

Anti-Aging: State of the Art

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Seminar Bioinformatics



Introduction

What is Aging?

How can we Slow down Aging?

What can I do?

Where can Bioinformatics Help?

Conclusion

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Goals for this Talk

You know ...

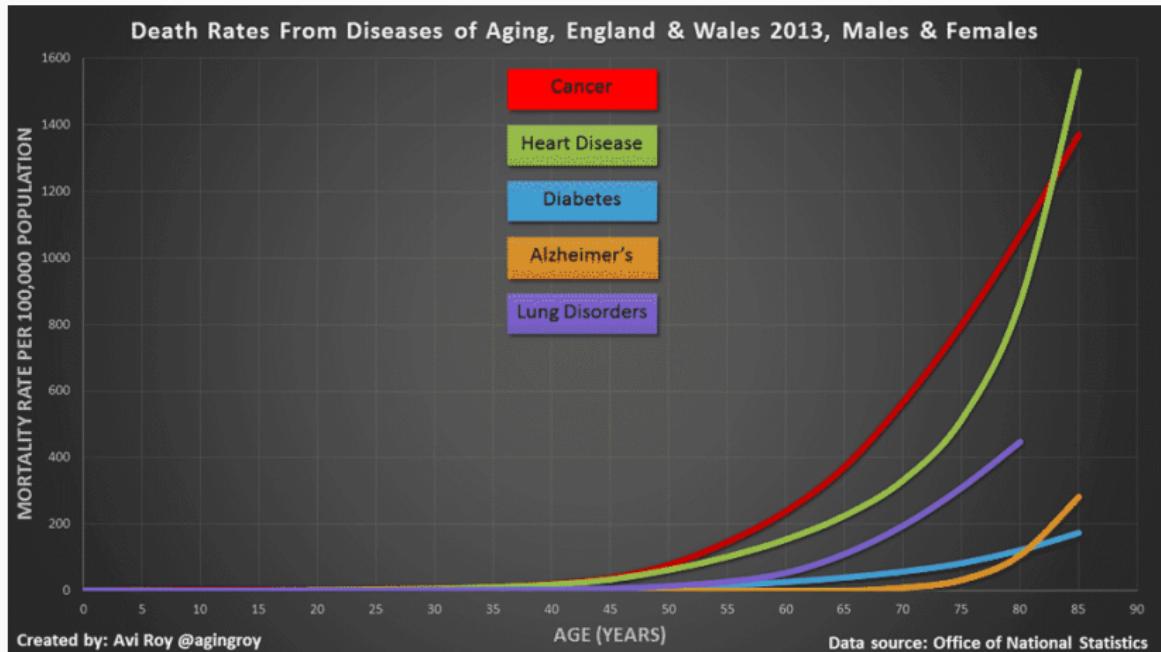
- What aging is
- Why it is a problem
- Why it is not necessary
- What current approaches are
- About personal anti-aging strategies
- How bioinformatics can help future research

Introduction

Why is Aging a Problem?

Is Aging Necessary?

All Causes for Death Correlate with Age



Same with all other primary causes!

Slowing Aging has Incredible Potential



Source: [Kaeberlein, 2019]

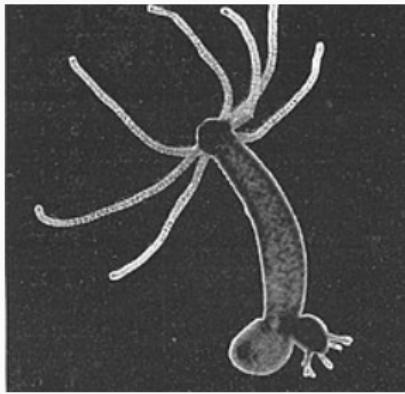
And yet it receives less than 1/100th of Funding!

Introduction

Why is Aging a Problem?

Is Aging Necessary?

Animals that do not Age



Hydra (biologically immortal)
[Martínez, 1998]



Greenland sharks: 400y [Pennisi, 2016]



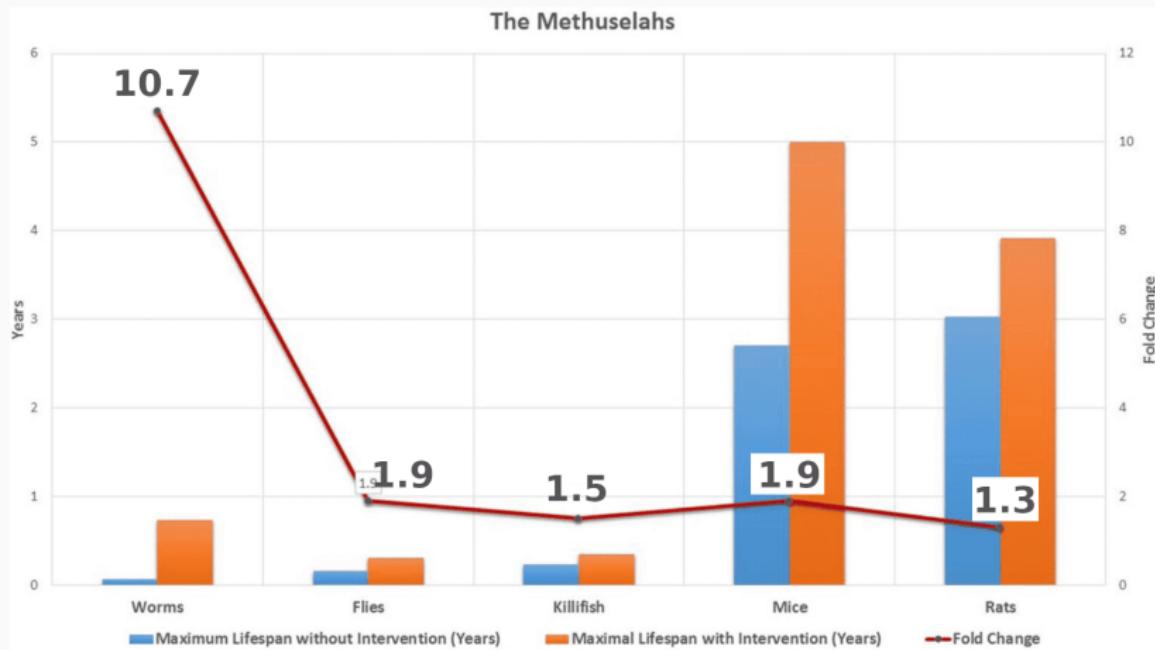
Naked Mole Rats
[Ruby and Smith, 2018], Picture (CC BY-SA 3.0): [Klementschitz, 2003]



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!

