Anti-Aging: State of the Art

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Seminar Bioinformatics

Why is aging a problem?

Is aging necessary?

What is aging?

How can we slow down aging?

What can I do?

How can bioinformatics help?

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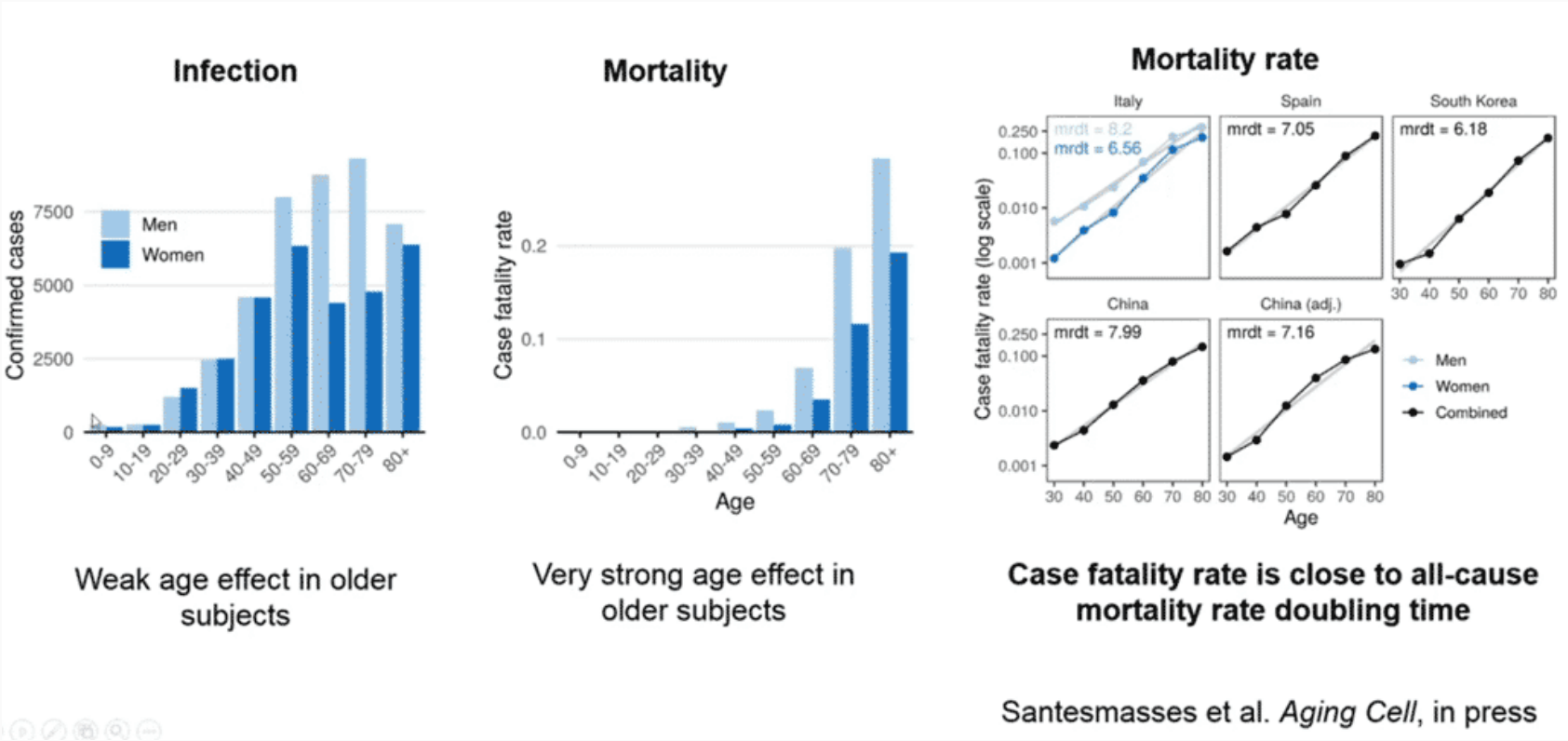
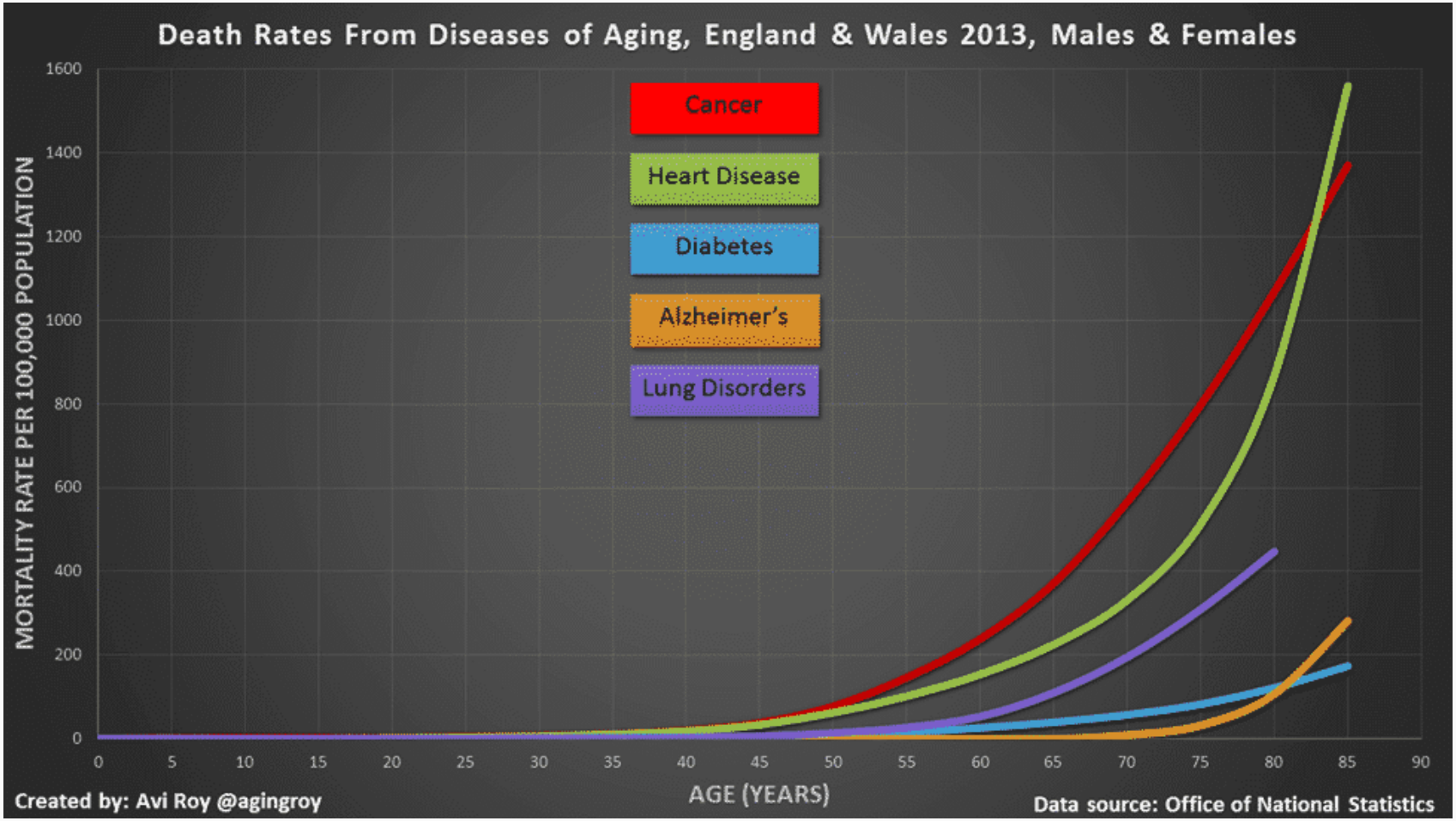
Corona Deaths correlate with Age



