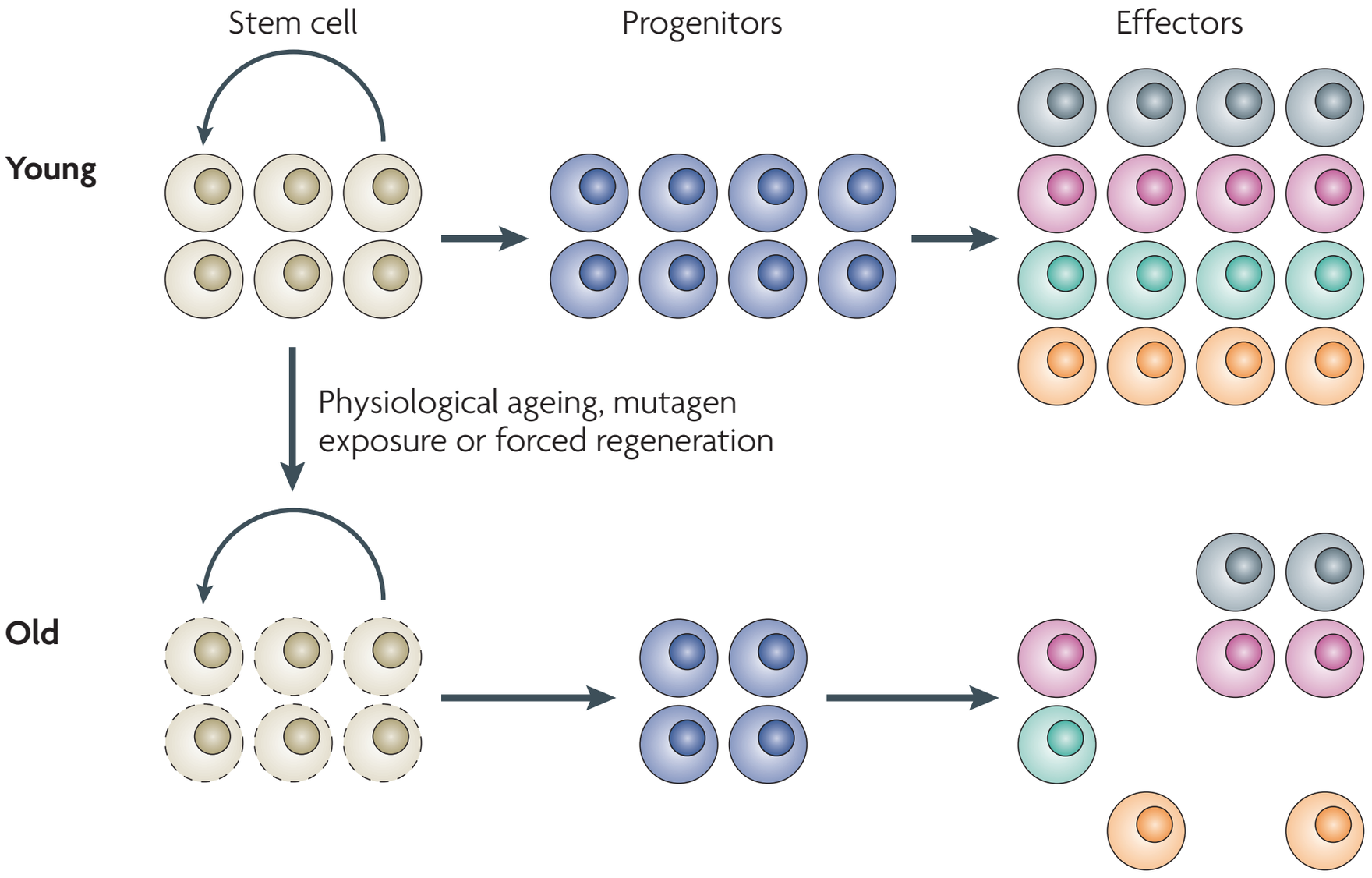


Dai, Z. et al., *Nat. Rev. Genet.*, **2020**, *21*, 737-753.