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What is Aging?

Definition and Hallmarks

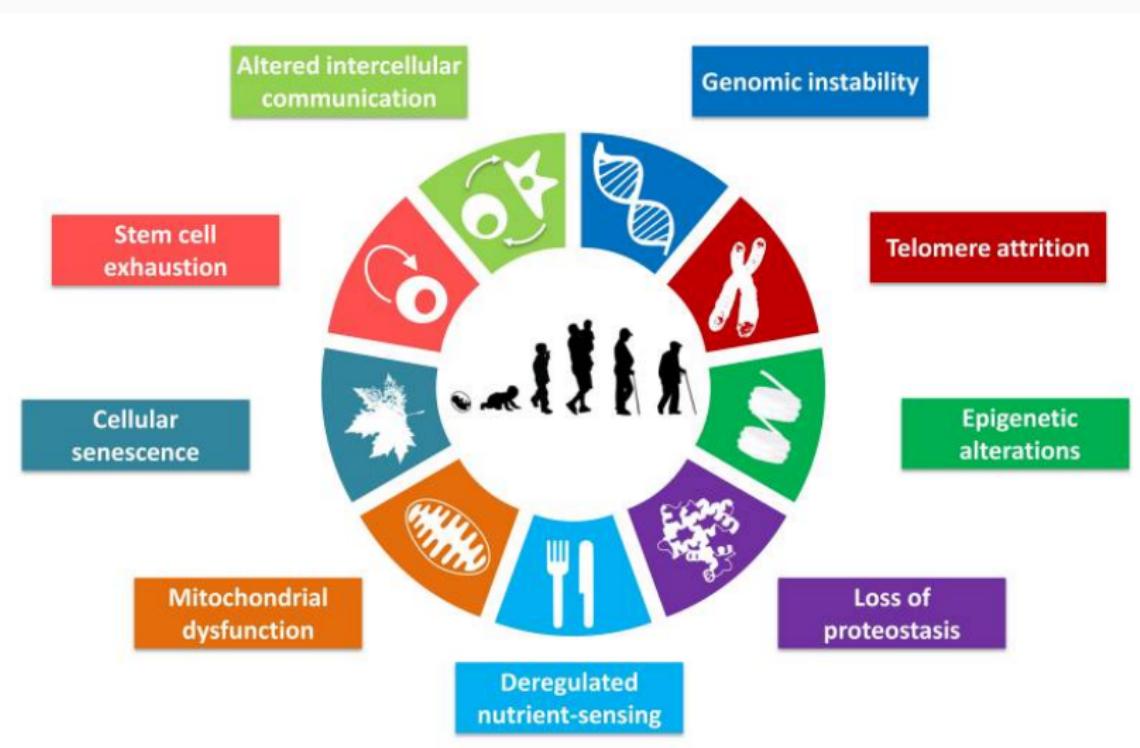
Aging

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]

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How can we Slow down Aging?

Overview

Metabolic Manipulation

Senolytics

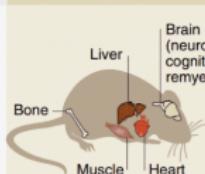
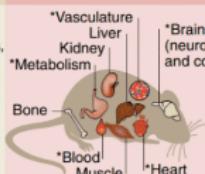
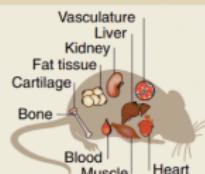
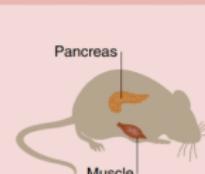
Other Approaches

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> ^{Δex7} progeroid mice	Median lifespan ✓ Maximum lifespan ✓ Model: <i>BubR1</i> progeroid mice	Median lifespan ✓ Maximum lifespan ✓ Model: <i>Lmna</i> ^{GOF/GOF} progeroid mice
	++	+++	++	+	

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

How can we Slow down Aging?

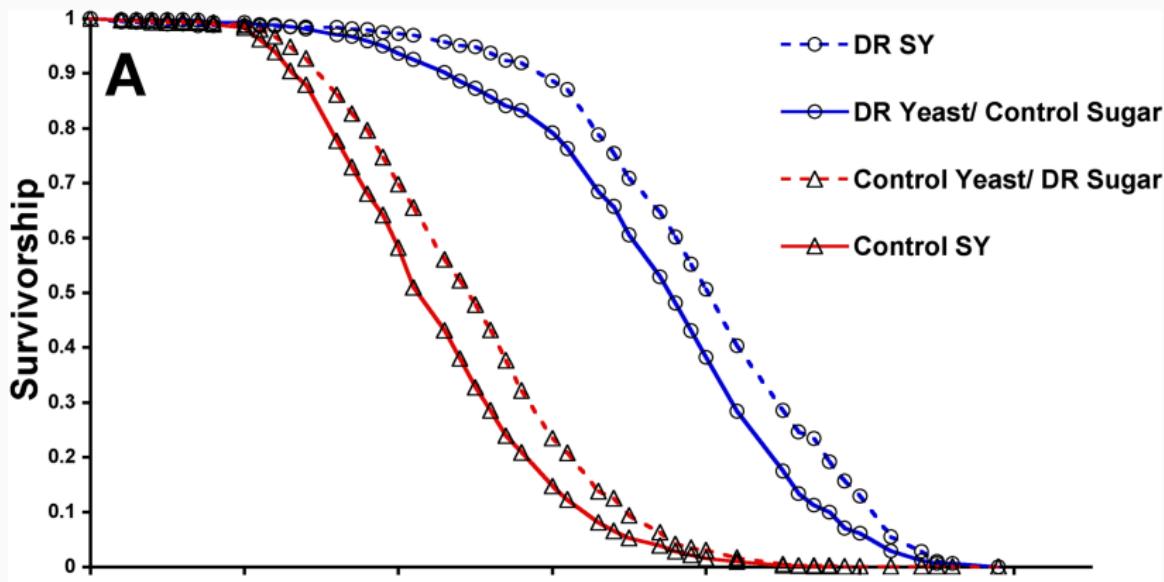
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Senolytics