[Santesmasses et al., 2020]

Conclusion: They don't die due to Corona, they die due to old age!

All causes for Death correlate with Age



Same with all other primary causes!

Slowing aging has incredible potential

[Kaeberlein, 2019]

And yet it receives less than 1/100th of Funding!

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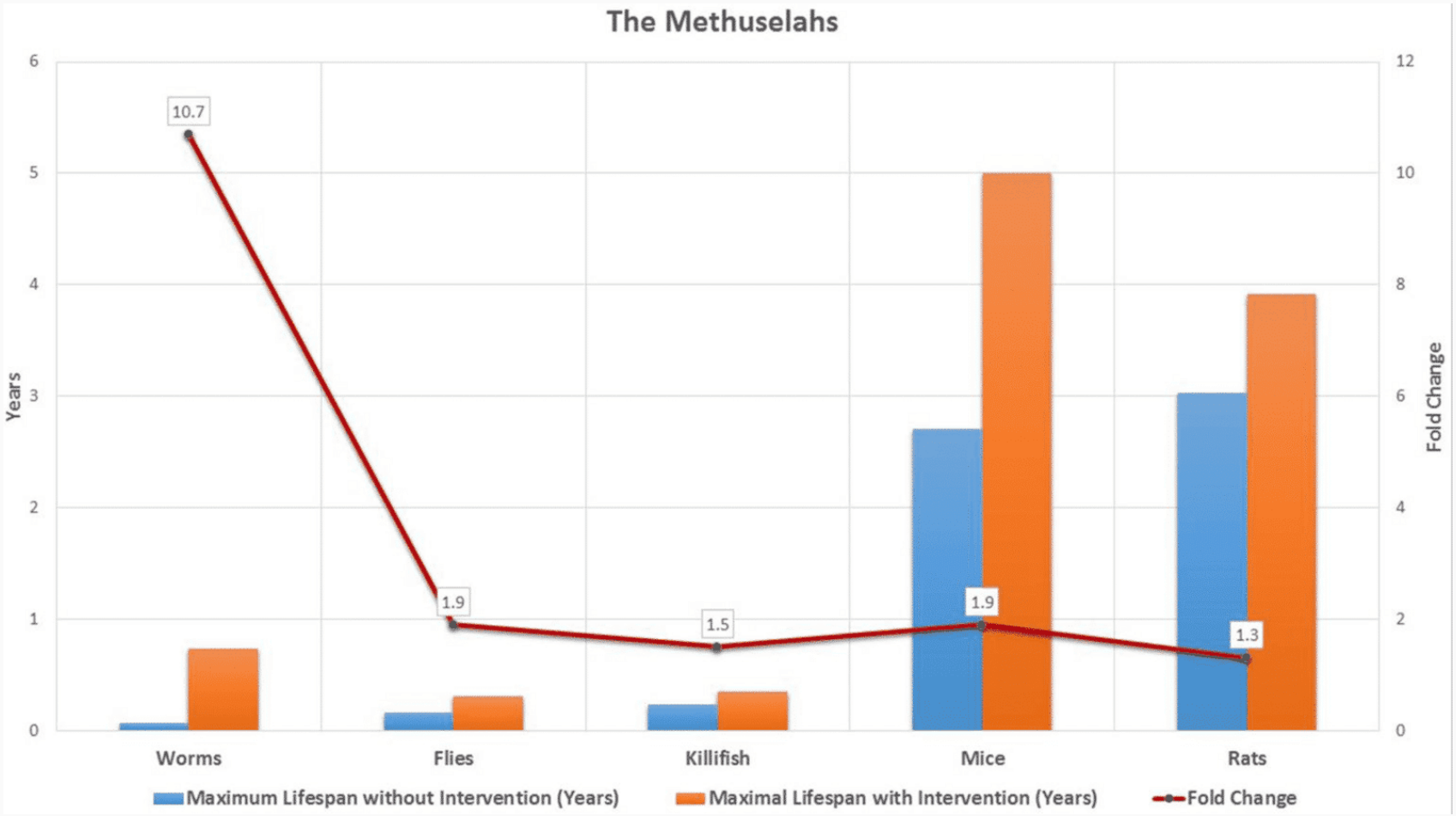
Animals that don't senescence (age)

- hydra (biologically immortal) [Martıñez, 1998]
- naked mole rats [Ruby and Smith, 2018]
- tortoises [Miller, 2001]
- some sharks: 400y [Pennisi, 2016]
- some clams: 500y [Munro and Blier, 2012]