Turning back the stem cell clock



Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

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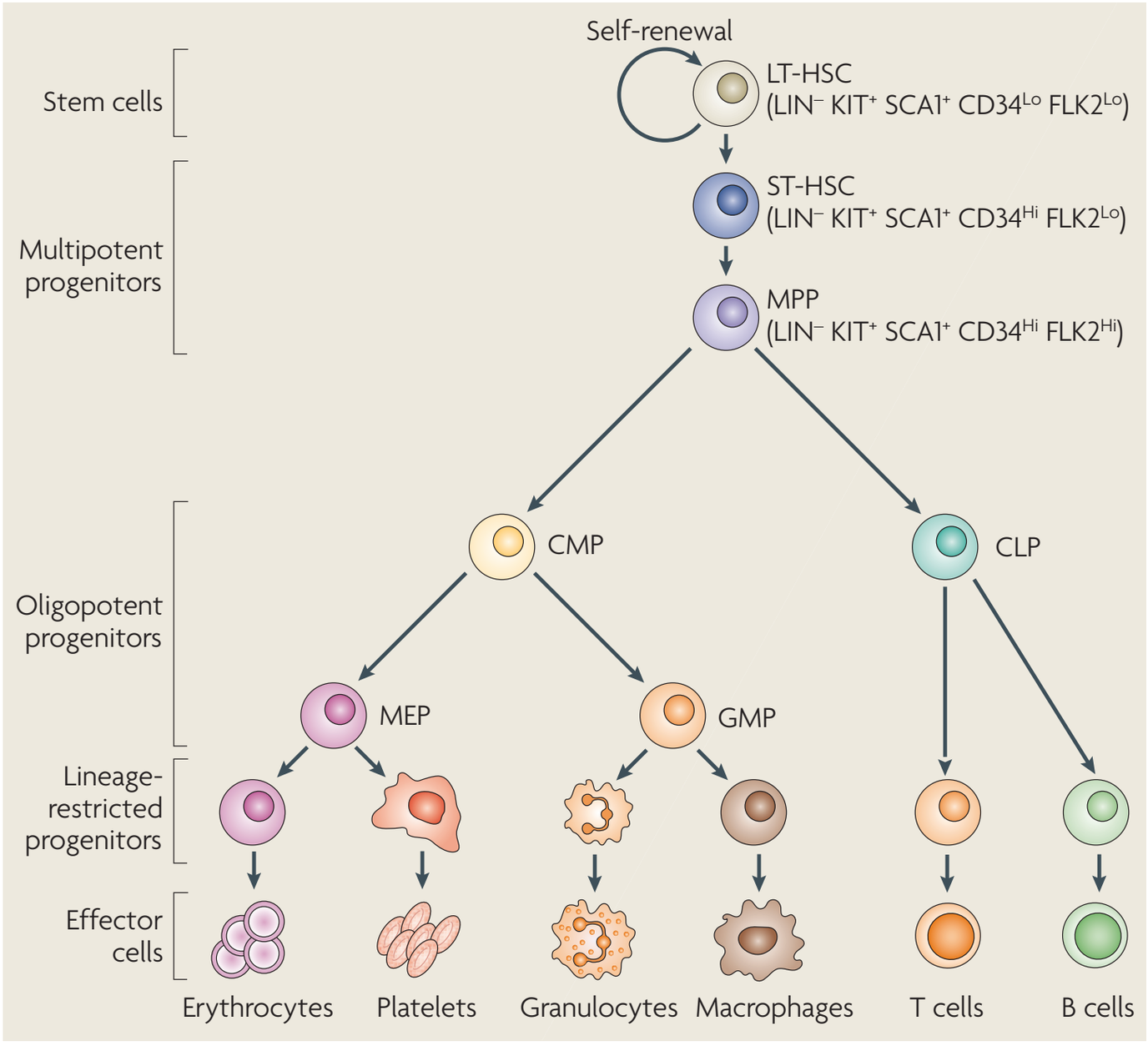

Shinya Yamanaka

what unique genes/proteins are expressed in stem cells?

Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

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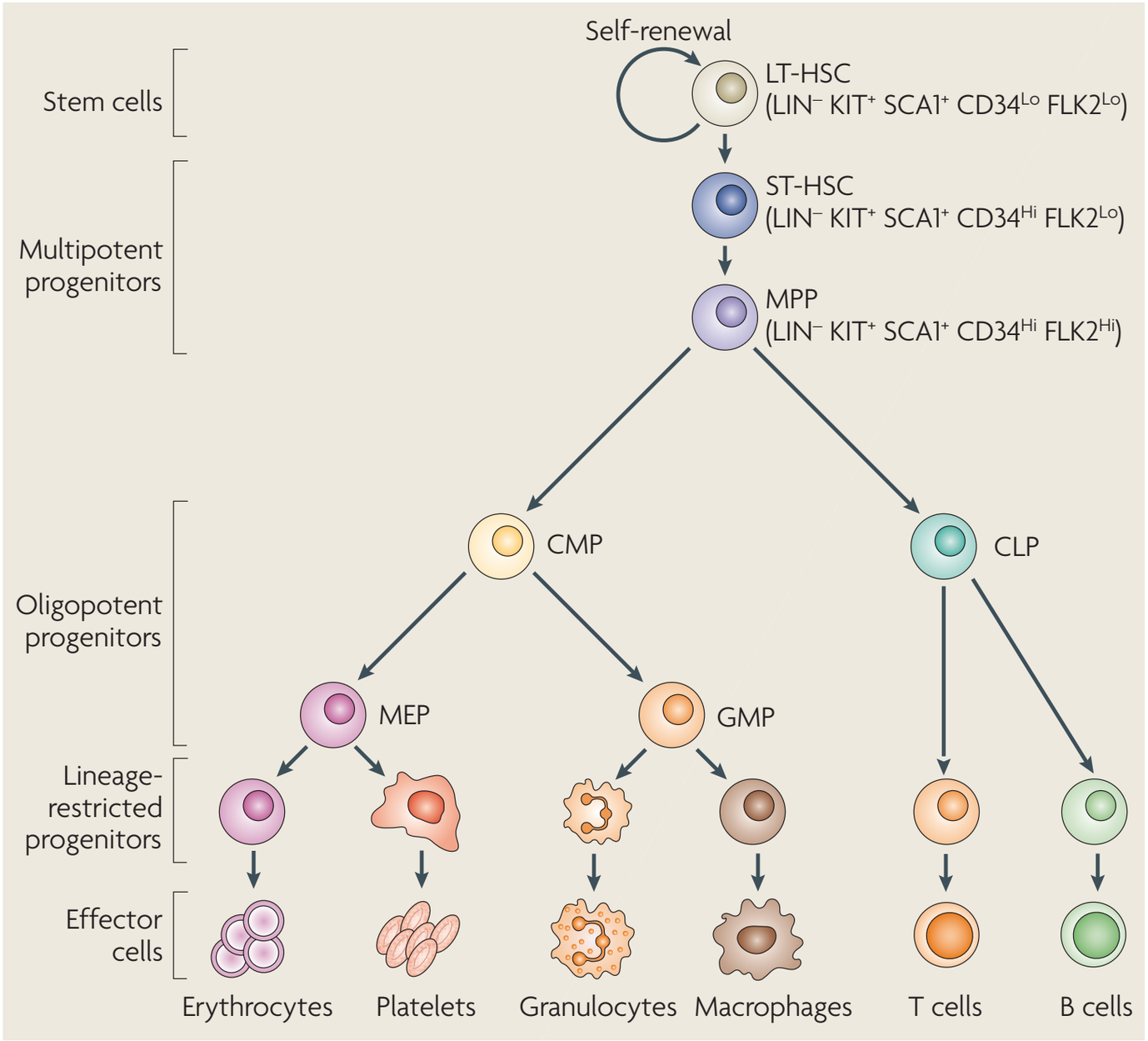
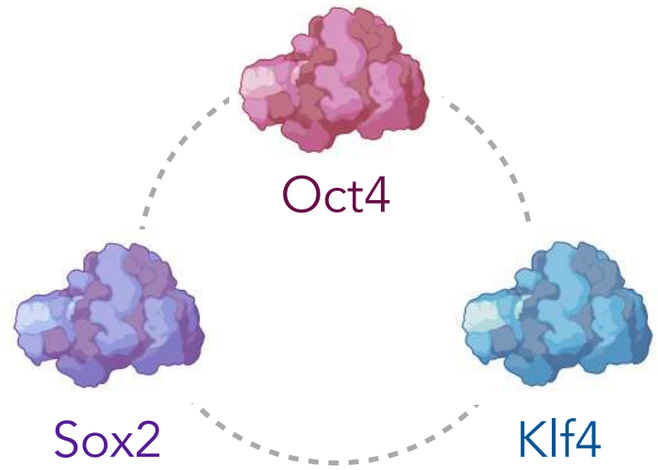