Other Approaches

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



Source: [Mair et al., 2005]

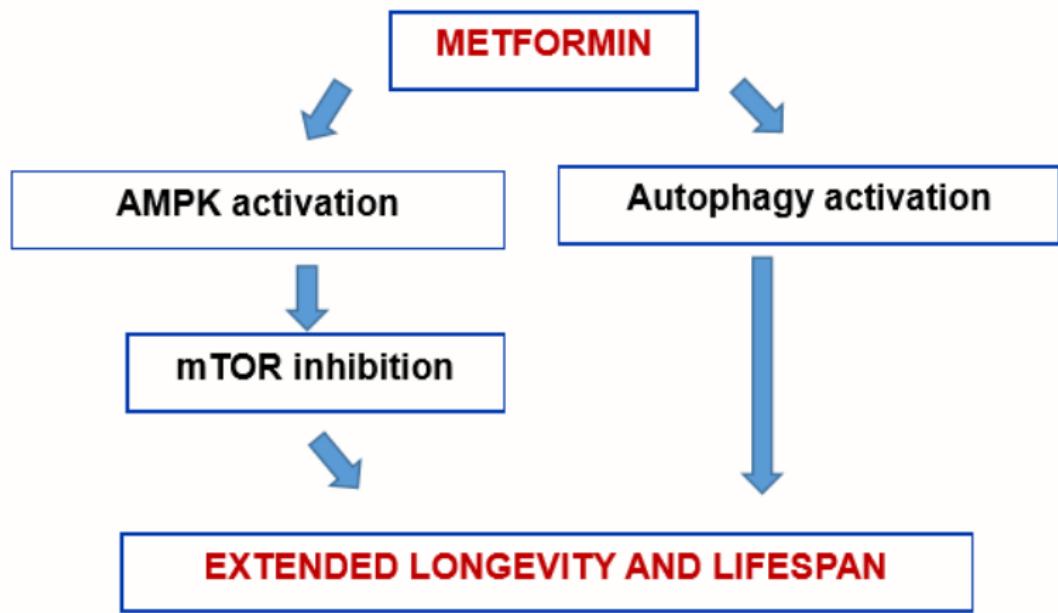
- DR = Dietary Restriction
- Control = No Restriction
- S = Sugar
- Y = Yeast

Dietary Restriction Effects

- 'Different' mitochondrial energy production (less Reactive Oxygen Species, ROS)
- Reduced protein synthesis and DNA duplication
- Increased repair capacity (SIRT and others)
- Increased removal of misfolded proteins (Autophagy)
- Reduced inflammation and proliferation

Overall: Optimizing energy and resource usage

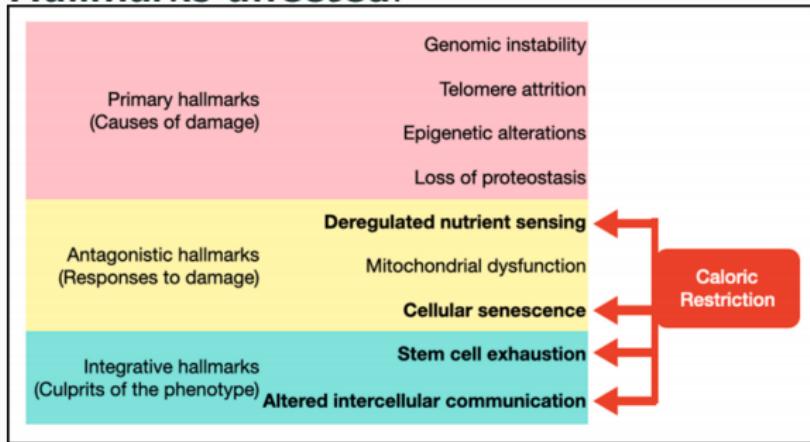
Metformin Effects



Source: [Podhorecka et al., 2017]

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?

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Metabolic Manipulation

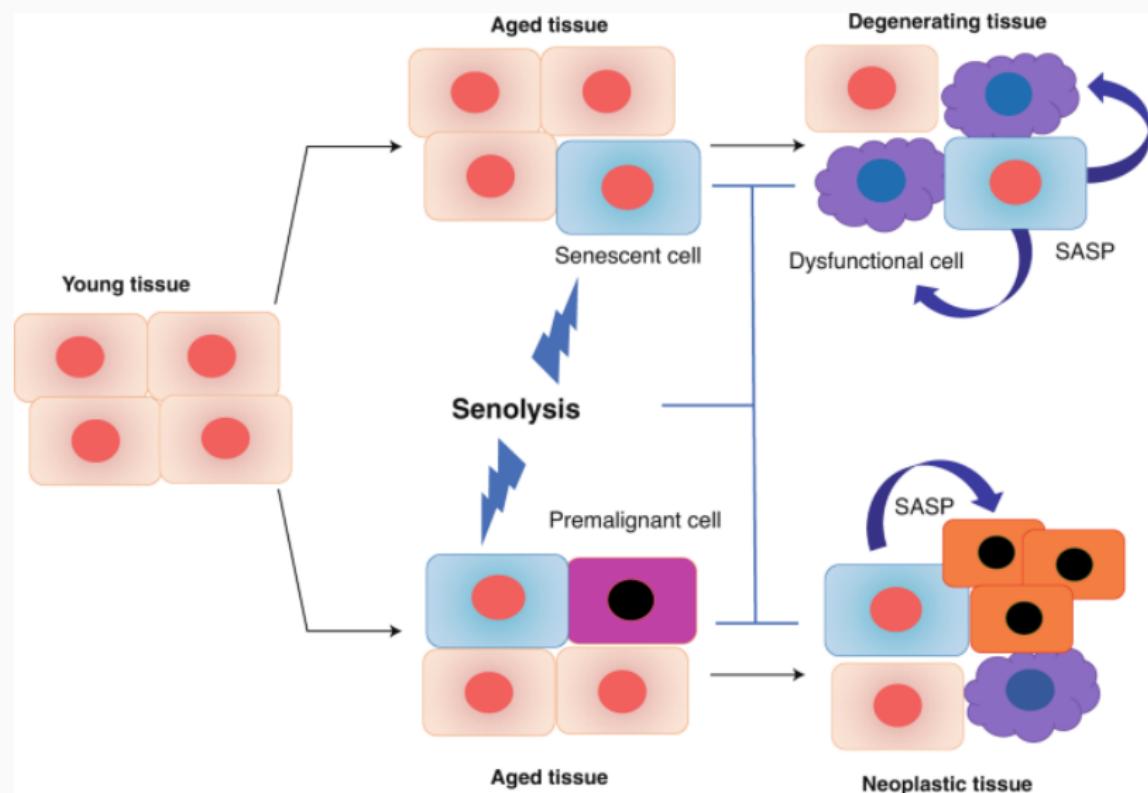
Senolytics

Other Approaches

Senescent Cells: What are they?

