

# Anti-Aging: State of the Art

---

Felix Karg

22. Juli 2021

Seminar Bioinformatics



## **Introduction**

**What is Aging?**

**How can we Slow down Aging?**

**What can I do?**

**Where can Bioinformatics Help?**

## **Conclusion**

# **Introduction**

**What is Aging?**

**How can we Slow down Aging?**

**What can I do?**

**Where can Bioinformatics Help?**

# **Conclusion**

# Goals for this Talk

You know ...

- What aging is
- Why it is a problem
- Why it is not necessary
- What current approaches are
- About personal anti-aging strategies
- How bioinformatics can help future research

**What are you interested in?**

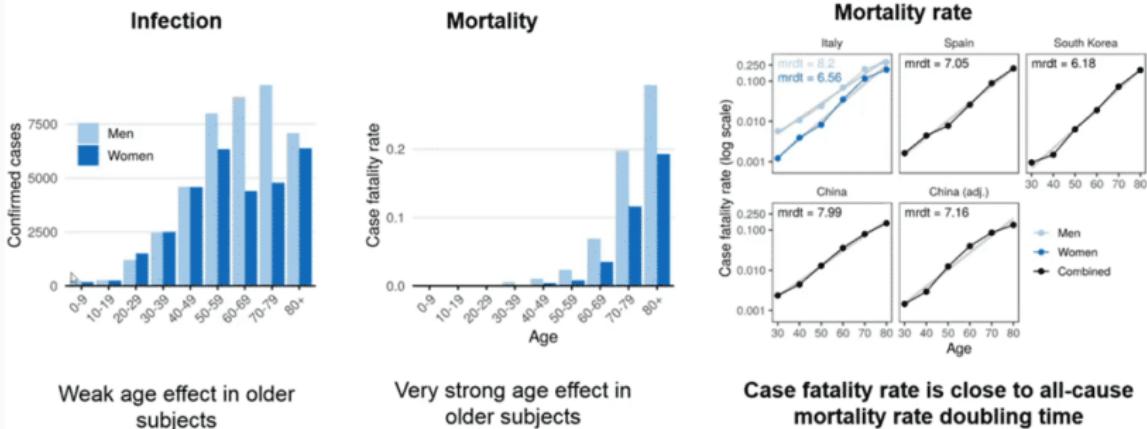
# Introduction

---

Why is Aging a Problem?

Is Aging Necessary?

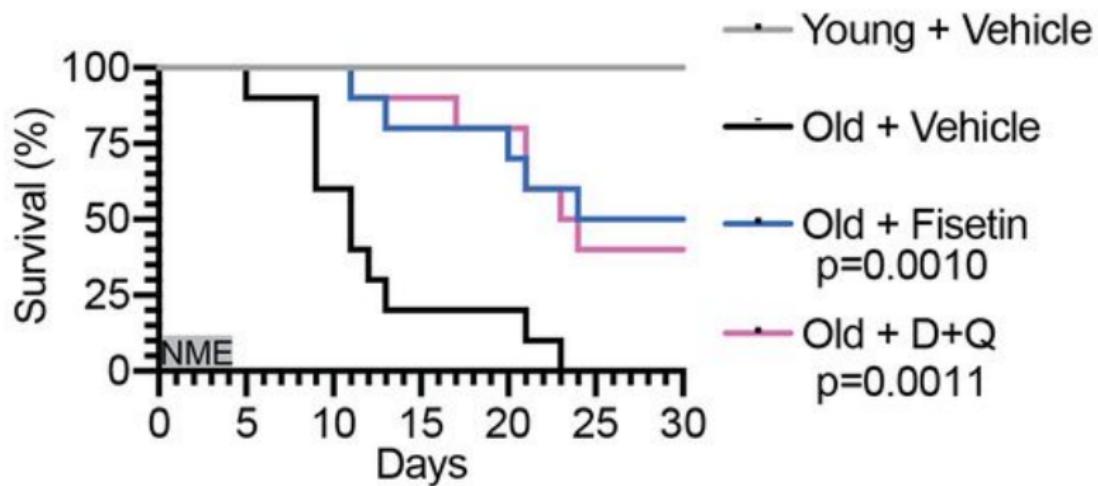
# Corona Deaths correlate with Age



Source: [Santesmasses et al., 2020]

Santesmasses et al. *Aging Cell*, in press

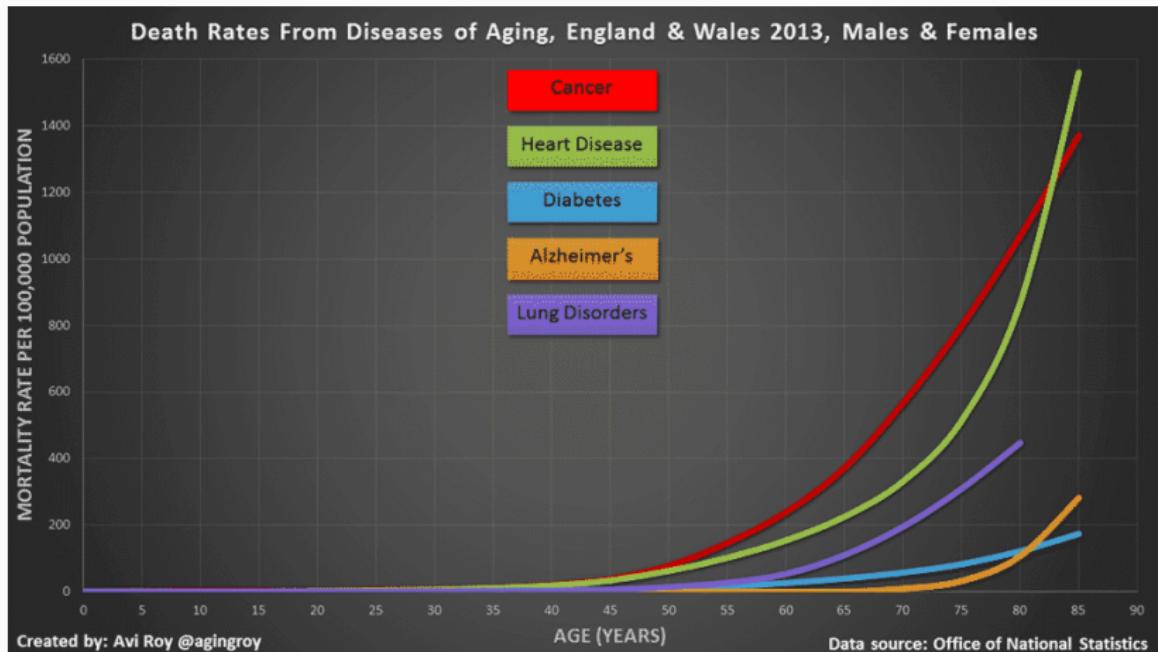
# Treating Corona with Senolytics (anti-aging approach) in Mice



Source: [Camell et al., 2021]

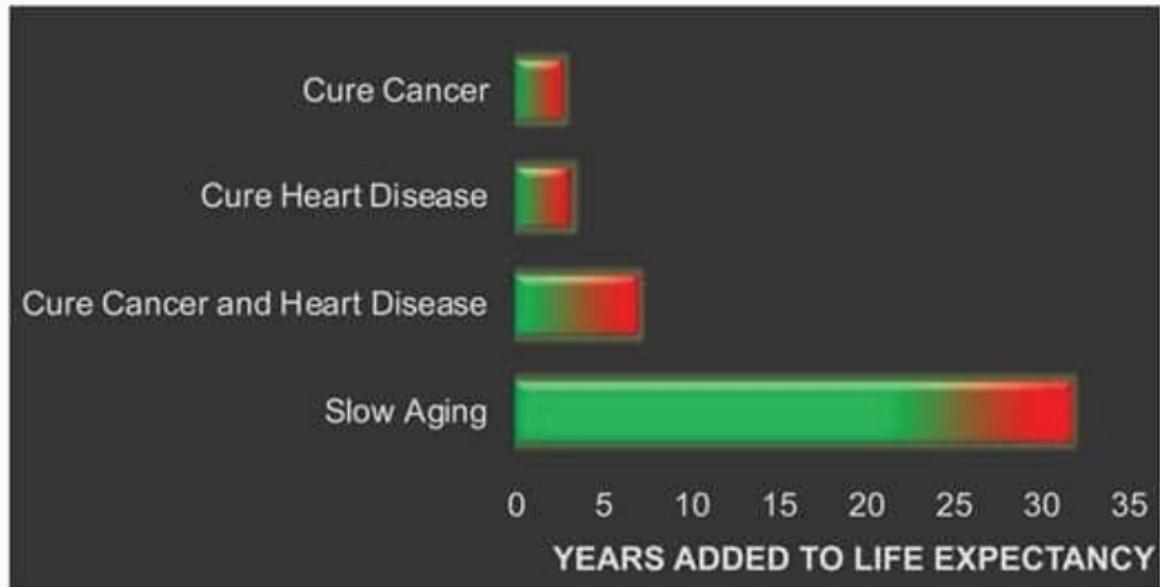
Hypothesis: They die due to old age, not Corona!