~40 transcription factors

3 key proteins



"OSK"

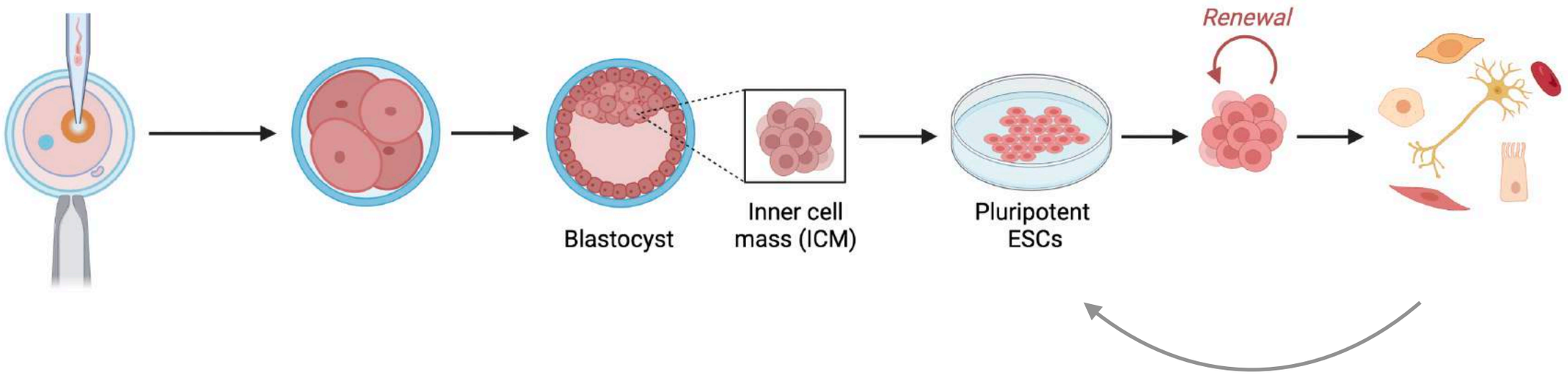
"Yamanaka Factors"

Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

Turning back the stem cell clock

only prior existing stem cell source:

human embryos

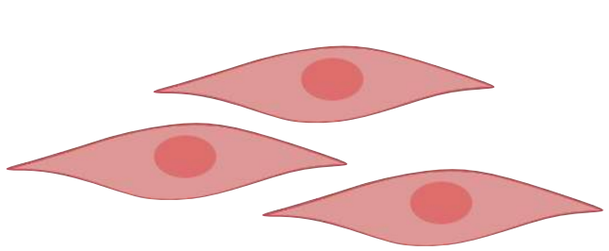


reprogram normal cells?

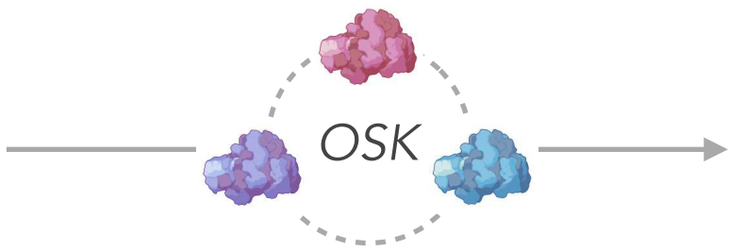
Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