- ‘Zombie-like death-resistant cells’
- Old or (partially) damaged cells
- Sending out Senescence-Associated Secretory Phenotype (SASP)
- SASP disrupts intercellular communication, causing inflammation and age-related diseases
- Cells manage to induce apoptosis (cell-suicide) or get removed by the immune system
- About 8% of cells in young, and 17% of cells in old mice are senescent [Folgueras et al., 2018]

Senolytics and Aged Cells



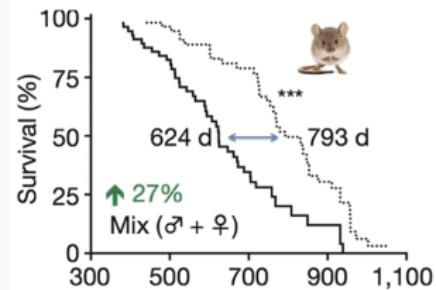
Source: [Dolgin, 2020]

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

Metabolic Manipulation

Senolytics

Other Approaches

Other Promising Approaches

- Blood Exchange (Parabiosis)
[Conese et al., 2017]
- Cellular Reprogramming [Ocampo et al., 2016]
- Thymic (Immune System) rejuvenation
[Fahy et al., 2019]
- Sirtuin activation for DNA repair
[Mohar and Malik, 2012]
- Many more ...

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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!

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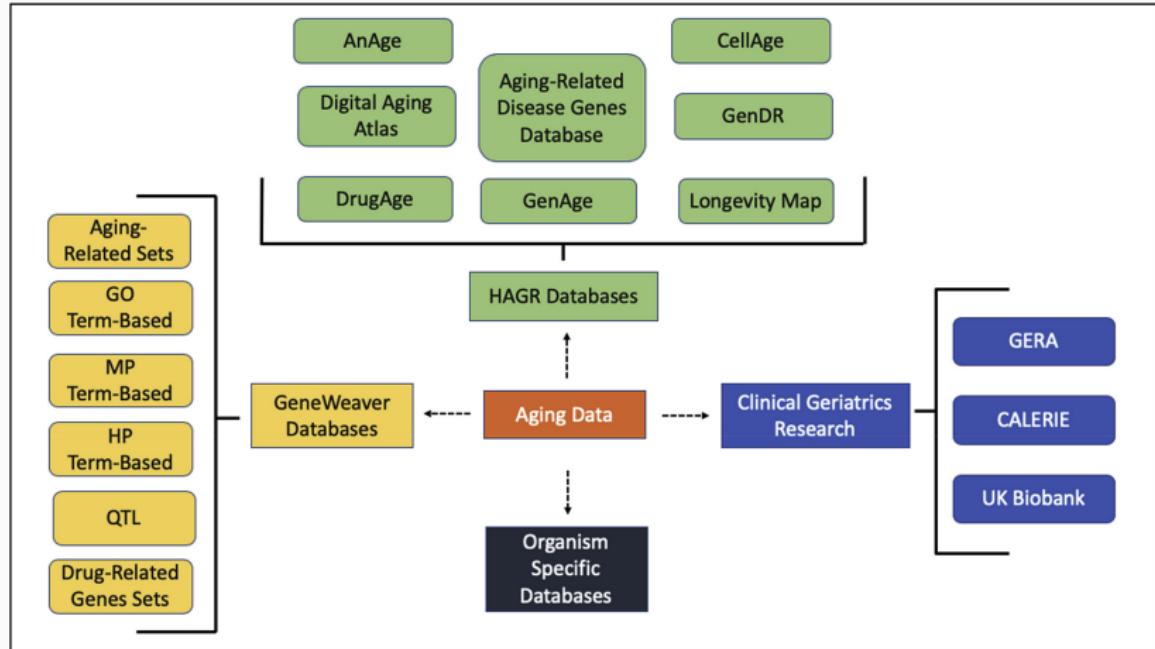
Where can Bioinformatics Help?

Databases and Tools for Analysis

Machine Learning and Aging

Improving Software for Biology

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]

Where can Bioinformatics Help?

Databases and Tools for Analysis

Machine Learning and Aging

Improving Software for Biology

Machine Learning for Aging

- 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]
- Establishing aging- and mortality-related gene expression profiles [Kerber et al., 2009]
- Much more ...

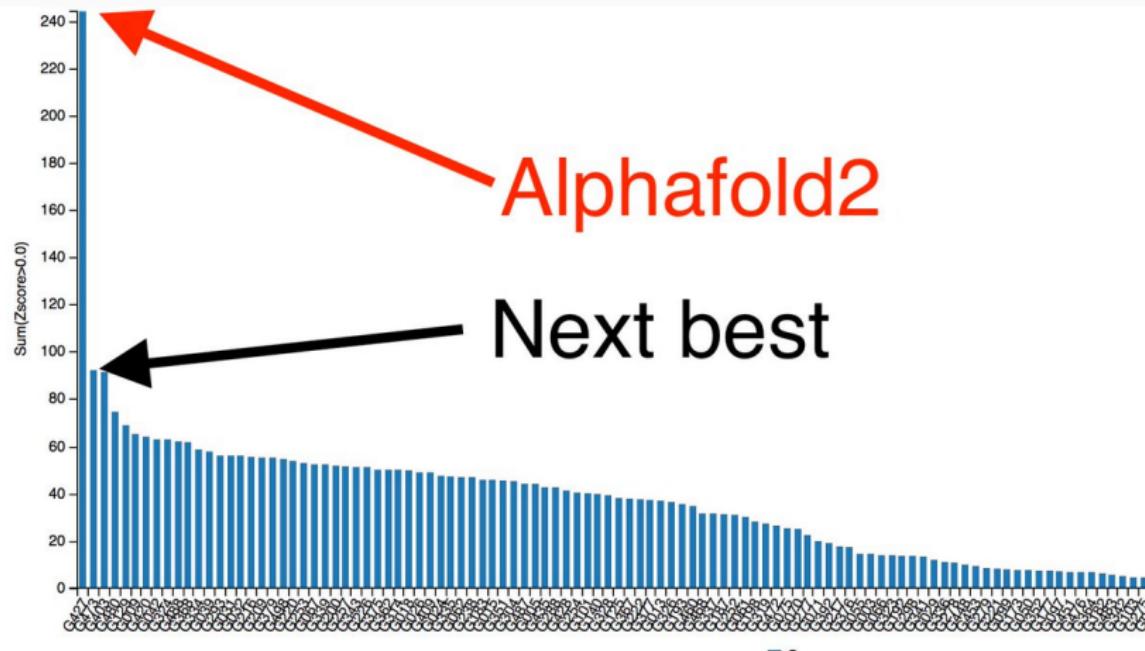
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Machine Learning and Aging