# All causes for Death correlate with Age



Same with all other primary causes!

# Slowing aging has incredible potential



Source: [Kaeberlein, 2019]

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

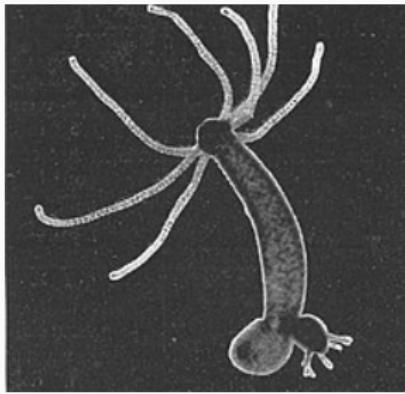
# **Introduction**

---

Why is Aging a Problem?

Is Aging Necessary?

# Animals that do not senesce (age)



Hydra (biologically immortal)  
[Martínez, 1998]



Greenland sharks: 400y [Pennisi, 2016]



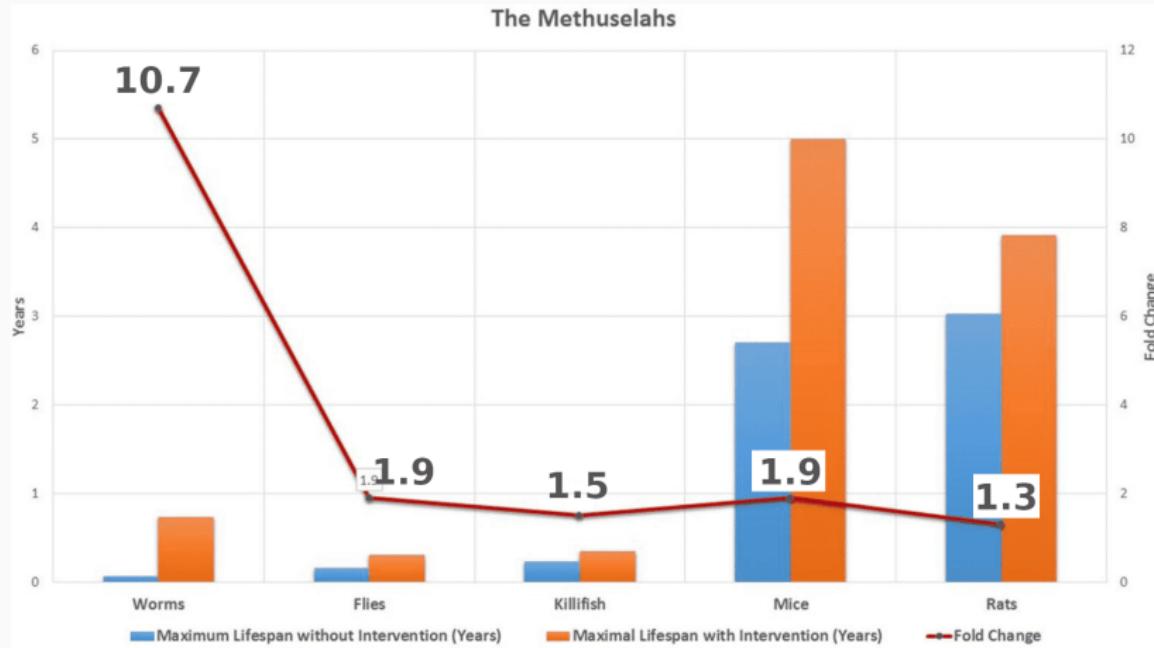
Naked Mole Rats  
[Ruby and Smith, 2018], Picture (CC BY-SA 3.0): [Klementschitz, 2003]



Tortoises [Miller, 2001], Picture (CC BY-SA 3.0): [Childzy, 2008]

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

# Extending Life in different animals



Source: [Bulterijs et al., 2015]

It is possible to extend biological Lifespan!

Introduction

**What is Aging?**

How can we Slow down Aging?

What can I do?

Where can Bioinformatics Help?

Conclusion

# What is Aging?

---

## Definition and Hallmarks

Problematic: Many Unknowns

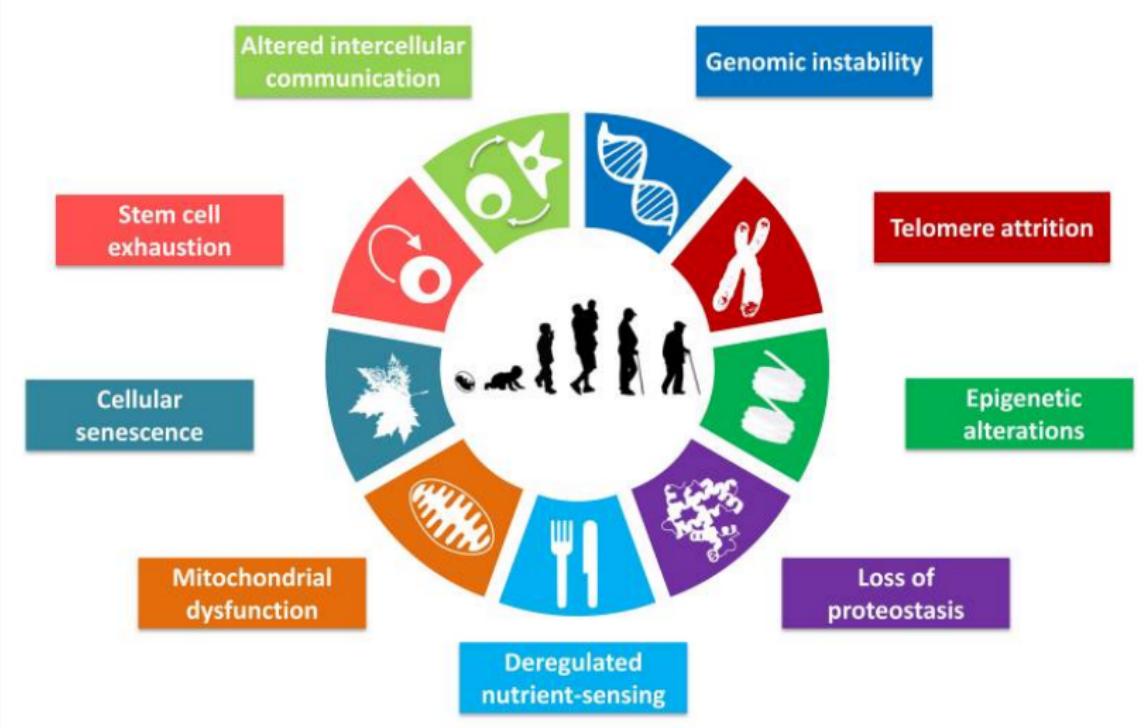
# Aging

## Definition [Sen et al., 2016]

Aging is characterized by progressive decline in tissue and organ function and increased risk of mortality.

But how can we measure it?

# Hallmarks of Aging: Measuring biological Age



Source: [López-Otín et al., 2013]

# **What is Aging?**

---

Definition and Hallmarks

**Problematic: Many Unknowns**

## 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 most sides
- Unclear if we can already see the full picture
- More research is needed

**Disclaimer: Any misrepresentation or  
mistaken interpretation is due to my  
shortcomings**

**Introduction**

**What is Aging?**

**How can we Slow down Aging?**

**What can I do?**

**Where can Bioinformatics Help?**

**Conclusion**

# How can we Slow down Aging?

---

Overview

Parabiosis

Metabolic Manipulation

Senolytics

Cellular Reprogramming

Other Approaches

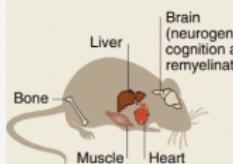
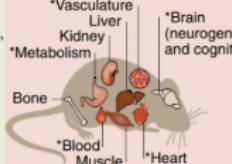
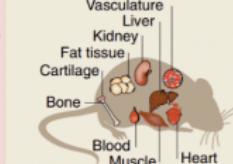
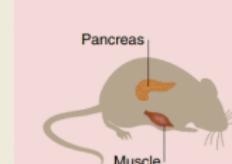
# Goal of Anti-Aging Research

---

As I understand it, the goal of anti-aging research is  
**the extension of the human lifespan.**

Ideally by stopping aging or achieving negligible senescence. Intermediate goals include slowing down aging, and increasing QALYs (Quality-Adjusted-Life-Years).