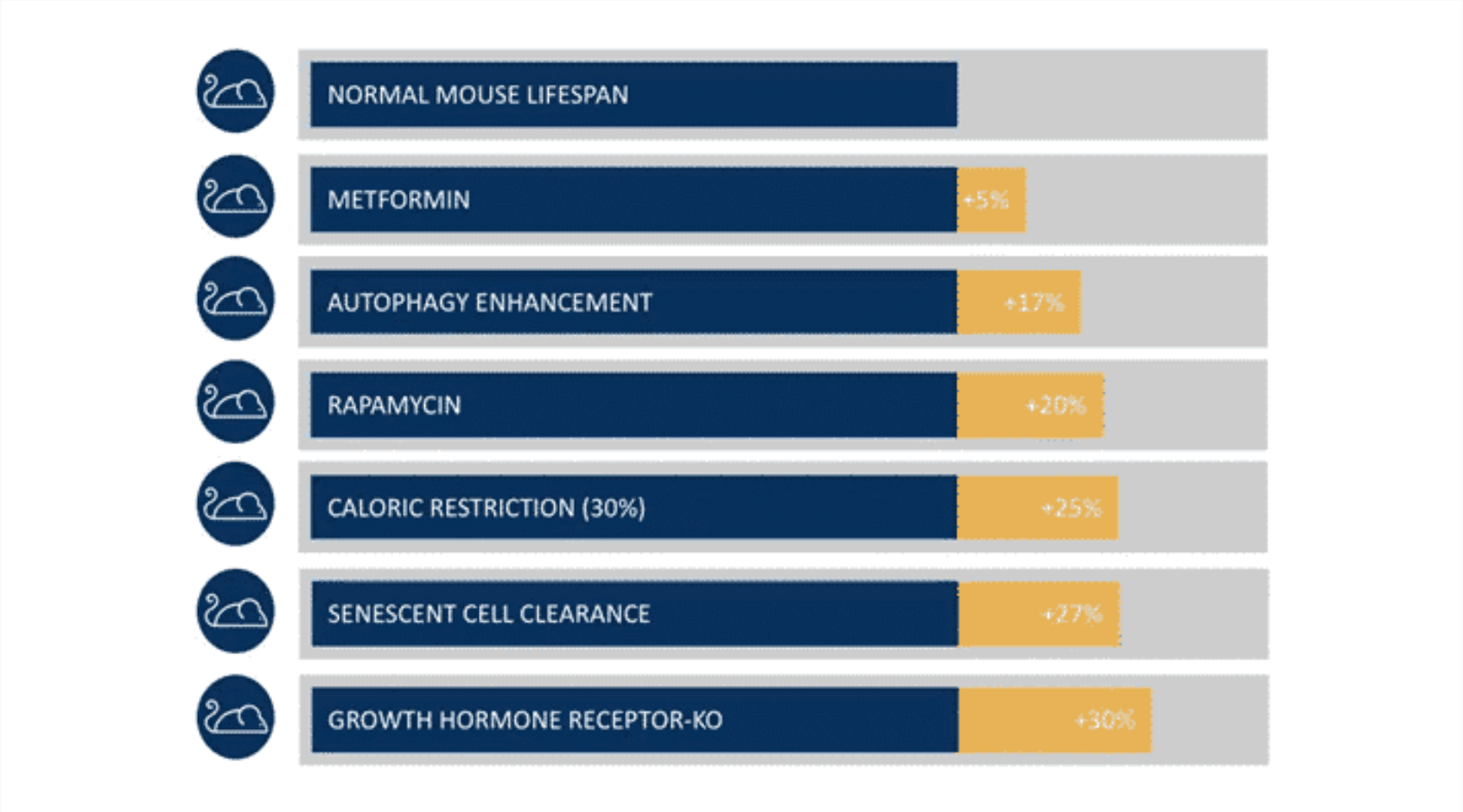
Conclusion: Biological creatures don't *have* to age

Extending Life in different animals



[Bulterijs et al., 2015]

Most effective Mice Treatments



[Brunemeier, 2020]

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What is aging?

Definition and Hallmarks

Effects of harsh conditions

Diseases of Aging

Core Mechanisms

Assumed Root Causes

Open Questions

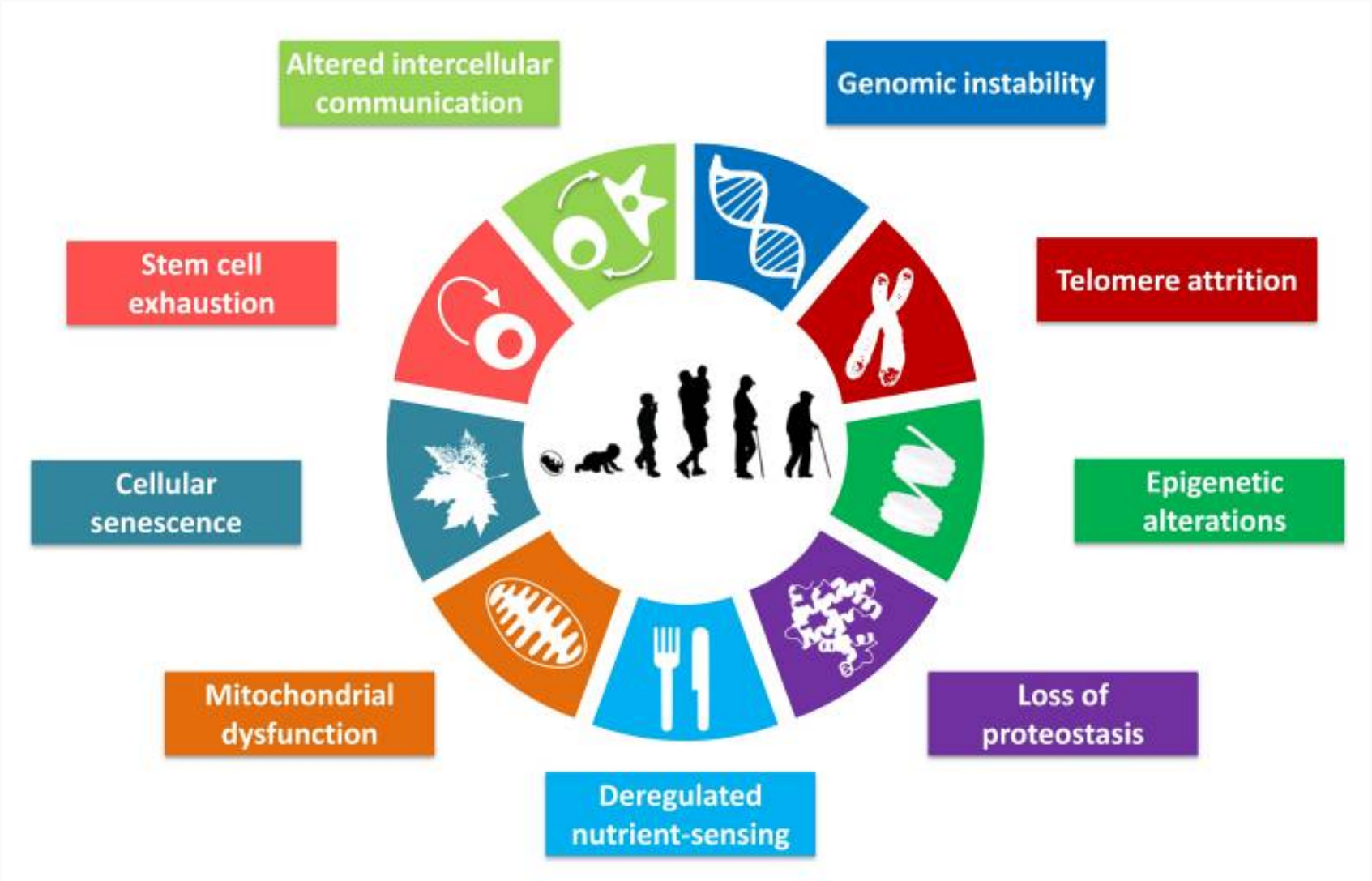
Aging

Definition

Aging is characterized by progressive decline in tissue and organ function and increased risk of mortality. From [Sen et al., 2016]

But how can we measure it?