Improving Software for Biology

Protein Folding Competition Results (CASP14, 2020)



Source: [Wagstaff, 2020]

Recent Breakthrough: AlphaFold2 [Jumper et al., 2021]

Bioinformatics helping Anti-Aging Research

- Most software used is not specialized
- Providing centralized Database-Access
- Maybe: Sophisticated tools for analysis
- A lot of basic research still necessary
(and in progress)
- Powerful simulations might be useful

Fundamentally speaking: Provide good Software for Biologists!

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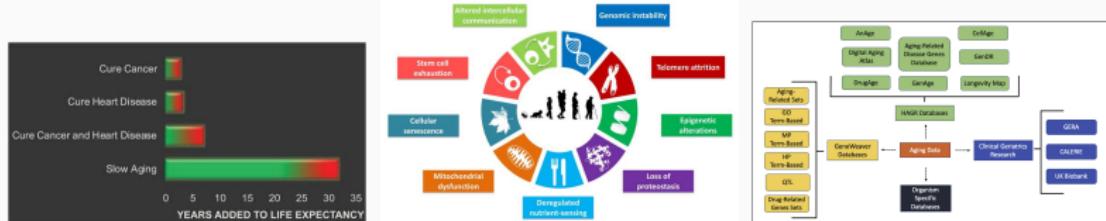
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Conclusion



- 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?

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.
-  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).

Sources ii

-  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.
-  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 iii



Childzy (2008).

Tortoise - wikipedia.

[https://en.wikipedia.org/wiki/Tortoise#/media/File:](https://en.wikipedia.org/wiki/Tortoise#/media/File:A._gigantea_Aldabra_Giant_Tortoise.jpg)

A._gigantea_Aldabra_Giant_Tortoise.jpg.

(Accessed on 2021-07-05).



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 iv

-  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.
-  Dolgin, E. (2020).
Send in the senolytics.
Nature Biotechnology.
-  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.
-  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.

Sources v

-  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.
-  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., Zilberman, F., Peters, A. H., Edelhofer, 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.
-  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.

Sources vi

-  Jumper et al. (2021).
Highly accurate protein structure prediction with alphafold.
Nature.
-  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 vii

-  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.
-  Klemenschitz, R. (2003).
Nacktmull - naked mole-rat - wikipedia.
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.
-  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.

Sources viii

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

Sources ix

-  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.
-  Mohar, D. S. and Malik, S. (2012).
The sirtuin system: the holy grail of resveratrol?
Journal of clinical & experimental cardiology, 3(11).
-  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.

Sources x

-  Ofenbauer, A. and Tursun, B. (2019).
Strategies for in vivo reprogramming.
Current opinion in cell biology, 61:9–15.
-  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.
-  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.

Sources xi

-  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.](https://www.sciencemag.org/news/2016/08/greenland-shark-may-live-400-years-smashing-longevity-record)
(Accessed on 2021-05-24).
-  Podhorecka, M., Ibanez, B., and Dmoszyńska, A. (2017).
Metformin-its potential anti-cancer and anti-aging effects.
Advances in Hygiene & Experimental Medicine/Postępy Higieny i Medycyny Doswiadczałnej, 71.

Sources xii

-  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).
-  Ruby, J. G. and Smith, M. (2018).
Naked mole-rat mortality rates defy Gompertzian laws by not increasing with age.
elife, 7:e31157.
-  Saul, D. and Kosinsky, R. L. (2021).
Epigenetics of Aging and Aging-Associated Diseases.
International Journal of Molecular Sciences, 22(1):401.

Sources xiii



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.



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 xiv



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).



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).

Sources xv

-  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.
-  Victorelli, S. and Passos, J. F. (2017).
Telomeres and cell senescence-size matters not.
EBioMedicine, 21:14–20.
-  Wagstaff, J. (2020).
james wagstaff on Twitter: "Alphafold2 dominant at #CASP14 - looking forward to finding out how! <https://t.co/kEzkk2v6zS>" / Twitter.
<https://twitter.com/jamesmwag/status/1333363332049477633>.
(Accessed on 2021-07-04).

Sources xvi



Walter, M. (2015).

Transposon regulation upon dynamic loss of DNA methylation.

PhD thesis, Université Pierre et Marie Curie-Paris VI.



Wentworth, J. S. (2020).

Homeostasis and “Root Causes” in Aging - LessWrong.