# Potential Strategies to Slow down Aging

	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
	Premature aging models	Median lifespan NT Maximum lifespan NT	Median lifespan ✓ Maximum lifespan ✓ Model: <i>Lmna</i> <sup>Δex7</sup> progeroid mice	Median lifespan ✓ Maximum lifespan ✓ Model: <i>BubR1</i> progeroid mice	Median lifespan ✓ Maximum lifespan ✓ Model: <i>Lmna</i> <sup>G60G6</sup> progeroid mice
Translational potential		++  Human umbilical plasma reverts features of ageing in aged mice  TIMP2 enriched in human umbilical plasma  Eotaxin and $\beta_2$ -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	

Source: [Mahmoudi et al., 2019], picture modified

# How can we Slow down Aging?

---

Overview

**Parabiosis**

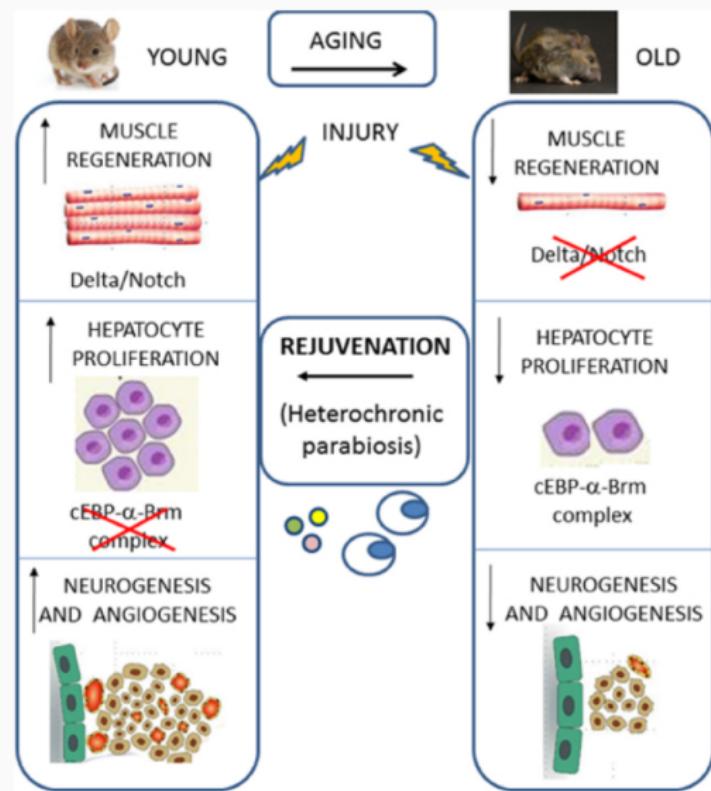
Metabolic Manipulation

Senolytics

Cellular Reprogramming

Other Approaches

# Parabiosis (Blood Exchange)



Source: [Conese et al., 2017]

## Method Evaluation: Parabiosis

### Hallmarks affected:

*'In principle, the heterochronic parabiosis reverts all phenotypic and molecular hallmarks of ageing by transferring soluble factors and cells.'* [Conese et al., 2017]

Alternatives: Blood Filtering and (Growth)

Hormone Therapy.

**Status:** In clinical trial, e.g. [Alkahest, 2020].

# How can we Slow down Aging?

---

Overview

Parabiosis

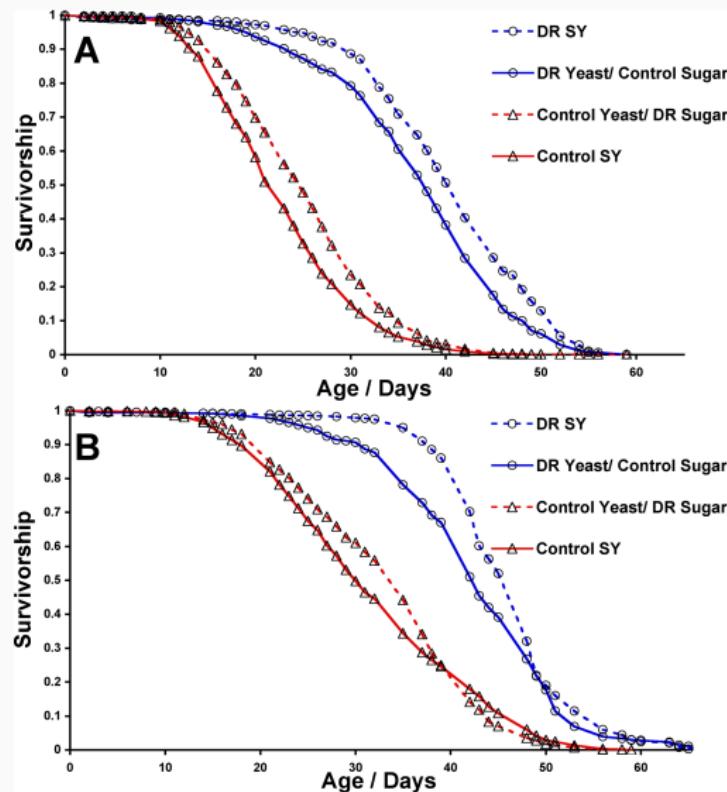
**Metabolic Manipulation**

Senolytics

Cellular Reprogramming

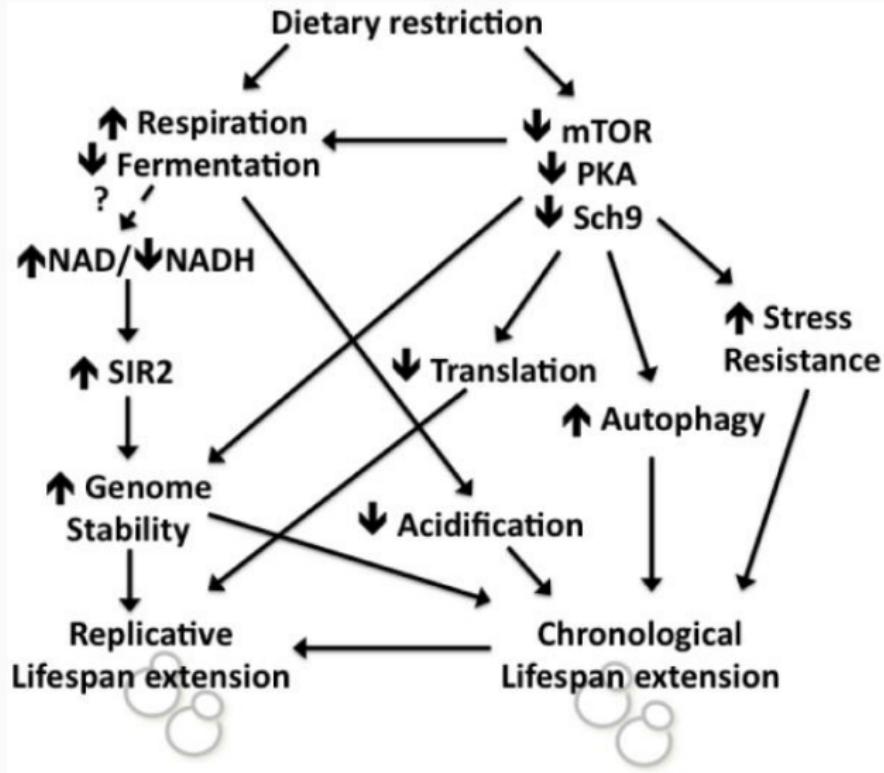
Other Approaches

# Dietary Restriction in *D. melanogaster* (Fruit Fly)



Source: [Mair et al., 2005]

# Dietary Restriction Pathways in Yeast



Source: [Kapahi et al., 2017]

# Dietary Restriction Effects

- 'Different' mitochondrial energy production (less ROS)
- Reduced protein synthesis, no dna duplication
- Increased repair capacity (SIRT and others)
- Increased removal of misfolded proteins
- Reduced intracellular (oxidative) stress
- Reduced inflammation and proliferation

Overall: Optimizing energy and resource usage

# Inhibiting mTOR receptors

---

Nutrient-Sensing pathways:

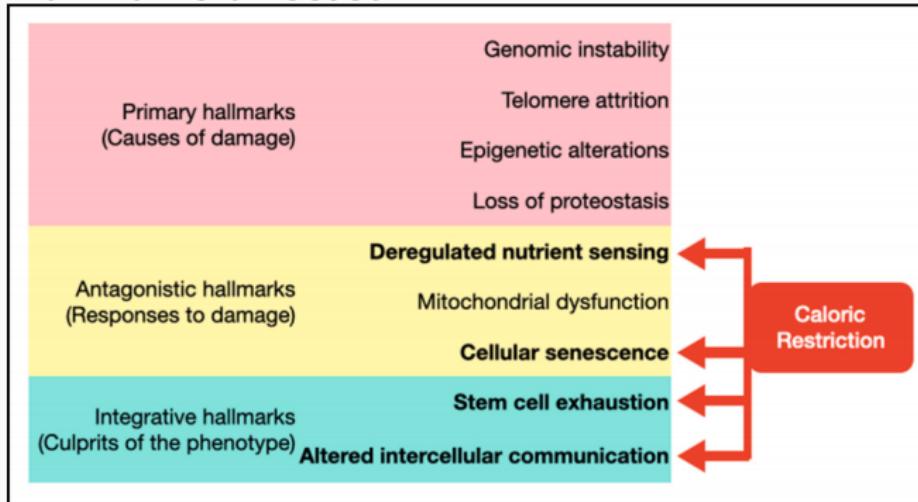
- AMPK
- mTOR
- IGF-1

Medications **in trial** to affect these pathways:

- Metformin [TAME, 2021]
- Rapamycin [AgelessRx, 2020]
- Many more ...