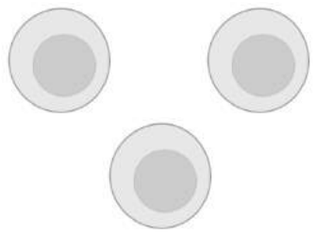
Turning back the stem cell clock

OSK reverts cells back to a "stemlike" state

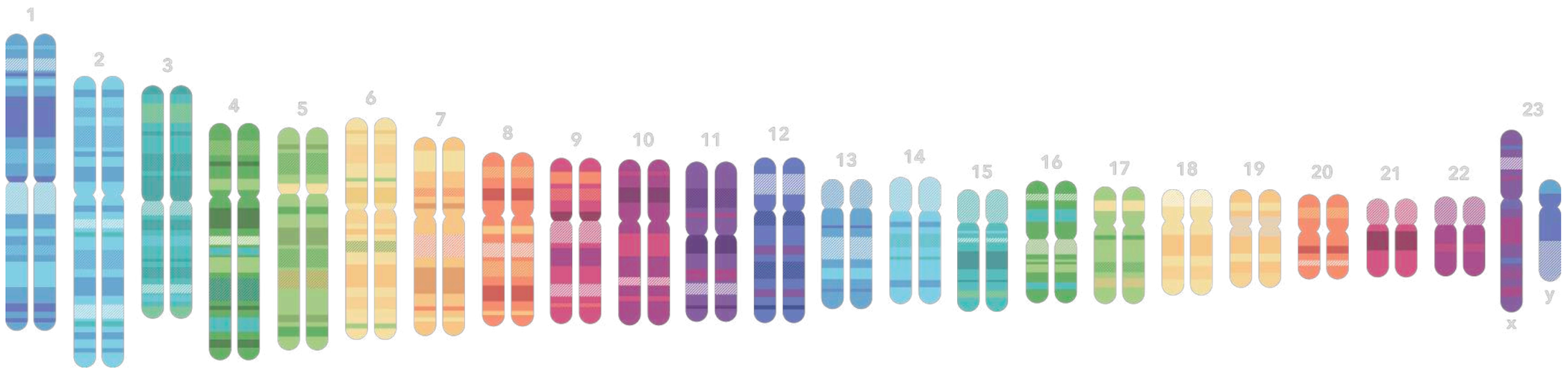


fully differentiated cells from donor (ie skin, etc)





induced pluripotent stem cells (iPSCs)



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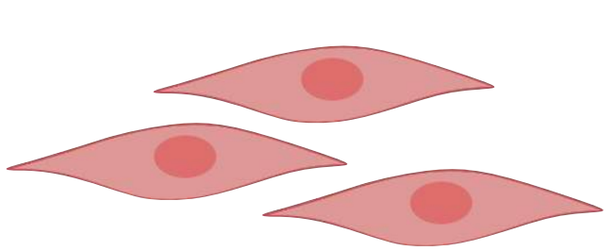

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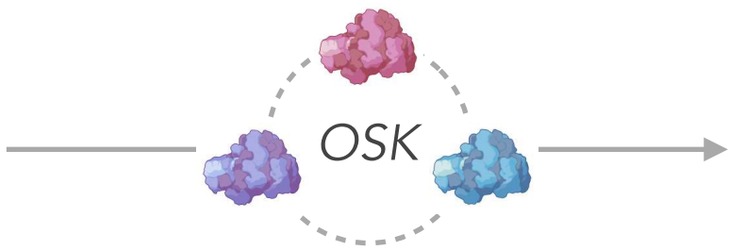

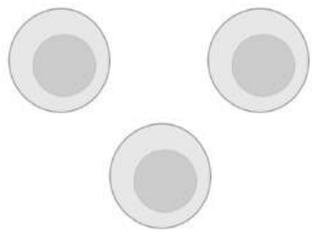

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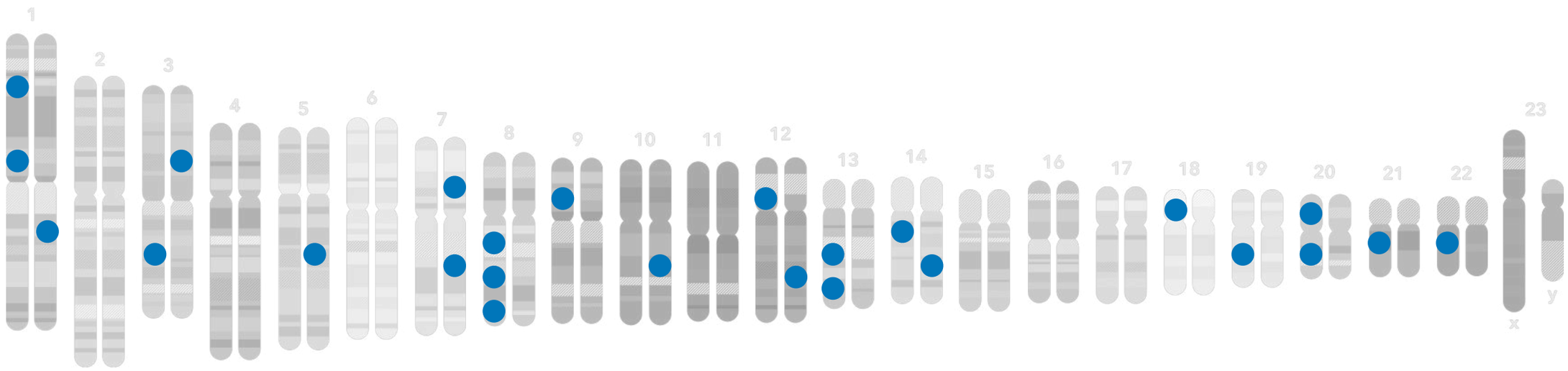

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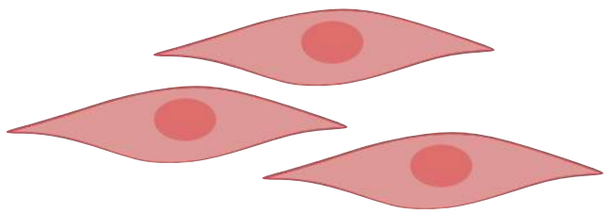

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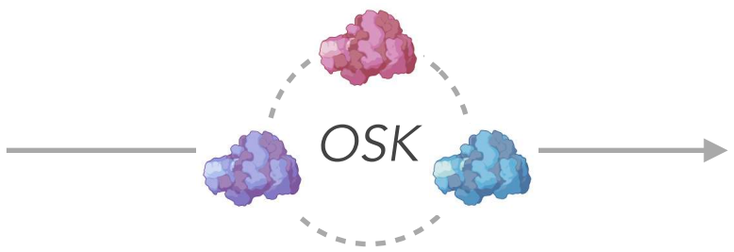