[https://www.lesswrong.com/s/3hfjaztptwEt2cCve/p/d4DvqS88Q29ZaAj3?
commentId=RuF49JiWpbEHXdMrw](https://www.lesswrong.com/s/3hfjaztptwEt2cCve/p/d4DvqS88Q29ZaAj3?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 xvii

-  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.
-  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.
-  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

Slowing down Aging (additional)

Misc

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

Slowing down Aging (additional)

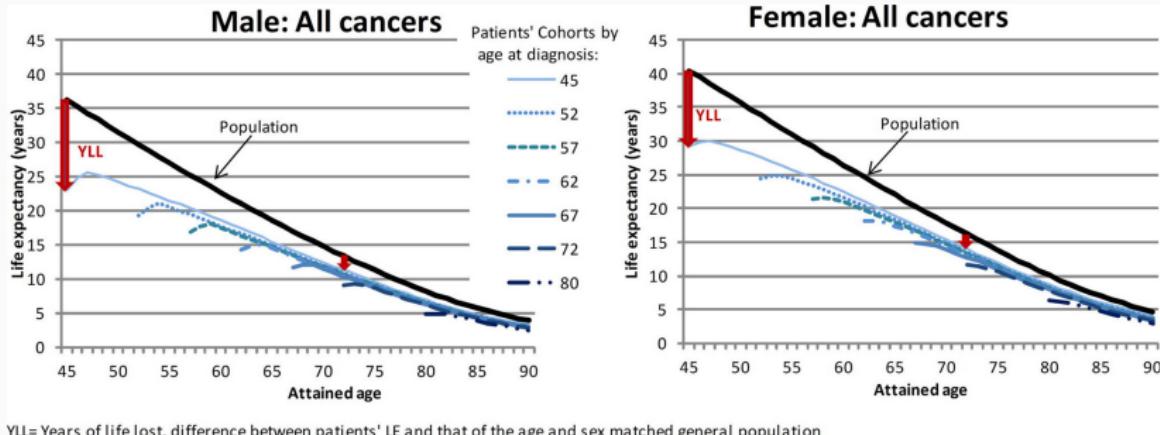
Misc

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

Slowing down Aging (additional)

Misc

Hallmarks of Aging

DNA Damage

Epigenetic information Loss

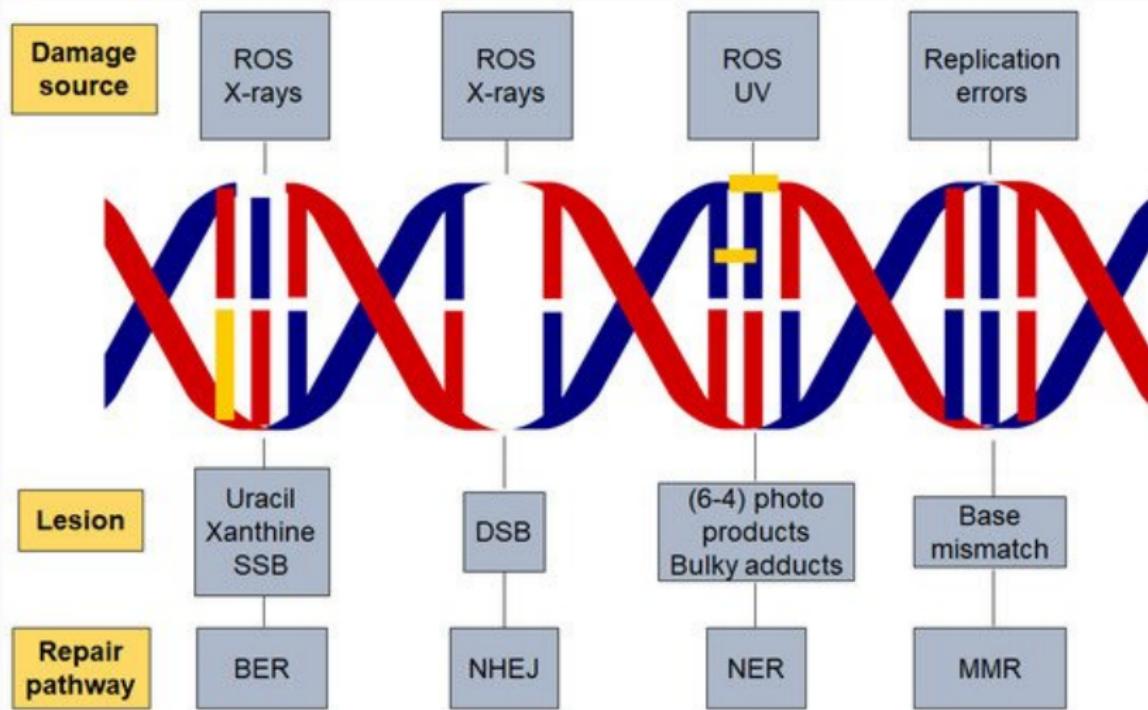
Damaged Mitochondria

Telomeres

Transposons

Timeframes

DNA Damage



[Alhmoud et al., 2020]