# Method Evaluation: Metabolic Manipulation

## Hallmarks affected:



Source: [Erbaba et al., 2020]

Lifespan extension: about 20-40% QALY [Swindell, 2012]

**State:** In clinical trial, e.g. [TAME, 2021]

# How can we Slow down Aging?

---

Overview

Parabiosis

Metabolic Manipulation

**Senolytics**

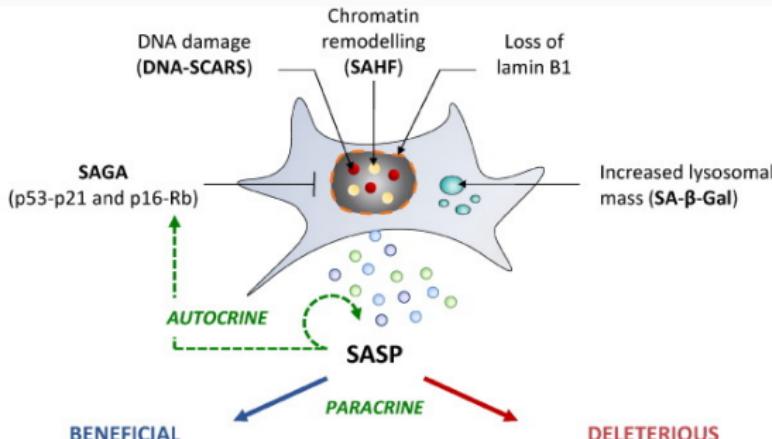
Cellular Reprogramming

Other Approaches

# Senescent Cells: What are they?

- Old or (partially) damaged cells
- Sending out Senescence-Associated Secretory Phenotype (SASP)
- SASP causes inflammation and age-related diseases, e.g. Arthritis, Atherosclerosis
- Cells induce apoptosis (suicide) or wait to get removed by immune system
- About 8% of cells in young, and 17% of cells in old mice are senescent [Folgueras et al., 2018]

# Senescent Cell Effects



Embryonic development



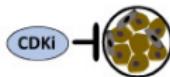
- Patterning
- Macrophage recruitment (clearance)

Wound healing



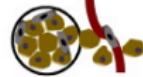
- Resolution of fibrotic scar
- Immune cell attraction
- Mobilisation of stem cells

Cancer suppression



- Reinforcement of senescence
- Immune clearance

Cancer progression



- Promotion of cancer cell aggressiveness
- Niche of chemoresistance
- Angiogenesis

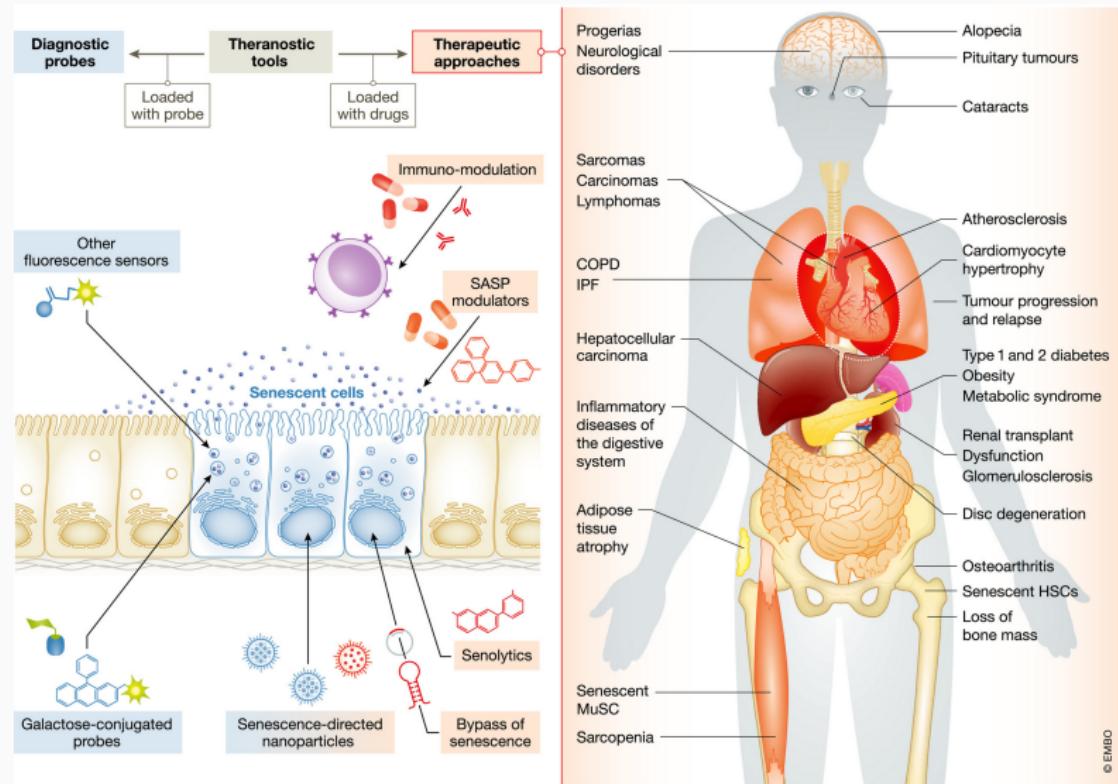
Aging



- Tissue dysfunction
- Chronic Inflammation
- Age-related diseases (e.g. Alzheimer, osteoarthritis, etc.)

Source: [Malaquin et al., 2016]

# Senolytics: Uses and Effects



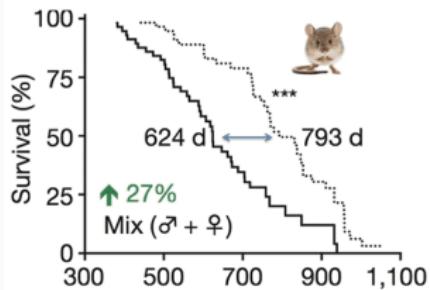
Source: [Paez-Ribes et al., 2019]

# Method Evaluation: Senolytics

## Hallmarks affected:

- Decelerate Cellular Senescence
- Improve Epigenetic Markers
- Restore Intercellular Communication (by reducing inflammation associated with senescent cells)

Lifespan extension: 27% median Life



Source: [Baker et al., 2016]