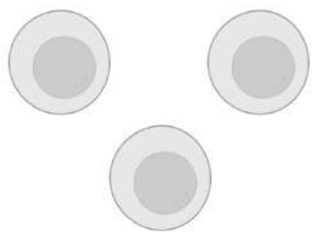

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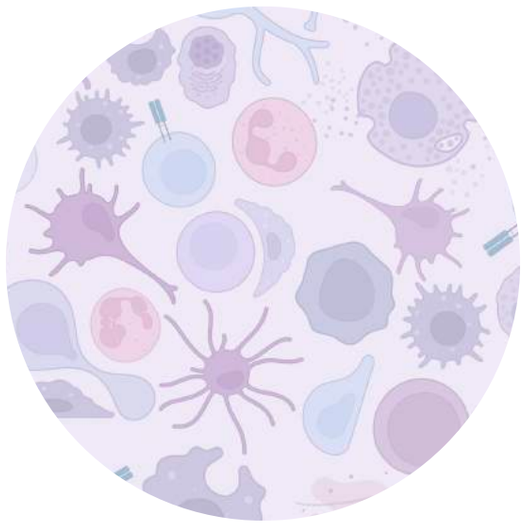
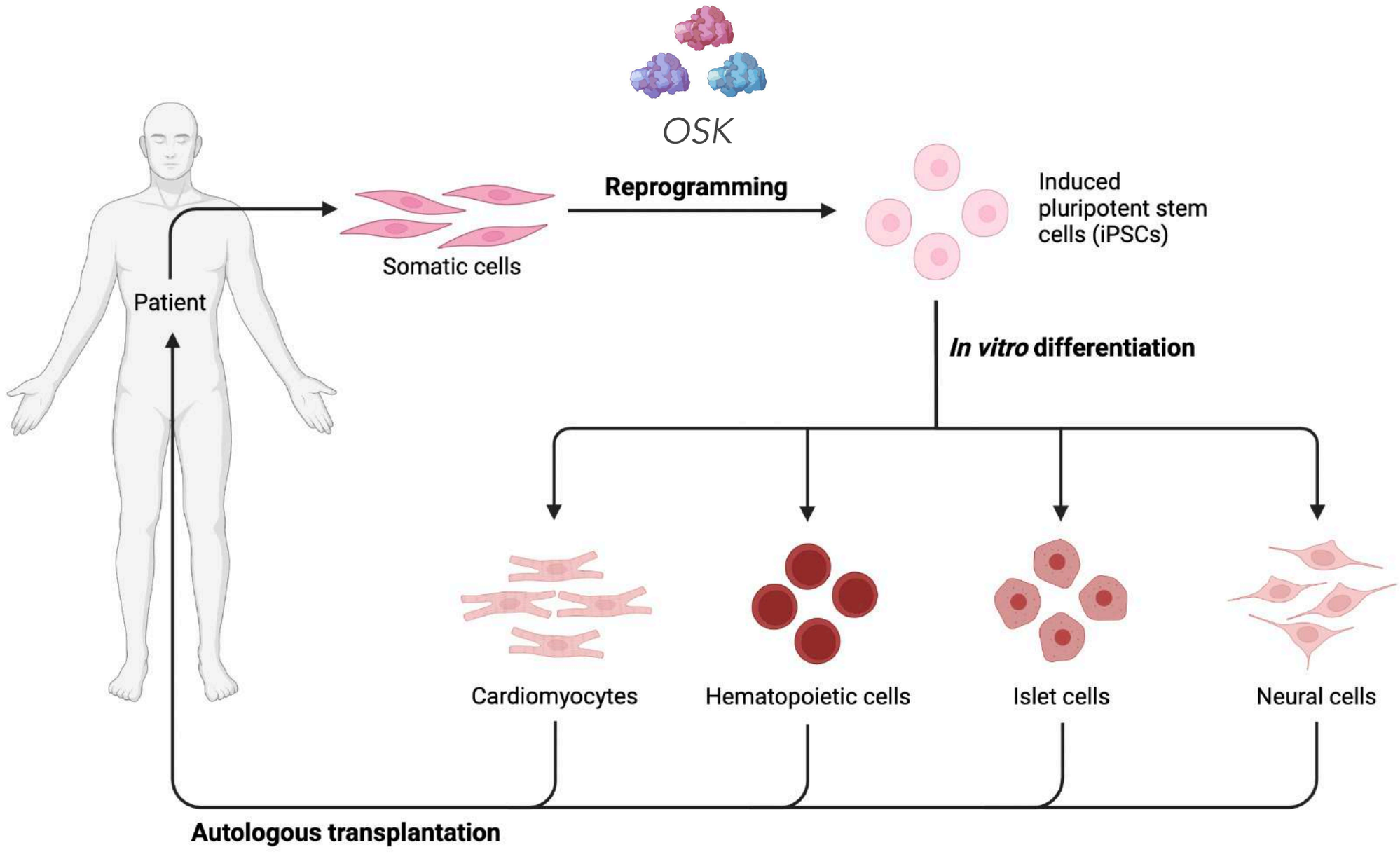


on demand cell production

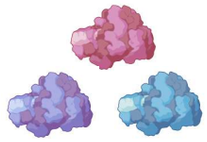
Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