Hallmarks of Aging

DNA Damage

Epigenetic information Loss

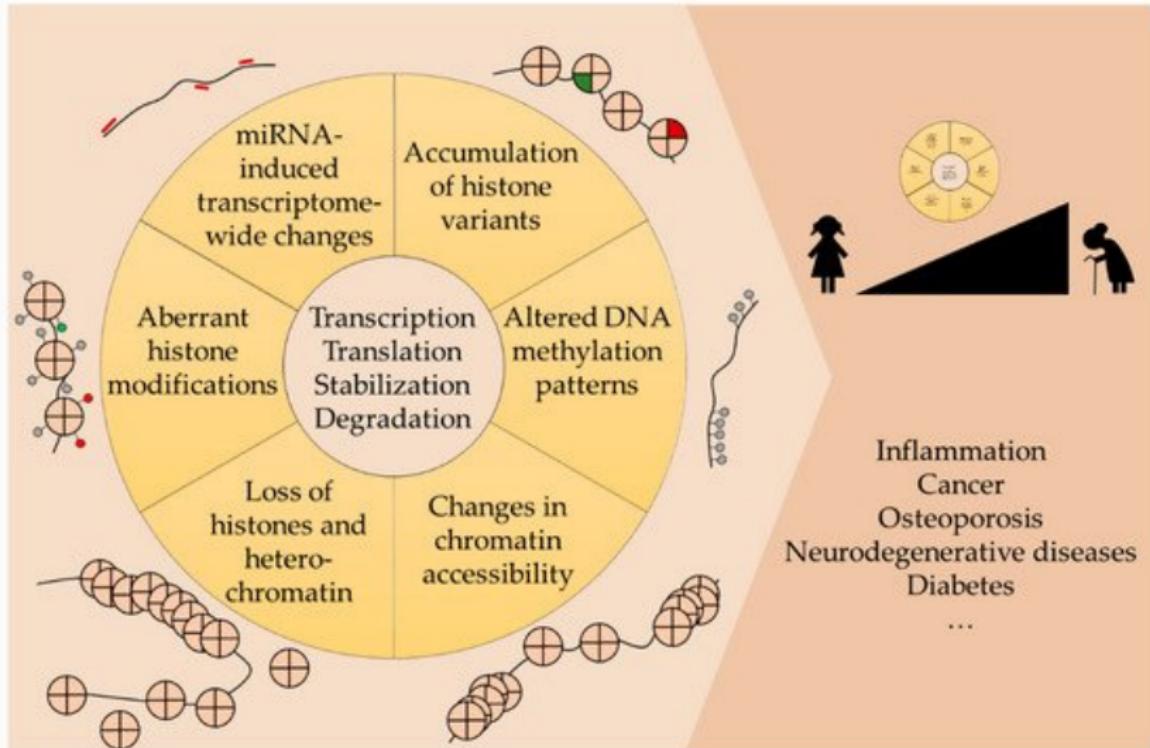
Damaged Mitochondria

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

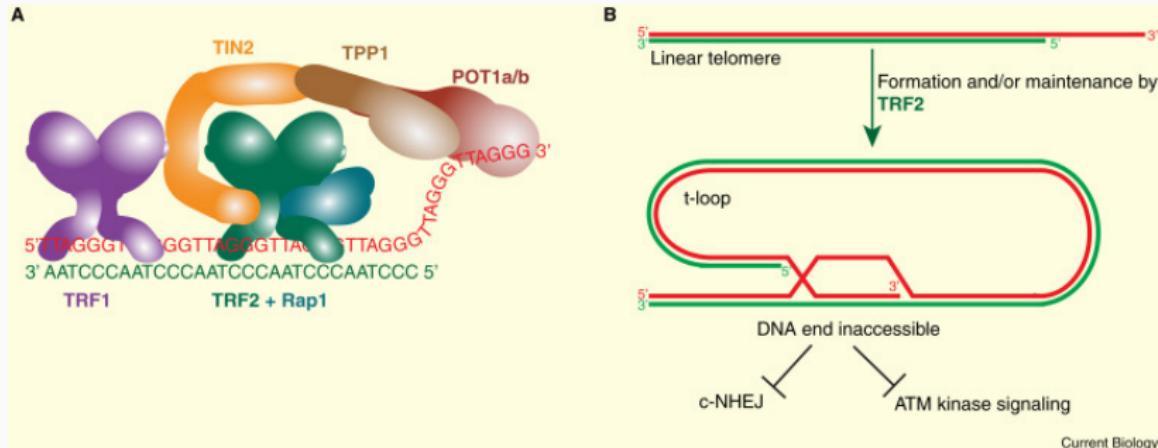
Damaged Mitochondria

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

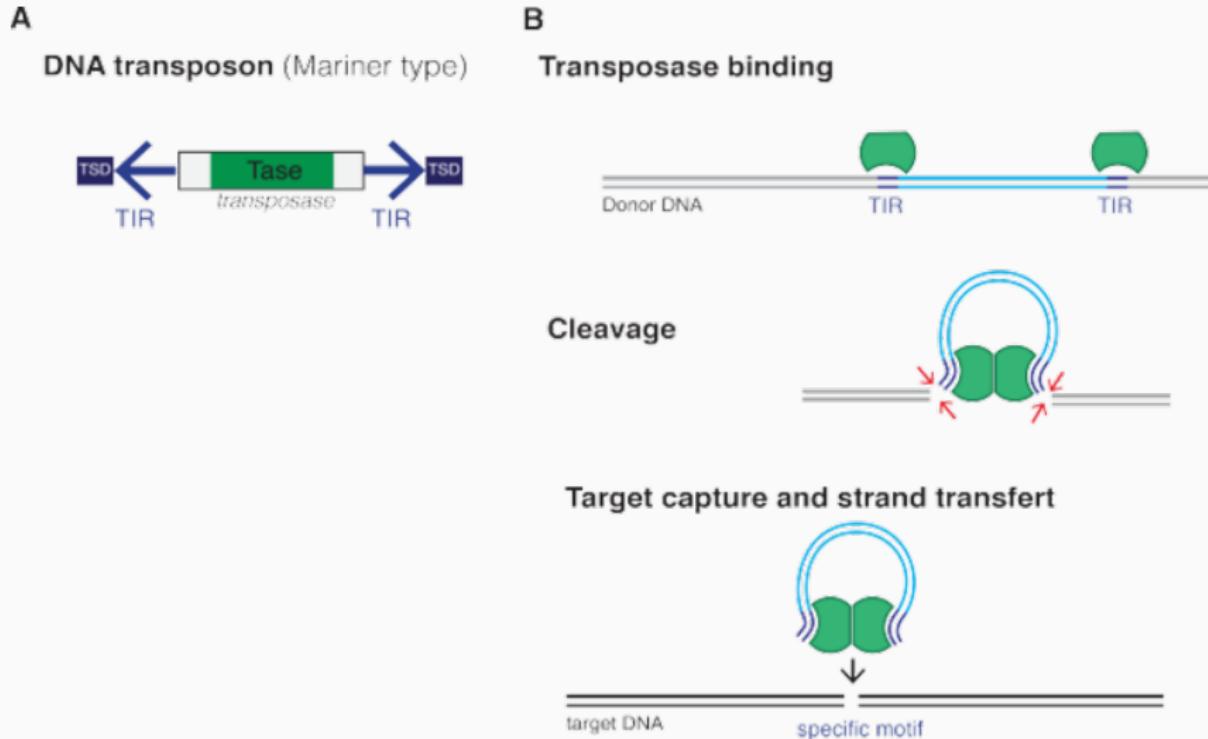
Damaged Mitochondria

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

Slowing down Aging (additional)

Misc

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

Additional

Common Pathways

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Slowing down Aging (additional)