**State: In clinical trial**

# How can we Slow down Aging?

---

Overview

Parabiosis

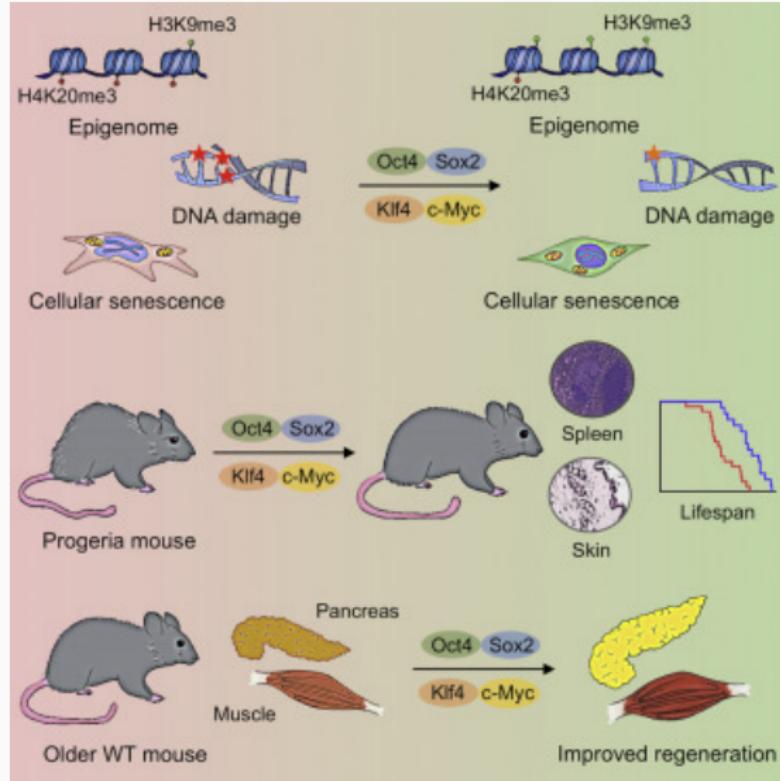
Metabolic Manipulation

Senolytics

**Cellular Reprogramming**

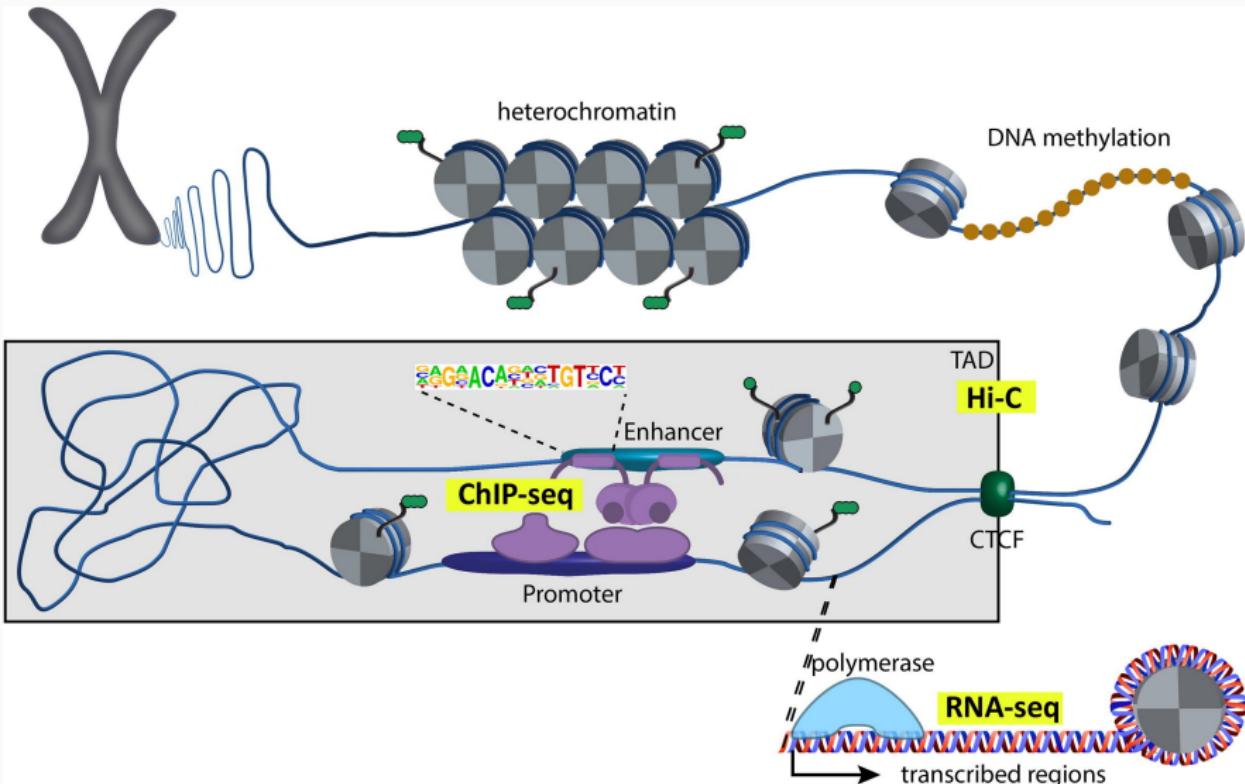
Other Approaches

# (Epigenetic) Cellular Reprogramming: What is it?



Source: [Ocampo et al., 2016]

# Epigenetics: What is it?



Source: [Höllbacher et al., 2020]

## (Epigenetic) Cellular Reprogramming: What is it?

---

- Basically: reset the corroding Epigenetic state to a 'younger' and functional one
- In fact, we can create induced pluripotent stem cells (iPSC) [Takahashi and Yamanaka, 2006]
- Cells activated with Yamanaka-factors are indistinguishable (regarding aging-hallmarks) from younger versions of themselves
- Idea: only activate them long enough to reverse aging hallmarks, but keep cell identity
- Seems to complement well with senolytics [Ofenbauer and Tursun, 2019]

# Method Evaluation: Cellular Reprogramming

---

## Hallmarks affected:

- Mitochondrial Dysfunction
- Shortening of Telomere length
- Changes in Epigenetic markers
- Genomic Instability
- Cellular Senescence

Lifespan extension: maximum by 20% and median by 33% [Ocampo et al., 2016]

**State: in clinical trial**

# **How can we Slow down Aging?**

---

Overview

Parabiosis

Metabolic Manipulation

Senolytics

Cellular Reprogramming

**Other Approaches**

## Other Promising Approaches

---

- Thymic rejuvenation has been shown to reverse biological age in humans [Fahy et al., 2019]
- Sirtuin enzyme activation  
[Mohar and Malik, 2012]
- Boosting mitochondrial function with NAD+ precursor molecules [Aman et al., 2018]
- Identifying genetic Markers [Kenyon, 2010]
- Many more ...

## Method Evaluation: Other Approaches

---

**Hallmarks affected:** ???

Lifespan extension: Most 5%-40%

State: Active research, some in animal or clinical trials

## Introduction

What is Aging?

How can we Slow down Aging?

**What can I do?**

Where can Bioinformatics Help?

## Conclusion

# What can I do?

---

Pharmacological  
Lifestyle

**This is NOT Medical Advice!**

# Pharmacological

---

List of medications taken regularly by anti-aging researchers:

- Metformin - calorie restriction mimetic that controls blood sugar
- Quercetin - anti-aging flavonoid 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

## Pharmacological II

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

- Rapamycin - an mTOR inhibitor that attenuates senescence
- NAD-boosters such as NMN (Nicotinamide) and NR - enhancers of stem cell function
- Dasatinib - a senolytic usually used in combination with quercetin

**But: a balanced lifestyle will get you much further**

## **What can I do?**

---

Pharmacological  
**Lifestyle**

## Lifestyle is more important

---

Available medication can add only so much, much more important are:

- Healthy and balanced diet [Willcox et al., 2007]
- Regular Exercise [Lee et al., 1995]
- Low-Stress Environment
- Close friends [Olsen et al., 1991]
- Fulfilling Life [Diener and Chan, 2011]
- Not suffering from depression  
[Cuijpers and Smit, 2002]

The statistical evidence is clear on this!

Introduction

What is Aging?

How can we Slow down Aging?

What can I do?

**Where can Bioinformatics Help?**

Conclusion

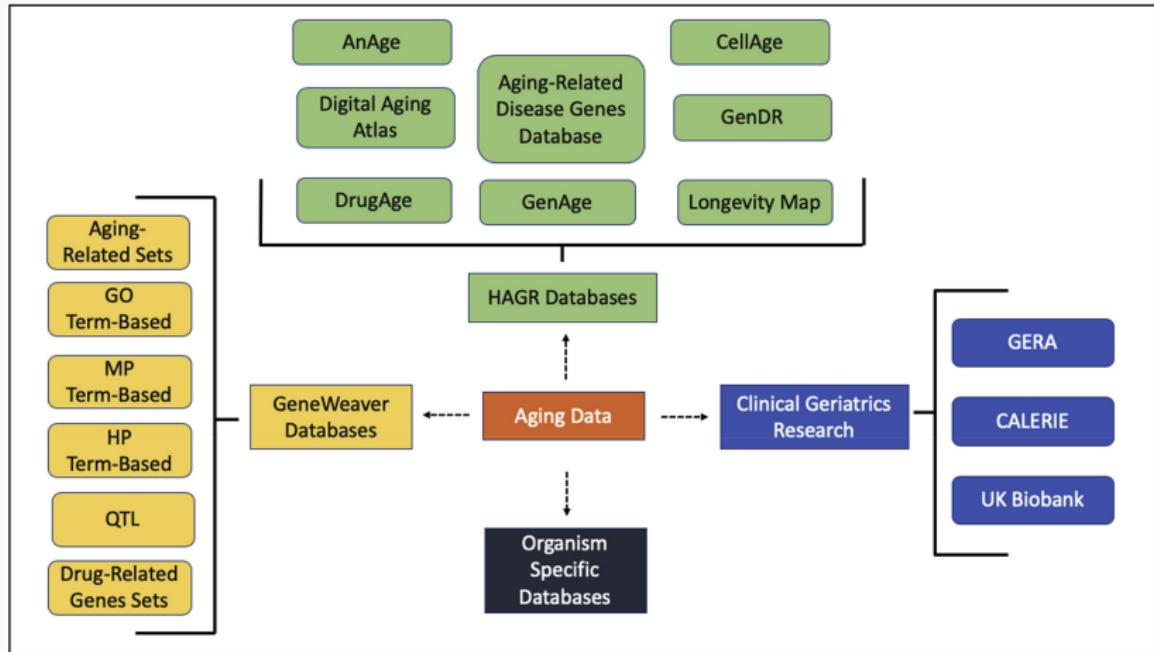
# Where can Bioinformatics Help?