Stem cell therapies

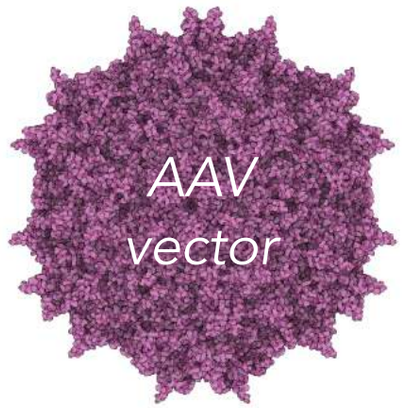


Sharpless, N. E. et al., *Nat. Rev. Mol. Cell Biol.*, **2007,** *8*, 707

in vivo epigenetic reprogramming

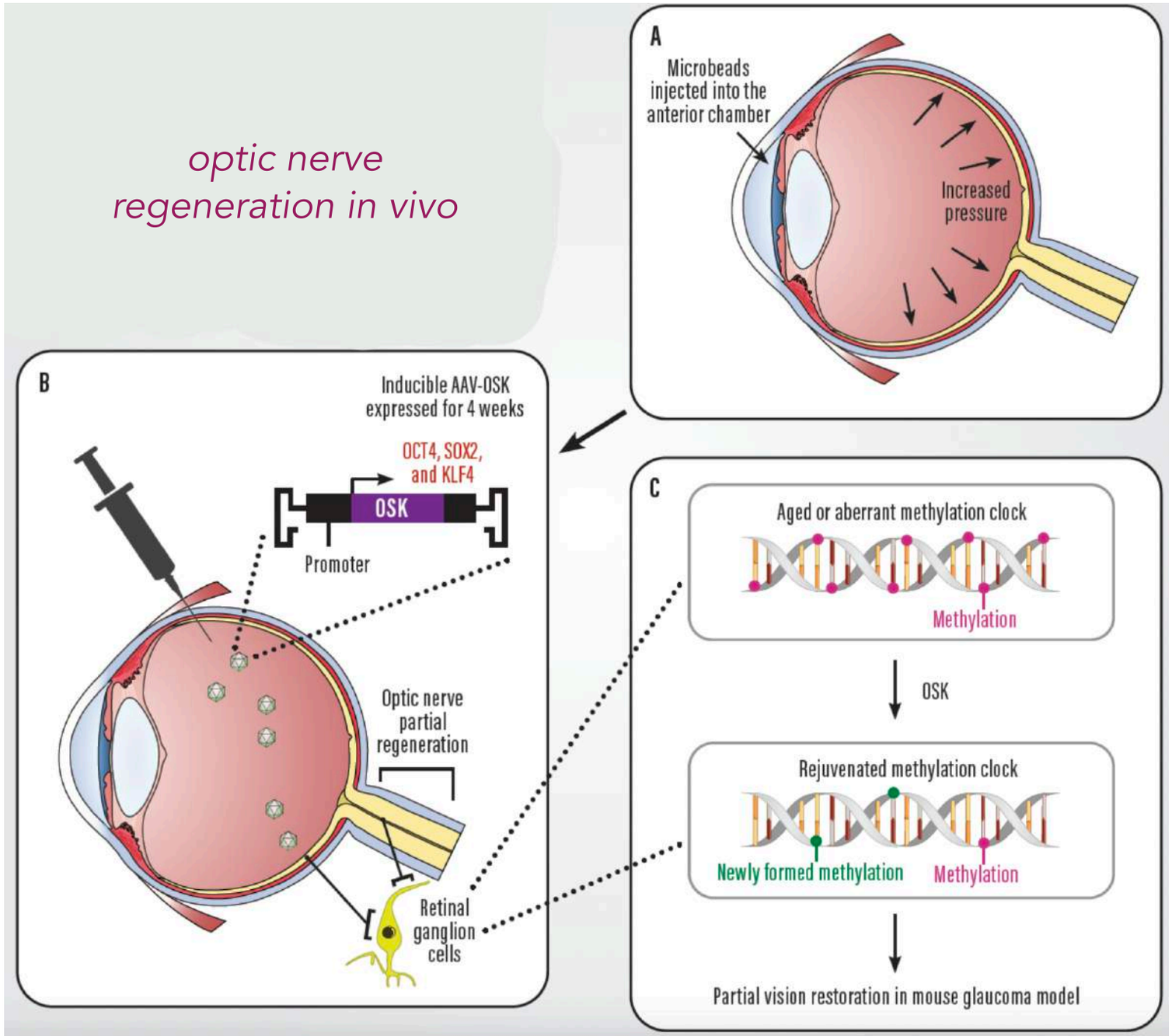


OSK



cell or tissue specific
delivery in vivo

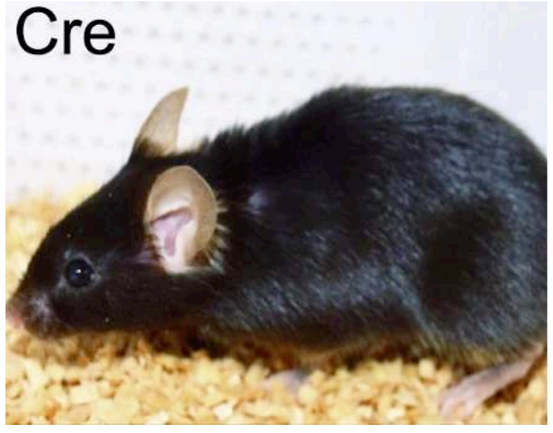
in vivo epigenetic reprogramming



David Sinclair

Lu, Y. et al. *Nature*, **2020,** *588(*7836), 124-129

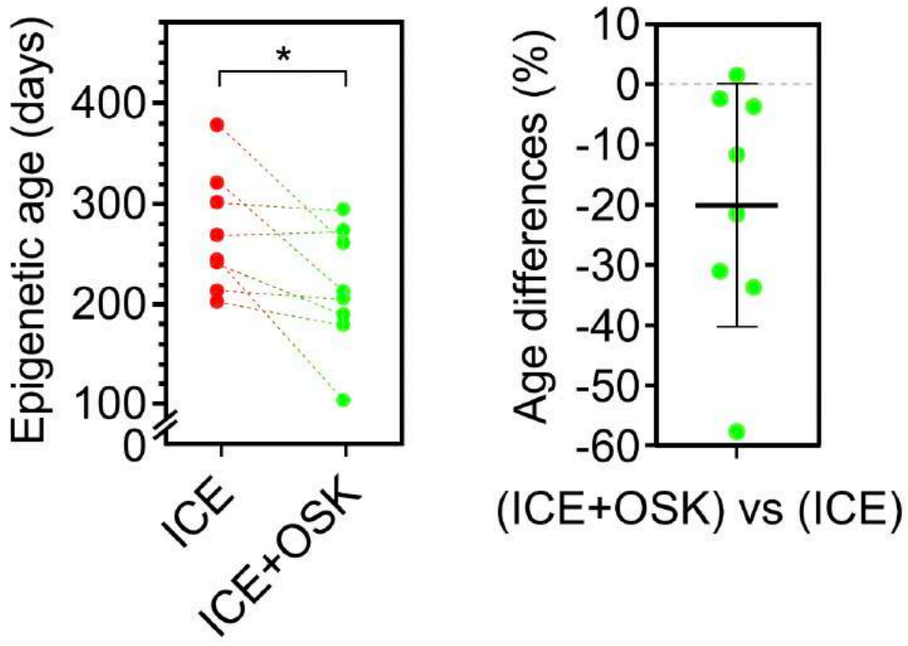
in vivo epigenetic reprogramming