Hallmarks of Aging



[López-Otín et al., 2013]

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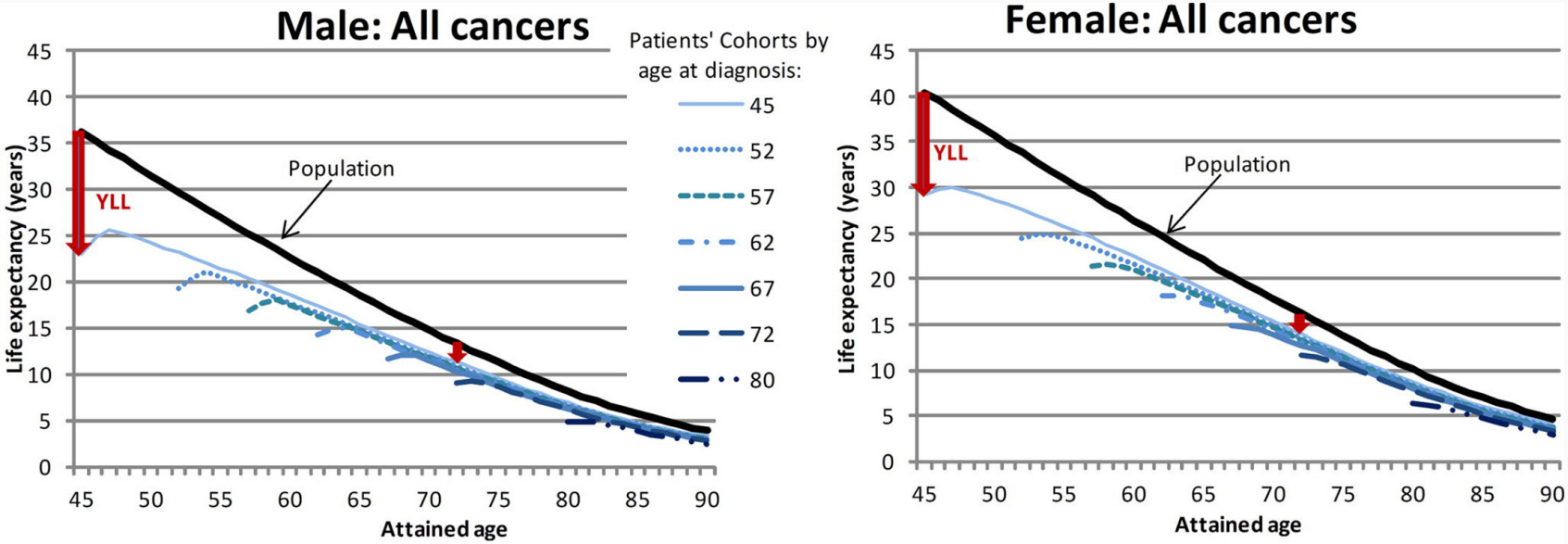
Life Expectancy after Cancer



YLL= Years of life lost, difference between patients' LE and that of the age and sex matched general population

[Botta et al., 2019]

Conclusion: Cancer causes the underlying 'aging clock' to speed up

Life Expectancy with Diabetes

Life Expectancy is at least 10 years lower with Diabetes Type 1 [Livingstone et al., 2015] and at least 5 years lower with Diabetes Type 2 [The British Diabetic Association, 2010].

Conclusion: Diabetes causes the underlying 'aging clock' to speed up

Life Expectancy under Physiological Stress

'There's a qualitative general pattern that various kinds of physiological stress - exposure to radiation or harsh chemicals (including smoking), chronic infection, malnutrition, sleep deprivation, etc - tend to accelerate aging.'

John S Wentworth [Wentworth, 2020]

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Similarities of Diseases of Aging

[Wentworth, 2021] At the cellular level:

- Decrease in cell count
- Increase in damaged proteins/DNA/fats
- Inflammation

Roughly this pattern for:

- Alzheimers
- Arthritis
- Atherosclerosis
- Muscle loss
- Osteoporosis
- Many more

Existence proof for common pathways

'someone who has one severe illness early is likely to have others' John S Wentworth

Most severe illnesses cause the 'aging clock' to speed up. Most diseases of aging have similar characteristics. This is direct evidence that there are *few underlying root causes* for aging.