---

Databases and Tools for Analysis

Machine Learning

# Available Databases are Decentralized



Source: [Kruempel et al., 2019]

# Computational Tools

---

- Prism - statistical analysis and graphing program
- Online Application for Survival Analysis (OASIS) - online tool for statistical analysis of lifespan data
- R packages: 'survival', 'flexsurf', 'survminer' - rapid generation of survival curves and statistical analysis
- Machine Learning approaches - gene classification, mortality related biomarker and gene expression profile identification

Source: [Kruempel et al., 2019]

## Areas for Improvement

---

- Centralized access to Databases - making study data available for further analysis in a *centralized* manner
- Increased Biobank usage - collecting biological and clinical data on representative populations
- Sophisticated Tools for Analysis - for the next tier of qualitative analysis
- Standardization - for easier access and interoperability

# **Where can Bioinformatics Help?**

---

Databases and Tools for Analysis  
**Machine Learning**

# Machine Learning

---

- Classifying genes and proteins into aging or non-aging-related [Townes et al., 2020]
- Identification of improved biomarkers for aging in humans [Putin et al., 2016], [Nakamura and Miyao, 2007]
- Establishing aging- and mortality-related gene expression profiles in humans [Kerber et al., 2009]
- Protein folding predictions [Jumper et al., 2021] [Baek et al., 2021]

## **Introduction**

**What is Aging?**

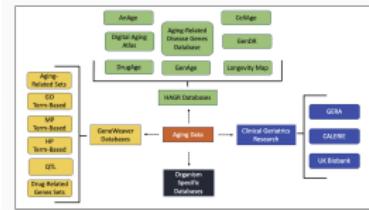
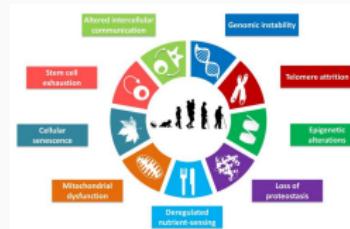
**How can we Slow down Aging?**

**What can I do?**

**Where can Bioinformatics Help?**

## **Conclusion**

# Conclusion



- There is a lot to do, and steady progress happening!
- We already know a lot!
- The first large-scale studies are happening!
- We will learn a lot in the next few years!

**What are your Questions?**

## Sources i

-  AgelessRx (2020).  
**Participatory evaluation (of) aging (with) rapamycin (for) longevity study - full text view - clinicaltrials.gov.**  
https://clinicaltrials.gov/ct2/show/NCT04488601.  
(Accessed on 2021-07-04).
-  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.

## Sources ii

-  Alkahest (2020).  
**A study to assess the tolerability and efficacy of akst1210 in patients on hemodialysis with cognitive impairment - full text view - clinicaltrials.gov.**  
<https://clinicaltrials.gov/ct2/show/NCT04527328?term=Alkahest&draw=2&rank=7>.  
(Accessed on 2021-07-04).
-  Aman, Y., Qiu, Y., Tao, J., and Fang, E. F. (2018).  
**Therapeutic potential of boosting nad+ in aging and age-related diseases.**  
*Translational Medicine of Aging*, 2:30–37.

## Sources iii

-  Baek, M., DiMaio, F., Anishchenko, I., and Dauparas, J. (2021).  
**Accurate prediction of protein structures and interactions using a three-track neural network.**  
*Science*.
-  Baker, D. J., Childs, B. G., Durik, M., Wijers, M. E., Sieben, C. J., Zhong, J., Saltness, R. A., Jeganathan, K. B., Verzosa, G. C., Pezeshki, A., et al. (2016).  
**Naturally occurring p16 Ink4a-positive cells shorten healthy lifespan.**  
*Nature*, 530(7589):184–189.

## Sources iv

-  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.

-  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 v

- Camell, C. D., Yousefzadeh, M. J., Zhu, Y., Prata, L. G. L., Huggins, M. A., Pierson, M., Zhang, L., O'Kelly, R. D., Pirtskhalava, T., Xun, P., et al. (2021).

**Senolytics reduce coronavirus-related mortality in old mice.**

*Science.*

- Childzy (2008).

**Tortoise - wikipedia.**

[https://en.wikipedia.org/wiki/Tortoise#/media/  
File:A.\\_gigantea\\_Aldabra\\_Giant\\_Tortoise.jpg.](https://en.wikipedia.org/wiki/Tortoise#/media/File:A._gigantea_Aldabra_Giant_Tortoise.jpg)  
(Accessed on 2021-07-05).

## Sources vi

-  Conese, M., Carbone, A., Beccia, E., and Angiolillo, A. (2017).  
**The fountain of youth: a tale of parabiosis, stem cells, and rejuvenation.**  
*Open Medicine*, 12(1):376–383.
-  Cuijpers, P. and Smit, F. (2002).  
**Excess mortality in depression: a meta-analysis of community studies.**  
*Journal of affective disorders*, 72(3):227–236.

## Sources vii

-  Diener, E. and Chan, M. Y. (2011).  
**Happy people live longer: Subjective well-being contributes to health and longevity.**  
*Applied Psychology: Health and Well-Being*, 3(1):1–43.
-  Erbaba, B., Arslan-Ergul, A., and Adams, M. M. (2020).  
**Effects of caloric restriction on the antagonistic and integrative hallmarks of aging.**  
*Ageing Research Reviews*, page 101228.

## Sources viii

-  Fahy, G. M., Brooke, R. T., Watson, J. P., Good, Z., Vasanawala, S. S., Maecker, H., Leipold, M. D., Lin, D. T., Kobor, M. S., and Horvath, S. (2019).  
**Reversal of epigenetic aging and immunosenescent trends in humans.**  
*Aging cell*, 18(6):e13028.
-  Folgueras, A. R., Freitas-Rodríguez, S., Velasco, G., and López-Otín, C. (2018).  
**Mouse models to disentangle the hallmarks of human aging.**  
*Circulation research*, 123(7):905–924.

## Sources ix

-  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 x

-  Höllbacher, B., Balázs, K., Heinig, M., and Uhlenhaut, N. H. (2020).

**Seq-ing answers: Current data integration approaches to uncover mechanisms of transcriptional regulation.**

*Computational and structural biotechnology journal*,  
18:1330–1341.

-  Jumper et al. (2021).

**Highly accurate protein structure prediction with alphafold.**

*Nature*.

# Sources xi

-  Kaeberlein, M. (2019).  
**It is Time to Embrace 21st-Century Medicine.**  
*Public Policy & Aging Report*, 29(4):111–115.
-  Kapahi, P., Kaeberlein, M., and Hansen, M. (2017).  
**Dietary restriction and lifespan: Lessons from invertebrate models.**  
*Ageing research reviews*, 39:3–14.
-  Karin, O., Agrawal, A., Porat, Z., Krizhanovsky, V., and Alon, U. (2018).  
**Senescent cells and the dynamics of aging.**  
*bioRxiv*, page 470500.

## Sources xii

-  Kenyon, C. J. (2010).  
**The genetics of ageing.**  
*Nature*, 464(7288):504–512.
-  Kerber, R. A., O'Brien, E., and Cawthon, R. M. (2009).  
**Gene expression profiles associated with aging and mortality in humans.**  
*Aging Cell*, 8(3):239–250.

## Sources xiii

-  Klementschitz, R. (2003).  
**Nacktmull - naked mole-rat - wikipedia.**  
[https://en.wikipedia.org/wiki/Naked\\_mole-rat#/media/File:Nacktmull.jpg](https://en.wikipedia.org/wiki/Naked_mole-rat#/media/File:Nacktmull.jpg).  
(Accessed on 2021-07-05).
-  Kruempel, J. C., Howington, M. B., and Leiser, S. F. (2019).  
**Computational tools for geroscience.**  
*Translational medicine of aging*, 3:132–143.

## Sources xiv

-  Lee, I.-M., Hsieh, C.-c., and Paffenbarger, R. S. (1995).  
**Exercise intensity and longevity in men: the harvard alumni health study.**  
*Jama*, 273(15):1179–1184.
-  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.

## Sources xv

-  López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., and Kroemer, G. (2013).  
**The hallmarks of aging.**  
*Cell*, 153(6):1194–1217.
-  Mahmoudi, S., Xu, L., and Brunet, A. (2019).  
**Turning back time with emerging rejuvenation strategies.**  
*Nature cell biology*, 21(1):32–43.

## Sources xvi

-  Mair, W., Piper, M. D. W., and Partridge, L. (2005).  
**Calories do not explain extension of life span by dietary restriction in drosophila.**  
*PLoS biology*, 3(7):e223.
-  Malaquin, N., Martinez, A., and Rodier, F. (2016).  
**Keeping the senescence secretome under control: molecular reins on the senescence-associated secretory phenotype.**  
*Experimental gerontology*, 82:39–49.

## Sources xvii

-  Martíñez, D. E. (1998).  
**Mortality patterns suggest lack of senescence in hydra.**  
*Experimental gerontology*, 33(3):217–225.
-  Miller, J. (2001).  
**Escaping senescence: demographic data from the three-toed box turtle (*Terrapene carolina triunguis*).**  
*Experimental Gerontology*, 36(4-6):829–832.

## Sources xviii

-  Mohar, D. S. and Malik, S. (2012).  
**The sirtuin system: the holy grail of resveratrol?**  
*Journal of clinical & experimental cardiology*, 3(11).
-  Nakamura, E. and Miyao, K. (2007).  
**A method for identifying biomarkers of aging and constructing an index of biological age in humans.**  
*The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 62(10):1096–1105.