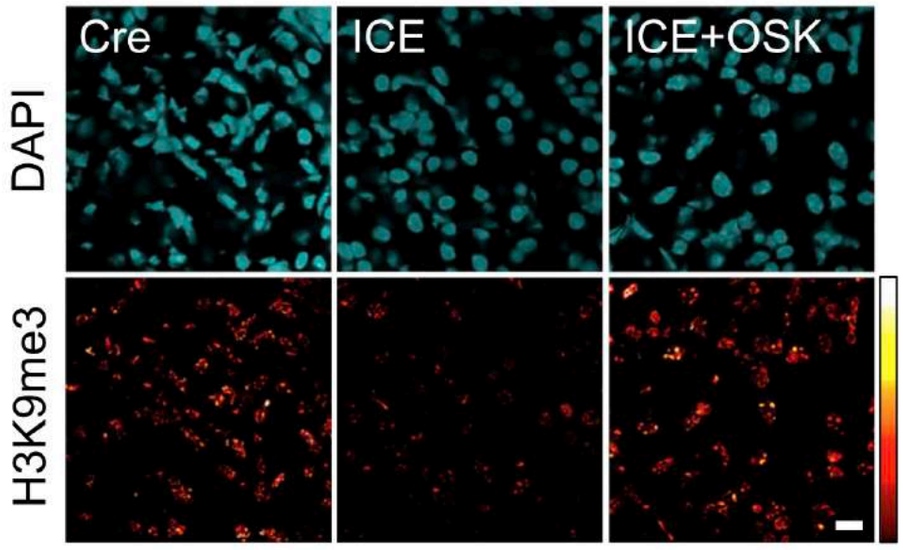


3 mo old

3 mo old

David Sinclair





Yang. J. et al., *Cell*, **2023,** *186*, 305-326

Living your best **supercentenarian** life

Sister Lucille Randon

Alés, France

born Feb 11, 1904

died Jan 17, 2023

age 118

Johanna Mazibuko

Jouberton, South Africa

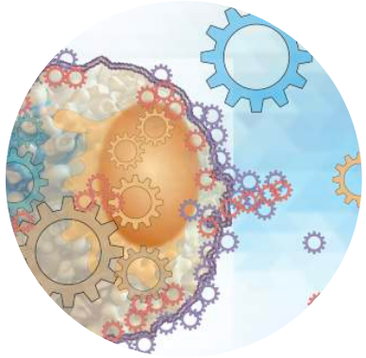
born May 11, 1894

died Mar 08, 2023

age 128

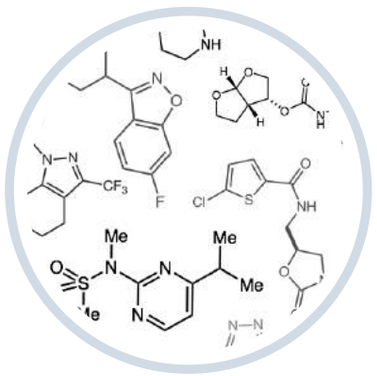
Living your best **supercentenarian** life

? ? ? ? ?