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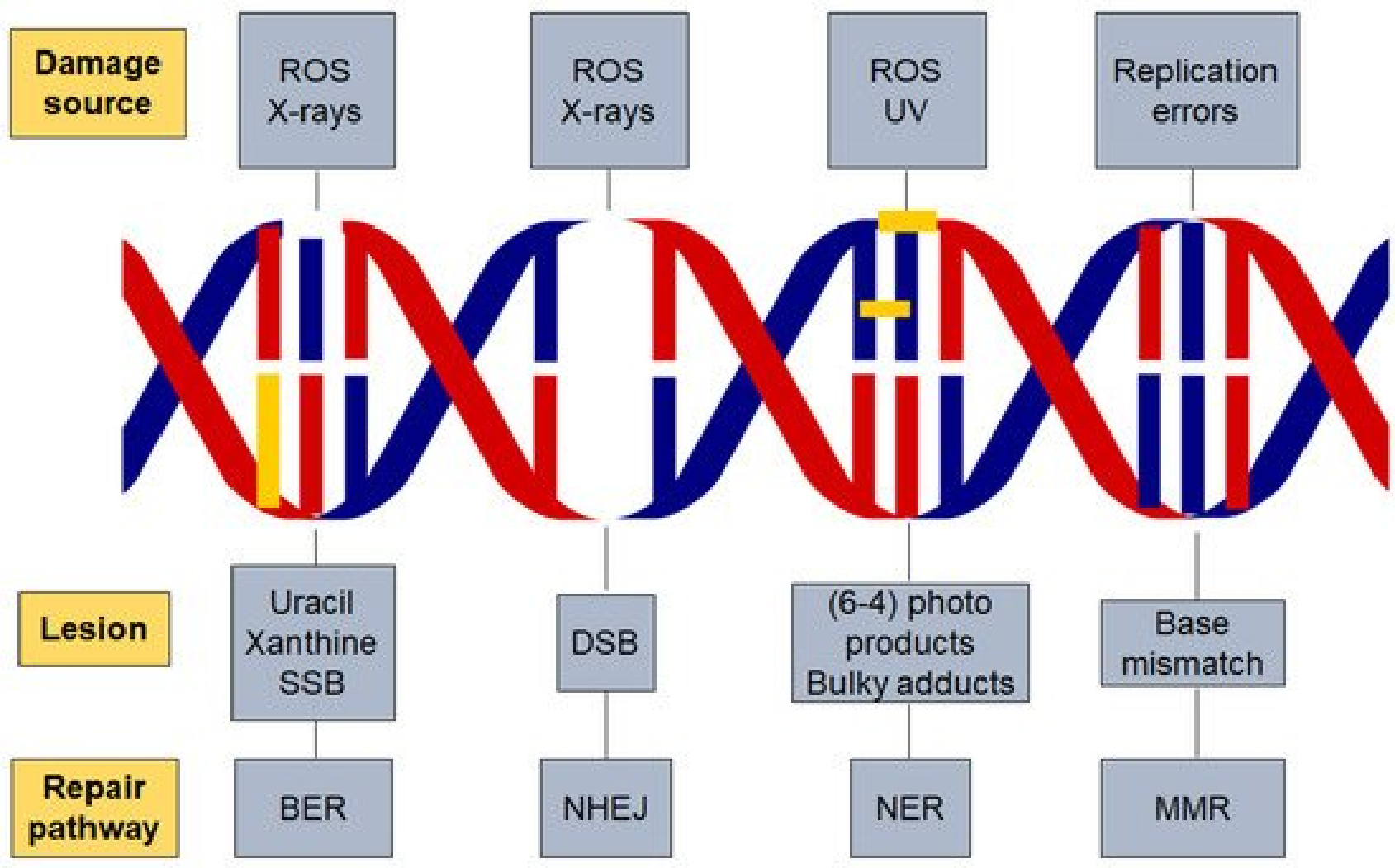
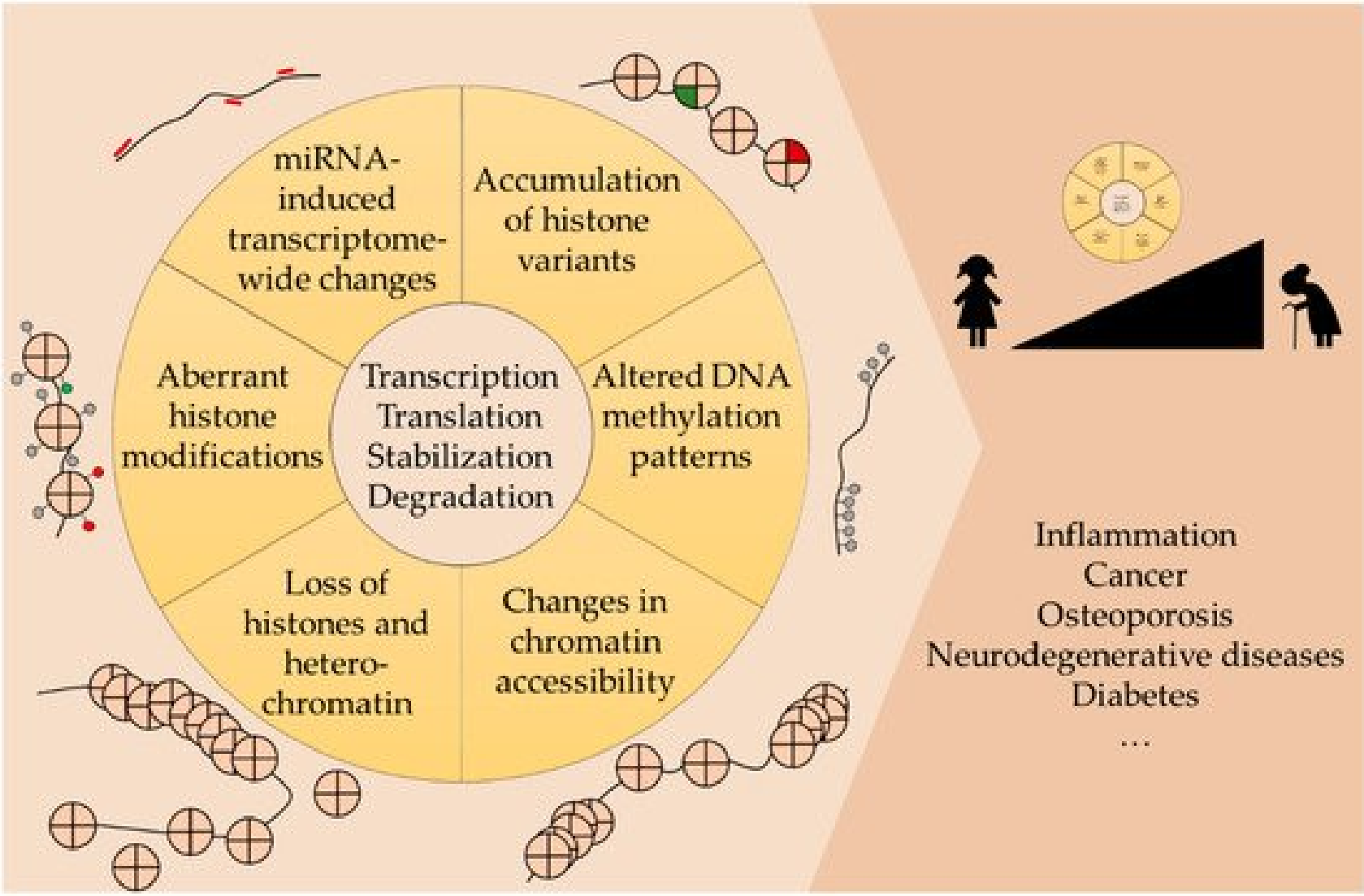
DNA Damage



[Alhmoud et al., 2020]