## Sources xix

-  Ocampo, A., Reddy, P., Martinez-Redondo, P.,  
Platero-Luengo, A., Hatanaka, F., Hishida, T., Li, M.,  
Lam, D., Kurita, M., Beyret, E., et al. (2016).  
**In vivo amelioration of age-associated hallmarks by partial reprogramming.**  
*Cell*, 167(7):1719–1733.
-  Ofenbauer, A. and Tursun, B. (2019).  
**Strategies for in vivo reprogramming.**  
*Current opinion in cell biology*, 61:9–15.

## Sources xx

-  Olsen, R. B., Olsen, J., Gunner-Svensson, F., and Waldstrøm, B. (1991).  
**Social networks and longevity. a 14 year follow-up study among elderly in denmark.**  
*Social science & medicine*, 33(10):1189–1195.
-  Paez-Ribes, M., González-Gualda, E., Doherty, G. J., and Muñoz-Espín, D. (2019).  
**Targeting senescent cells in translational medicine.**  
*EMBO molecular medicine*, 11(12):e10234.

## Sources xxi

-  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).

**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-longevity-record>

(Accessed on 2021-05-24).

## Sources xxiii

-  Putin, E., Mamoshina, P., Aliper, A., Korzinkin, M.,  
Moskalev, A., Kolosov, A., Ostrovskiy, A., Cantor, C.,  
Vijg, J., and Zhavoronkov, A. (2016).  
**Deep biomarkers of human aging: application of  
deep neural networks to biomarker development.**  
*Aging (Albany NY)*, 8(5):1021.
-  Ricón, J. L. (2020).  
**Nintil - The Longevity FAQ.**  
<https://nintil.com/longevity>.  
(Accessed on 2021-06-01).

## Sources xxiv

-  Ruby, J. G. and Smith, M. (2018).  
**Naked mole-rat mortality rates defy Gompertzian laws by not increasing with age.**  
*elife*, 7:e31157.
-  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.

## Sources xxv

-  Saul, D. and Kosinsky, R. L. (2021).  
**Epigenetics of Aging and Aging-Associated Diseases.**  
*International Journal of Molecular Sciences*, 22(1):401.
-  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.

## Sources xxvi

-  Swindell, W. R. (2012).  
**Dietary restriction in rats and mice: a meta-analysis and review of the evidence for genotype-dependent effects on lifespan.**  
*Ageing research reviews*, 11(2):254–270.
-  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.

## Sources xxvii

-  Takahashi, K. and Yamanaka, S. (2006).  
**Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors.**  
*cell*, 126(4):663–676.
-  TAME, A. (2021).  
**TAME - Targeting Aging with Metformin - American Federation for Aging Research.**  
<https://www.afar.org/tame-trial>.  
(Accessed on 2021-07-04).

## Sources xxviii

-  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](https://www.diabetes.org.uk/resources-s3/2017-11/diabetes_in_the_uk_2010.pdf).  
(Accessed on 2021-05-27).
-  Townes, F. W., Carr, K., and Miller, J. W. (2020).  
**Identifying longevity associated genes by integrating gene expression and curated annotations.**  
*PLoS Computational Biology*, 16(11):e1008429.

## Sources xxix

-  Victorelli, S. and Passos, J. F. (2017).  
**Telomeres and cell senescence-size matters not.**  
*EBioMedicine*, 21:14–20.
-  Walter, M. (2015).  
**Transposon regulation upon dynamic loss of DNA methylation.**  
PhD thesis, Université Pierre et Marie Curie-Paris VI.

# Sources xxx

 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 xxxi

-  Willcox, B. J., Willcox, D. C., Todoriki, H., Fujiyoshi, A., Yano, K., He, Q., Curb, J. D., and Suzuki, M. (2007).  
**Caloric restriction, the traditional okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span.**  
*Annals of the New York Academy of Sciences*,  
1114(1):434–455.

## Sources xxxii

 Xie, K., Ryan, D. P., Pearson, B. L., Henzel, K. S., Neff, F., Vidal, R. O., Hennion, M., Lehmann, I., Schleif, M., Schröder, S., et al. (2018).

**Epigenetic alterations in longevity regulators,  
reduced life span, and exacerbated aging-related  
pathology in old father offspring mice.**

*Proceedings of the National Academy of Sciences*,  
115(10):E2348–E2357.

## Sources xxxiii

-  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**

## Common Pathways

## Hallmarks of Aging

## Root Causes

## 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]

## Artificially 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

**Additional**

**Common Pathways**

**Hallmarks of Aging**

**Root Causes**

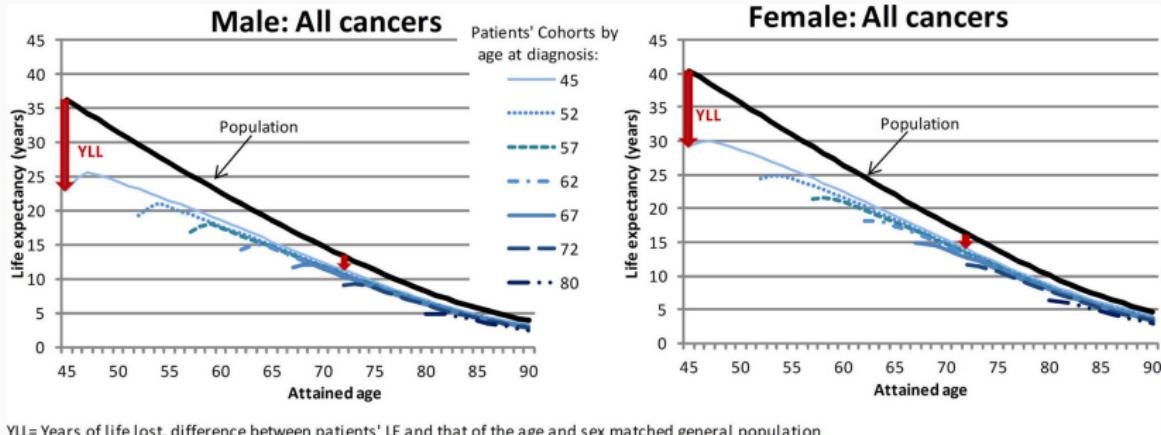
# **Common Pathways**

---

**Effects of harsh conditions**

Diseases of Aging

# 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  
reformulate to indication or something

## 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]

find papers showing that these things cause hallmarks of aging to deteriorate

## **Common Pathways**

---

Effects of harsh conditions

**Diseases of Aging**

# 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      | ● Muscle loss  |
| ● Arthritis       | ● Osteoporosis |
| ● Atherosclerosis | ● 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.

Additional

Common Pathways

**Hallmarks of Aging**

Root Causes

# Hallmarks of Aging

---

DNA Damage

Epigenetic information Loss

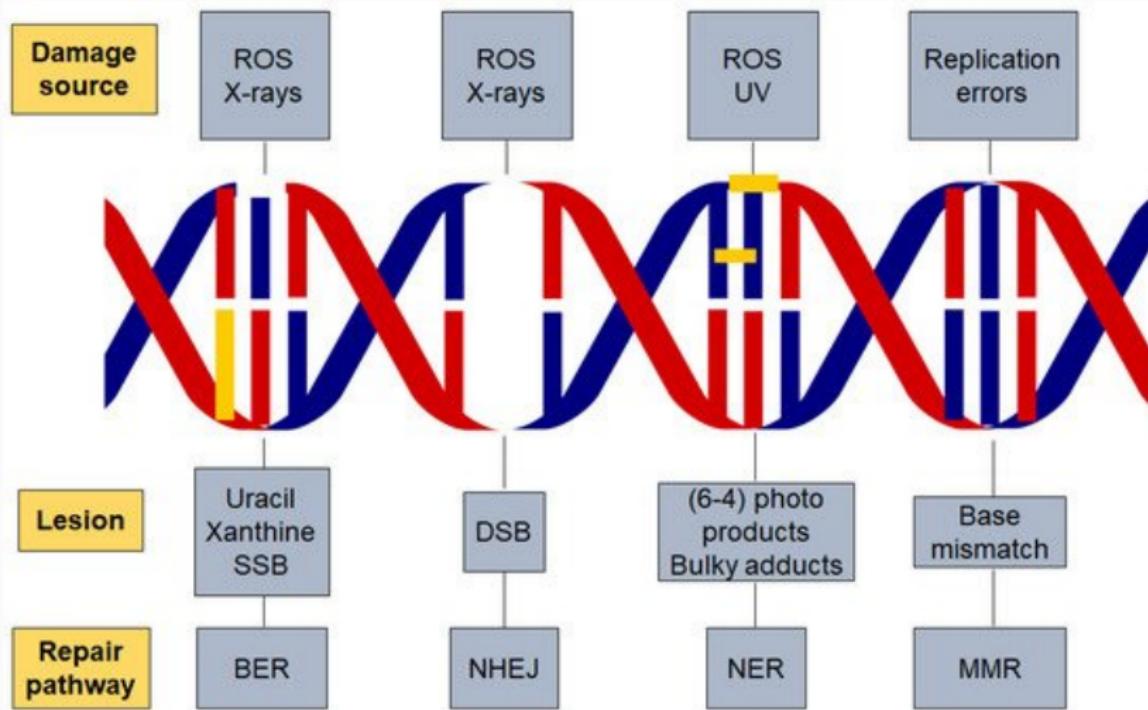
Damaged Mitochondria

Telomeres

Transposons

Timeframes

# DNA Damage



[Alhmoud et al., 2020]