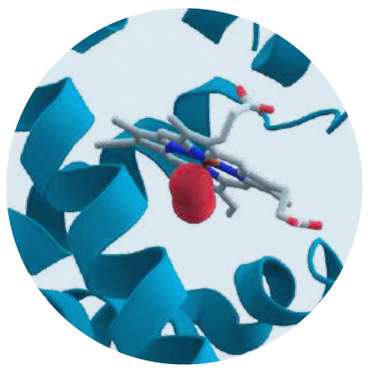
stem cell therapy

metabolism optimization

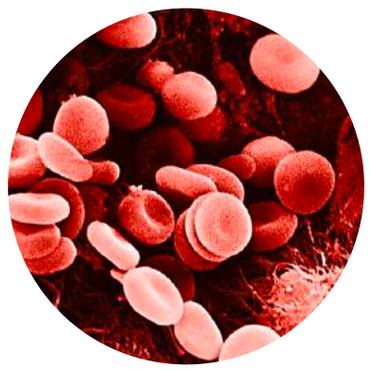


pharmaceuticals

epigenetic reprogramming



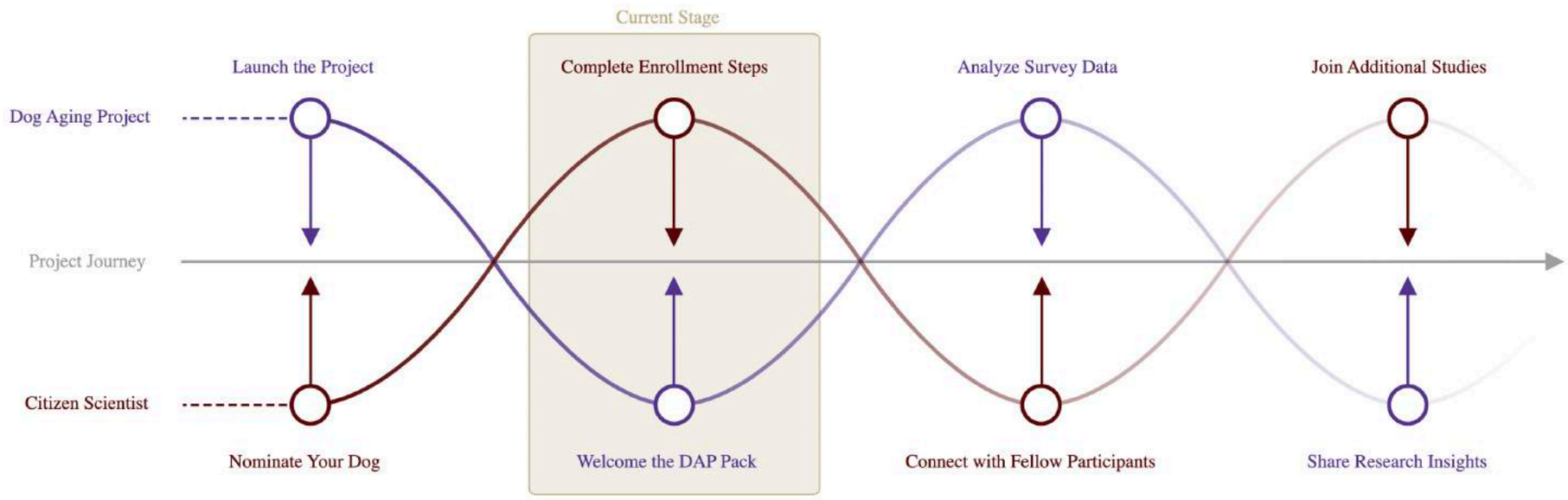
hormone therapy



blood supplements

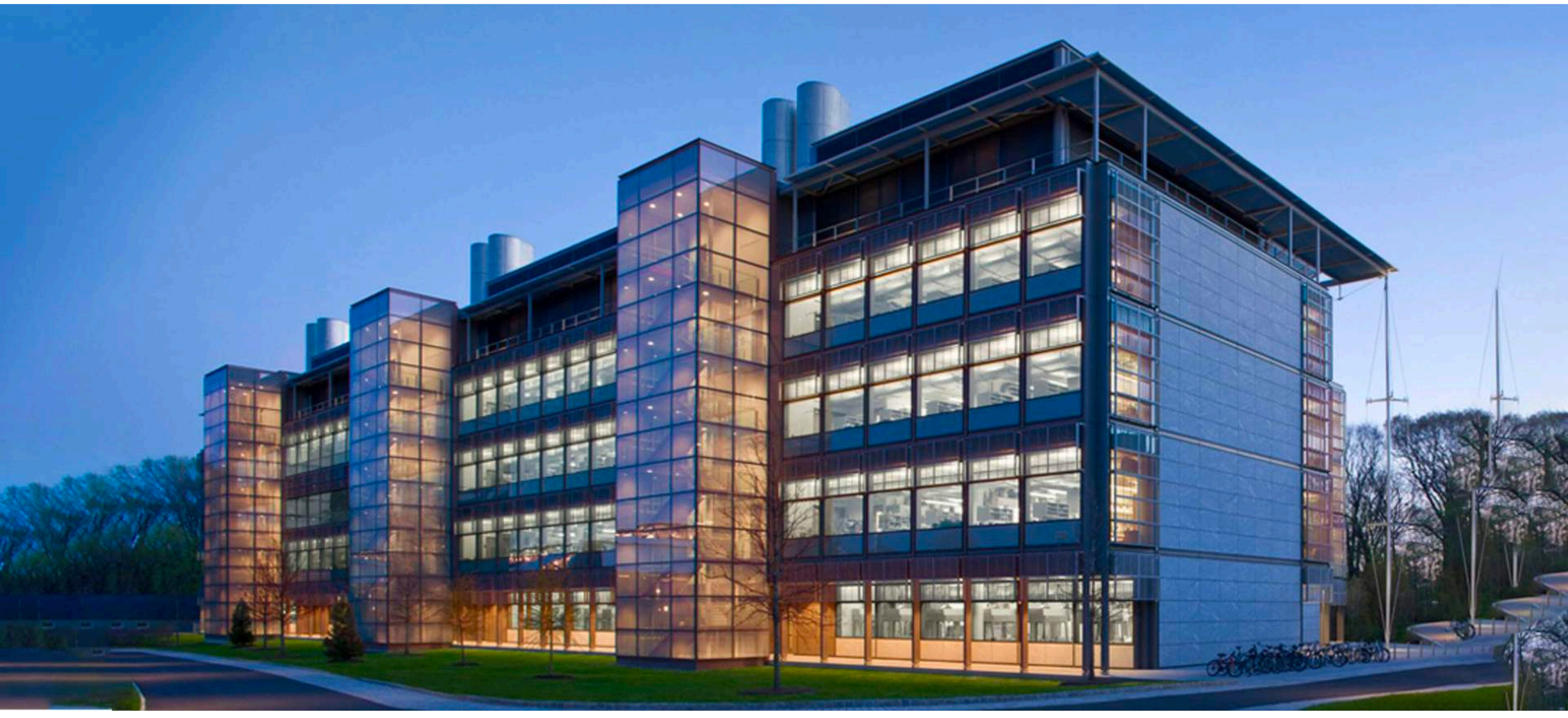
The *Dog Aging Project*

- dozens of trials to test different interventions, doses, timing, etc
- **you** can volunteer your dog
- results ongoing over next few years/decades



Thank you

Thank you



PRINCETON UNIVERSITY
DEPARTMENT OF
CHEMISTRY