Epigenetic Information Loss

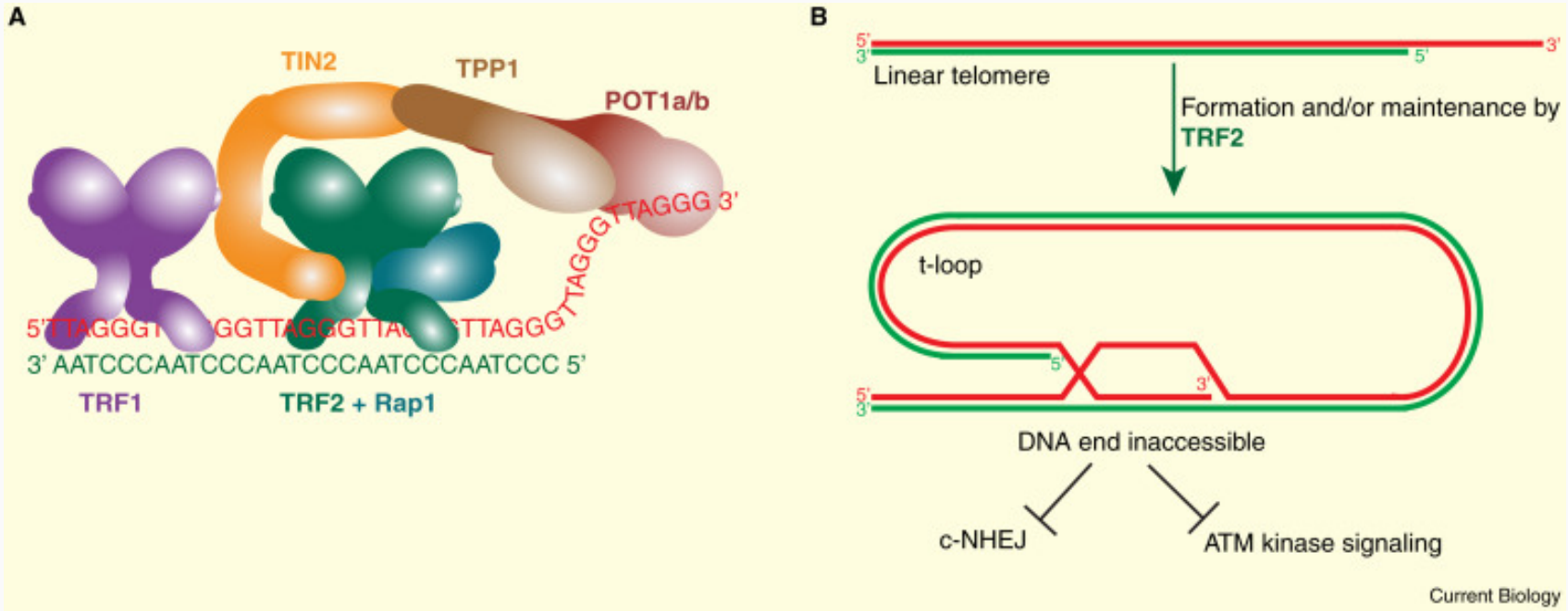


[Saul and Kosinsky, 2021]

Mitochondria

Produce energy, explain fail-state and ROS

Telomeres



[Schmutz and de Lange, 2016]

Telomere attrition

- Telomere length is only really relevant for stem cells, others don't divide
- Telomerase is active in stem cells
- True telomere damage cannot be repaired, so telomeres accumulate damage [Ricón, 2020]
- Short telomeres cause cells to induce apoptosis
- So it's a good measure for total cell damage [Victorelli and Passos, 2017]

Transposons

cause DNA damage, though rather additionally, as species without transposons also age

about 50% of human dna are 'dead' (broken) transposons,

about 100 (of 11 major families) are still active

they are suppressed most of the time, but 'let loose' a bit on other pressing matters (e.g. repairing dna damage)

Cell Senescence

sending out SASP

inflammation due to SASP

induce apoptosis themselves or wait to get removed by immune system

mice: about 8% in young, 17% in old

Timeframes for Pathways

- DNA Damage: Repaired within Hours or faster [Frankenberg-Schwager, 1989]
- Senescent Cells: Removed within Days [Karin et al., 2018]
- Epigenetic Markers: Varies, but most are replaced within Weeks [Ginno et al., 2020] [Yamagata et al., 2012]

Conclusion: Either the amount of Damage/Senescent Cells increases or Reparation/Removal decreases

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Problem: Many Theories

- Everything is interlinked
- Very hard to distinguish cause and effect
- At least one Theory for every Hallmark
- Every prestigious lab has its own Theory
- A lot of speculation on all sides
- Unclear if we can already see the full picture

Disclaimer: Purely Speculation including many Unknowns

Mitochondrial dysfunction

Turns out, mitochondrial dysfunction accounts for telomere-dependent senescence
[Passos et al., 2007].

Assumed root causes: free radicals and transposon damage

Maybe not in too much detail? Could fill 30min itself [Wentworth, 2021]

p21 and reactive oxygen feedback for senescence [Passos et al., 2010]

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Questions Unanswered

- Where are the ROS produced? Mitochondria are the top candidate - there's a known mechanism for ROS production by mitochondria, as well as experimental evidence that mitochondrion-targeted antioxidants specifically reduce ROS-induced damage.
- How do the ROS and/or damaged molecules move between compartments, e.g. nucleus/cytoplasm/extracellular? I have seen very little on this, and consider it a major blindspot. I'm not sure if it's a blindspot for the field or if I just haven't found the right cluster of papers.
- Are the quantitative changes in DNA/protein/fat damage compatible with a single underlying cause? Do they match plausible estimates of ROS from dysfunctional

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Goal

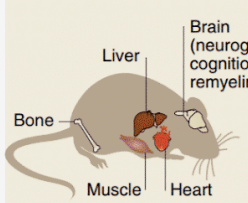
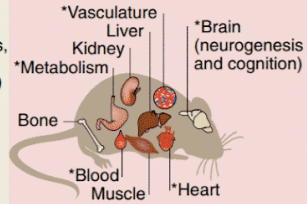
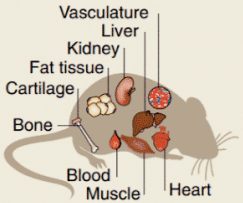
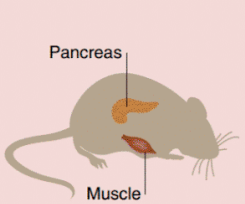
Goal of anti-aging research: stop aging / neglegible senescence
intermediate goals: slow down aging, increase QUALYs (QUality-Adjusted-Life-Years)