# Hallmarks of Aging

---

DNA Damage

**Epigenetic information Loss**

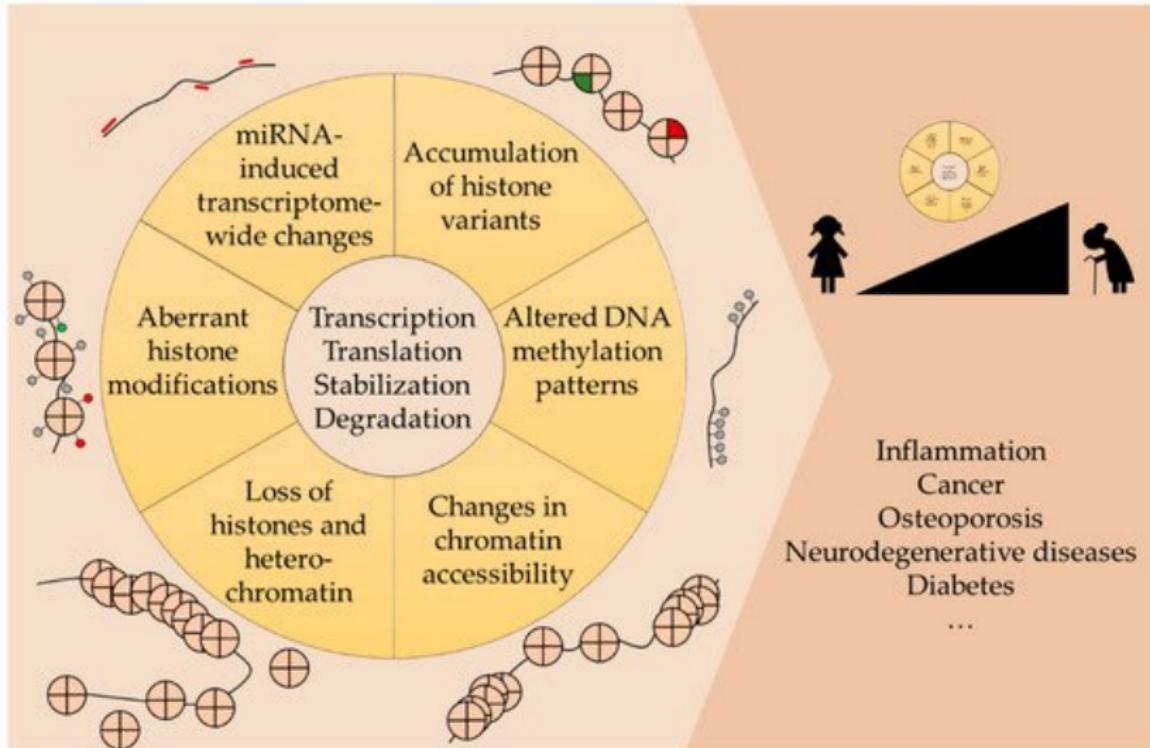
Damaged Mitochondria

Telomeres

Transposons

Timeframes

# Epigenetic Information Loss



[Saul and Kosinsky, 2021]

# Hallmarks of Aging

---

DNA Damage

Epigenetic information Loss

**Damaged Mitochondria**

Telomeres

Transposons

Timeframes

# Mitochondria

Produce energy, explain fail-state and ROS

# Hallmarks of Aging

---

DNA Damage

Epigenetic information Loss

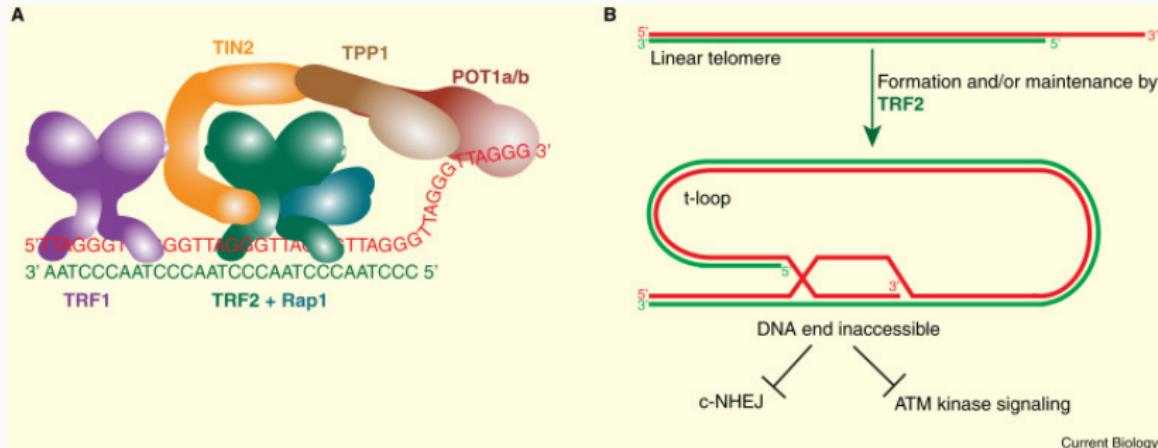
Damaged Mitochondria

**Telomeres**

Transposons

Timeframes

# 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]

# Hallmarks of Aging

---

DNA Damage

Epigenetic information Loss

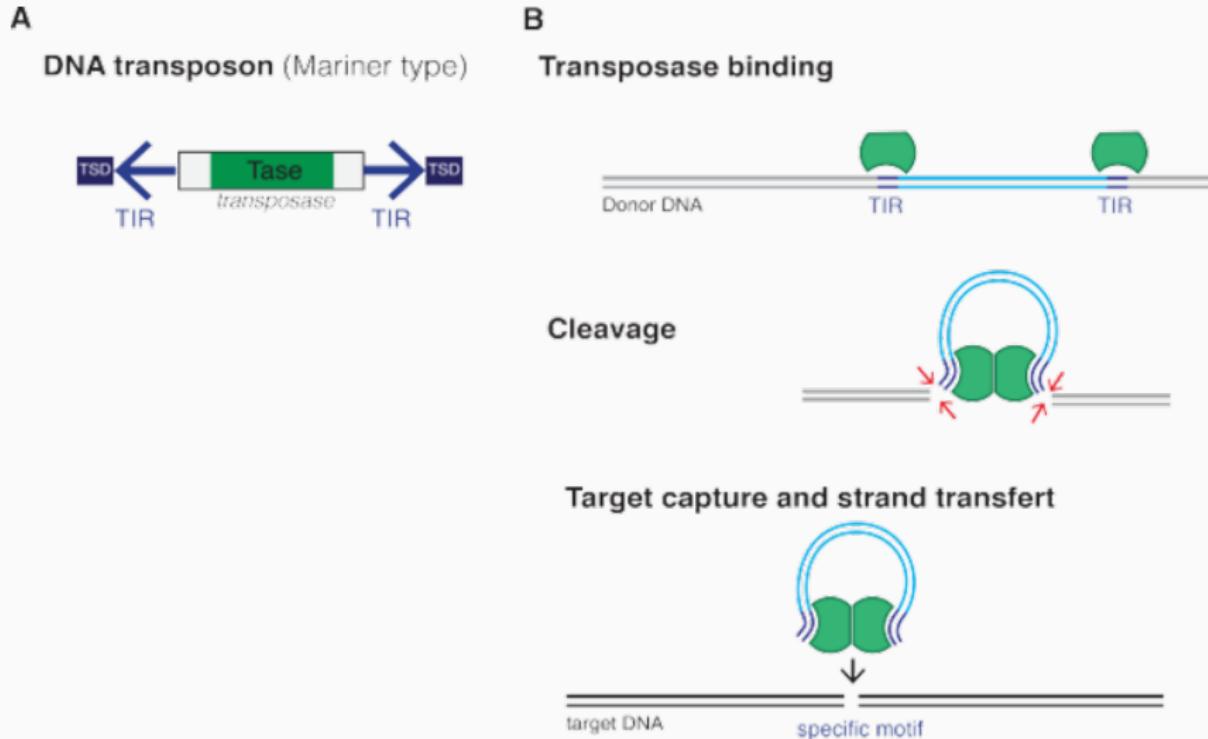
Damaged Mitochondria

Telomeres

**Transposons**

Timeframes

# Transposons



[Walter, 2015]

Also: mice from older fathers live shorter [Xie et al., 2018]

# Hallmarks of Aging

---

DNA Damage

Epigenetic information Loss

Damaged Mitochondria

Telomeres

Transposons

**Timeframes**

## 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

**Additional**

**Common Pathways**

**Hallmarks of Aging**

**Root Causes**

# **Root Causes**

---

**Assumed Root Causes**

**Open Questions**

**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]

# **Root Causes**

---

Assumed Root Causes

**Open Questions**

## 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