Potential strategies

Picture with blood exchange, senolytics, cellular reprogramming and others

full slide for each of them

Comparison

	Blood factors (parabiosis and blood factors)	Metabolic manipulation (diet regimens and dietary restriction mimetics)	Ablation of senescent cells (genetic ablation or senolytic drugs)	Cellular reprogramming (partial reprogramming)
Rejuvenation (WT mice)				
Lifespan extension — WT	Median lifespan: NT Maximum lifespan: NT	Median lifespan: ✓ Maximum lifespan: ✓	Median lifespan: ✓ Maximum lifespan: ✕	Median lifespan: NT Maximum lifespan: NT
Lifespan extension — Premature ageing models	Median lifespan: NT Maximum lifespan: NT	Median lifespan: ✓ Maximum lifespan: ✓ Model: *Lmna*$^{-/-}$ progeroid mice	Median lifespan: ✓ Maximum lifespan: ✓ Model: *BubR1* progeroid mice	Median lifespan: ✓ Maximum lifespan: ✓ Model: *Lmna*^{G608G} progeroid mice
Mode of action	Blood factors	Inhibition of mTOR pathways → mTOR Blood factors? Autophagy?	Elimination of senescent cells	Epigenomic remodelling?
Potential trade-offs	Stem cell exhausion?	Tissue repair impairment Immune response impairment (to infections) Increased risk for amenorrhoea and osteoporosis upon prolonged/severe diet regimens	Tissue-repair impairment Tissue-specific fibrosis? Haematopoietic system toxicity Gastrointestinal tract toxicity	Tumorigenesis Tissue dysfunction from loss of cellular identity?
Translational potential	++ Human umbilical plasma reverts features of ageing in aged mice TIMP2 enriched in human umbilical plasma Eotaxin and β_2-microglobulin levels increase with age in human plasma In clinical trial	+++ Fasting-mimicking diet improves body weight, blood pressure, cholesterol and IGF1 levels and other physiological readouts when applied in humans Rapamycin and metformin improve risk factors associated with cancer, diabetes and cardiovascular disease In clinical trial	++ Senolytics eliminate human senescent cells in vitro In clinical trial	+ Cellular reprogramming erases age-associated features in human cells in vitro

[Mahmoudi et al., 2019]

How can we slow down aging?

Overview

Parabiosis

mTOR Inhibitors

Senolytics

Cellular Reprogramming

Other Approaches

Parabiosis (Blood Exchange)

Parabiosis (heterochronic parabiosis) is putting young blood into old mice, to make the old mice biologically younger. This is achieved in the lab by connecting the circulatory systems of young mice and old mice. Certain factors in the blood help to rejuvenate muscle, heart brain and liver tissues in old mice and restore their biological function.

Equivalent procedures that modify the compounds within blood in humans such as apheresis (blood filtering) could be used to slow aging in humans and thereby prevent or slow the progression of many types of age-related diseases including Alzheimer's disease.

Recently, a group of Russian biohackers recently took part in the first plasma dilution experiments in humans. In a research

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mTOR Inhibitors (Metabolic manipulation)

Dietary restriction has been shown to extend healthy lifespan across several species. Drugs that mimic the metabolic effects of dietary restriction also have beneficial effects on lifespan. Nutrient-sensing biochemical pathways (such as IGF-1, mTOR and AMPK) play a key role in these effects. Metformin is a drug that is FDA-approved for diabetes that extends healthy lifespan in mice by inhibiting mTOR and activating autophagy. Metformin is currently being tested in a large clinical trial in humans to test its anti-aging properties.

Source: here Hallmarks of aging targeted: The widespread mechanisms of action of metformin help to improve all of the 9 hallmarks of aging, shown below. I'll save the details for those interested, who can read a more thorough review here.

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Overview

Parabiosis

mTOR Inhibitors

Senolytics

Cellular Reprogramming

Other Approaches

Senolytics (Drugs killing senescent cells)

Senescent cells are a kind of 'zombie'-like cell that accumulate with age. They are death-resistant cells that secrete proinflammatory factors associated with a range of age-related diseases (below, right):

Cellular senescence is associated with multiple human disorders. The development of galactose-conjugated and fluorescent probes to detect and highlight senescent cells offers an important opportunity for longitudinal monitoring of senescence in clinical trials. Pharmacologically active small compounds known as senolytics inhibit pro-survival pathways in senescent cells leading to apoptosis, a therapeutic strategy that may additionally be enhanced by the use of immune modulators promoting natural clearance of senescent cells. Finally, nanoparticles encapsulating cytotoxic drugs, tracers

How can we slow down aging?

Cellular Reprogramming

Cellular reprogramming is the conversion of terminally differentiated cells (old cells) into induced pluripotent stem cells (IPSCs) ('young' cells). Cells can be re-programmed to a youthful state using a cocktail of 4 factors known as Yamanaka factors, a finding for which a Nobel prize was awarded in 2012.

Induced pluripotent stem cells (IPSCs) have essentially unlimited regenerative capacity and carry the promise for tissue replacement to counter age-related decline. Partial reprogramming in mice has shown promising results in alleviating age-related symptoms without increasing the risk of cancer.

(A) The diagram depicts cellular programming to pluripotency, in other words, the conversion of terminally differentiated

How can we slow down aging?

Other Approaches

Although not covered here, there are many other promising strategies for rejuvenation including thymic rejuvenation which has been shown to reverse biological age in humans, sirtuin enzyme activation with drugs such as resveratrol, and boosting mitochondrial function with NAD+ precursor molecules. All of these show the potential to increase healthy lifespan by targeting the hallmarks of aging.

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Pharmacological

Some medicaments: Not medical advice!

- Metformin - calorie restriction mimetic that controls blood sugar
- Quercetin - anti-aging flavenoid that acts as a senolytic
- Resveratrol - sirtuin enzyme activator and calorie restriction mimetic
- Vitamin D - blood tested to optimize, ideally 2000IU per day
- Vitamin B12 - as many people are deficient

On the more extreme end (for older people or people with a higher risk tolerance):

- Rapamycin - an mTOR inhibitor that attenuates senescence

Lifestyle

Exercise, low-calorie-diet, others

Research!

A lot to be done, just see what you can do

Donate!

A lot of money is needed

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How can bioinformatics help?

- **Analysis**
- Simulation

Analysis

Large datasets, ever-more data

Analysis

Will need new tools and software

How can bioinformatics help?

Analysis

Simulation

Simulation

current Pharmaceutical battle: better simulator

Simulation II

AlphaFold2 and others

Questions?

Sources i

Alhmoud, J. F., Woolley, J. F., Moustafa, A.-E. A., and Malki, M. I. (2020).
DNA damage/repair management in cancers.
Cancers, 12(4):1050.

Botta, L., Dal Maso, L., Guzzinati, S., Panato, C., Gatta, G., Trama, A., Rugge, M., Tagliabue, G., Casella, C., Caruso, B., et al. (2019).
Changes in life expectancy for cancer patients over time since diagnosis.
Journal of advanced research, 20:153–159.

Sources ii

- Brunemeier, S. (2020).
  Geroscience and Biotech Venture Capital - YouTube.
  https://www.youtube.com/watch?v=AM97A_5jFgk&t=645s.
  (Accessed on 2021-05-26).
- Bulterijs, S., Hull, R. S., Björk, V. C., and Roy, A. G. (2015).
  It is time to classify biological aging as a disease.
  Frontiers in genetics, 6:205.

Sources iii


Frankenberg-Schwager, M. (1989).
Review of repair kinetics for DNA damage induced in eukaryotic cells in vitro by ionizing radiation.
Radiotherapy and oncology, 14(4):307–320.


Ginno, P. A., Gaidatzis, D., Feldmann, A., Hoerner, L., Imanci, D., Burger, L., Zilbermann, F., Peters, A. H., Edenhofer, F., Smallwood, S. A., et al. (2020).
A genome-scale map of DNA methylation turnover identifies site-specific dependencies of DNMT and TET activity.
Nature communications, 11(1):1–16.

Sources iv


Kaeberlein, M. (2019).
It is Time to Embrace 21st-Century Medicine.
Public Policy & Aging Report, 29(4):111–115.


Karin, O., Agrawal, A., Porat, Z., Krizhanovsky, V., and Alon, U. (2018).
Senescent cells and the dynamics of aging.
bioRxiv, page 470500.

Sources v

Livingstone, S. J., Levin, D., Looker, H. C., Lindsay, R. S., Wild, S. H., Joss, N., Leese, G., Leslie, P., McCrimmon, R. J., Metcalfe, W., et al. (2015).
Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010.
Jama, 313(1):37–44.

López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., and Kroemer, G. (2013).
The hallmarks of aging.
Cell, 153(6):1194–1217.

Sources vi

Mahmoudi, S., Xu, L., and Brunet, A. (2019).
Turning back time with emerging rejuvenation strategies.
Nature cell biology, 21(1):32–43.

Martıñez, D. E. (1998).
Mortality patterns suggest lack of senescence in hydra.
Experimental gerontology, 33(3):217–225.

Sources vii


Miller, J. (2001).
Escaping senescence: demographic data from the three-toed box turtle (Terrapene carolina triunguis).

Experimental Gerontology, 36(4-6):829–832.


Munro, D. and Blier, P. U. (2012).
The extreme longevity of Arctica islandica is associated with increased peroxidation resistance in mitochondrial membranes.
Aging cell, 11(5):845–855.

Sources viii

Passos, J. F., Nelson, G., Wang, C., Richter, T., Simillion, C., Proctor, C. J., Miwa, S., Olijslagers, S., Hallinan, J., Wipat, A., et al. (2010).
Feedback between p21 and reactive oxygen production is necessary for cell senescence.
Molecular systems biology, 6(1):347.

Passos, J. F., Saretzki, G., Ahmed, S., Nelson, G., Richter, T., Peters, H., Wappler, I., Birket, M. J., Harold, G., Schaeuble, K., et al. (2007).

Sources ix

Mitochondrial dysfunction accounts for the stochastic heterogeneity in telomere-dependent senescence.
PLoS Biol, 5(5):e110.

Pennisi, E. (2016).
Greenland shark may live 400 years, smashing longevity record — Science — AAAS.
https://www.sciencemag.org/news/2016/08/greenland-shark-may-live-400-years-smashing-longevi

(Accessed on 2021-05-24).

Sources x

- Ricón, J. L. (2020).
  Nintil - The Longevity FAQ.
  https://nintil.com/longevity.
  (Accessed on 2021-06-01).
- Ruby, J. G. and Smith, M. (2018).
  Naked mole-rat mortality rates defy Gompertzian laws by not increasing with age.
  elife, 7:e31157.

Sources xi

- Santesmasses, D., Castro, J. P., Zenin, A. A., Shindyapina, A. V., Gerashchenko, M. V., Zhang, B., Kerepesi, C., Yim, S. H., Fedichev, P. O., and Gladyshev, V. N. (2020). **COVID-19 is an emergent disease of aging.** *Aging Cell*, 19(10):e13230.
- Saul, D. and Kosinsky, R. L. (2021). **Epigenetics of Aging and Aging-Associated Diseases.** *International Journal of Molecular Sciences*, 22(1):401.

Sources xii


Schmutz, I. and de Lange, T. (2016).
Shelterin.
Current Biology, 26(10):R397–R399.


Sen, P., Shah, P. P., Nativio, R., and Berger, S. L. (2016).
Epigenetic mechanisms of longevity and aging.
Cell, 166(4):822–839.


Szekely, A. M., Bleichert, F., Nümann, A., Van Komen, S., Manasanch, E., Nasr, A. B., Canaan, A., and Weissman, S. M. (2005).
Werner protein protects nonproliferating cells from oxidative DNA damage.

Molecular and cellular biology, 25(23):10492.


The British Diabetic Association (2010).
Diabetes in the UK 2010: Key statistics on diabetes.
https://www.diabetes.org.uk/resources-s3/2017-11/diabetes_in_the_uk_2010.pdf.
(Accessed on 2021-05-27).


Victorelli, S. and Passos, J. F. (2017).
Telomeres and cell senescence-size matters not.
EBioMedicine, 21:14–20.

Sources xiv

Wentworth, J. S. (2020).
Homeostasis and "Root Causes" in Aging - LessWrong.
https://www.lesswrong.com/s/3hfjaztptwEt2cCve/p/d4DvqS88Q29ZaJAj3?commentId=RuF49JiWpbEHXdMrw.
(Accessed on 2021-05-31).

Wentworth, J. S. (2021).
Core Pathways of Aging - LessWrong.
https://www.lesswrong.com/posts/ui6mDLdqXkaXiDMJ5/core-pathways-of-aging.
(Accessed on 2021-05-26).

Sources xv


Yamagata, Y., Szabó, P., Szüts, D., Bacquet, C., Arányi, T., and Páldi, A. (2012).
Rapid turnover of DNA methylation in human cells.
Epigenetics, 7(2):141–145.

Additional

Additional

Speeding up Aging

Werner Syndrome

- 'Premature aging', median age of death: 47
- Autosomal Recessive (does not affect carrier)
- Caused by mutation in WRN gene
- WRN important for DNA-Repair, especially after oxidative damage [Szekely et al., 2005]

Artifially speed up aging

Study with mice injected restriction enzyme activate with drug to induce repeated DNA damage, they age considerably faster. Same with knocking out SIRT1 and others