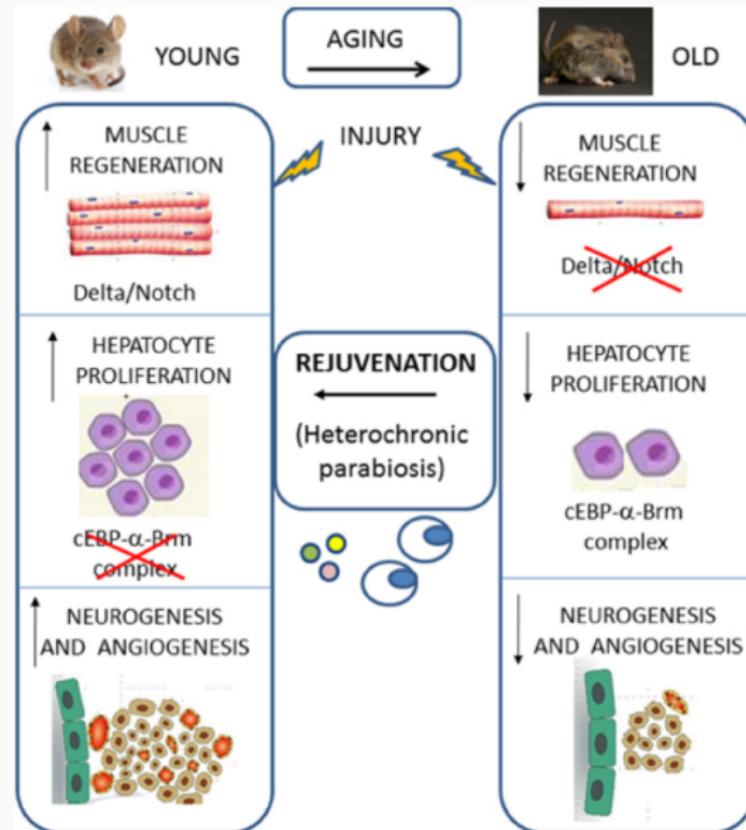
Parabiosis

Dietary Restriction

Cellular Reprogramming

Senolytics

Parabiosis (Blood Exchange)



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].

Slowing down Aging (additional)

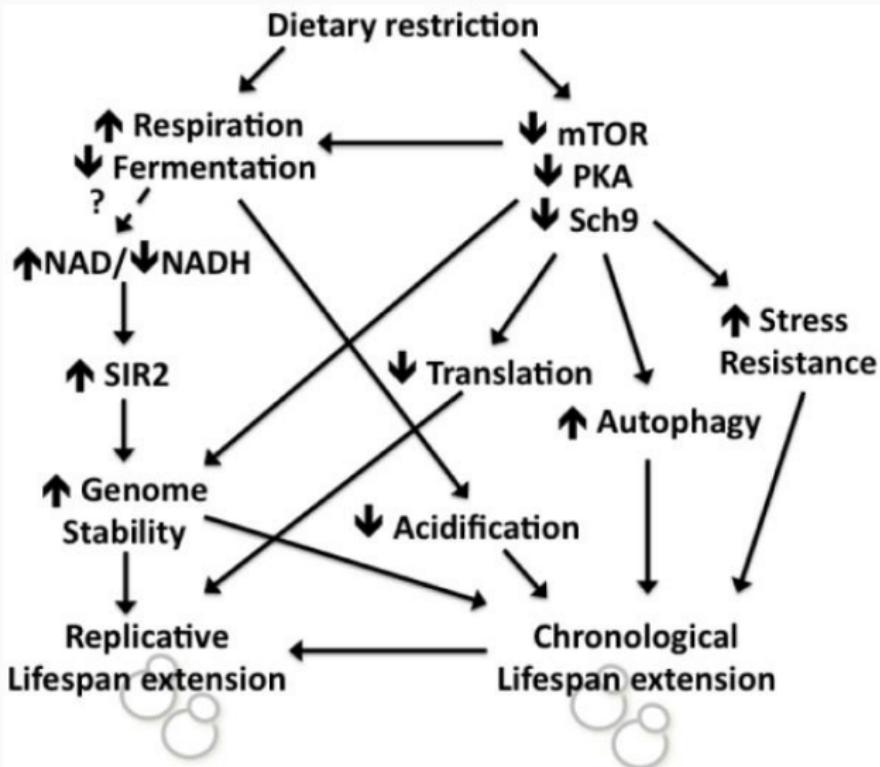
Parabiosis

Dietary Restriction

Cellular Reprogramming

Senolytics

Dietary Restriction Pathways in Yeast



Source: [Kapahi et al., 2017]

Same Effects without Diet

Nutrient-Sensing pathways affected by Dietary Restriction, and easy to target:

- AMPK
- mTOR
- IGF-1

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

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

Slowing down Aging (additional)

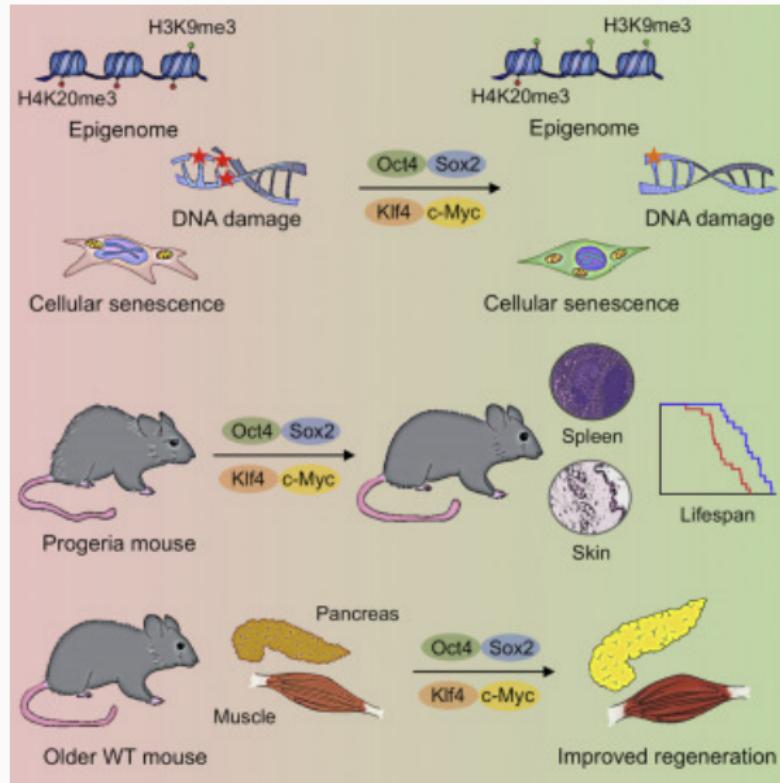
Parabiosis

Dietary Restriction

Cellular Reprogramming

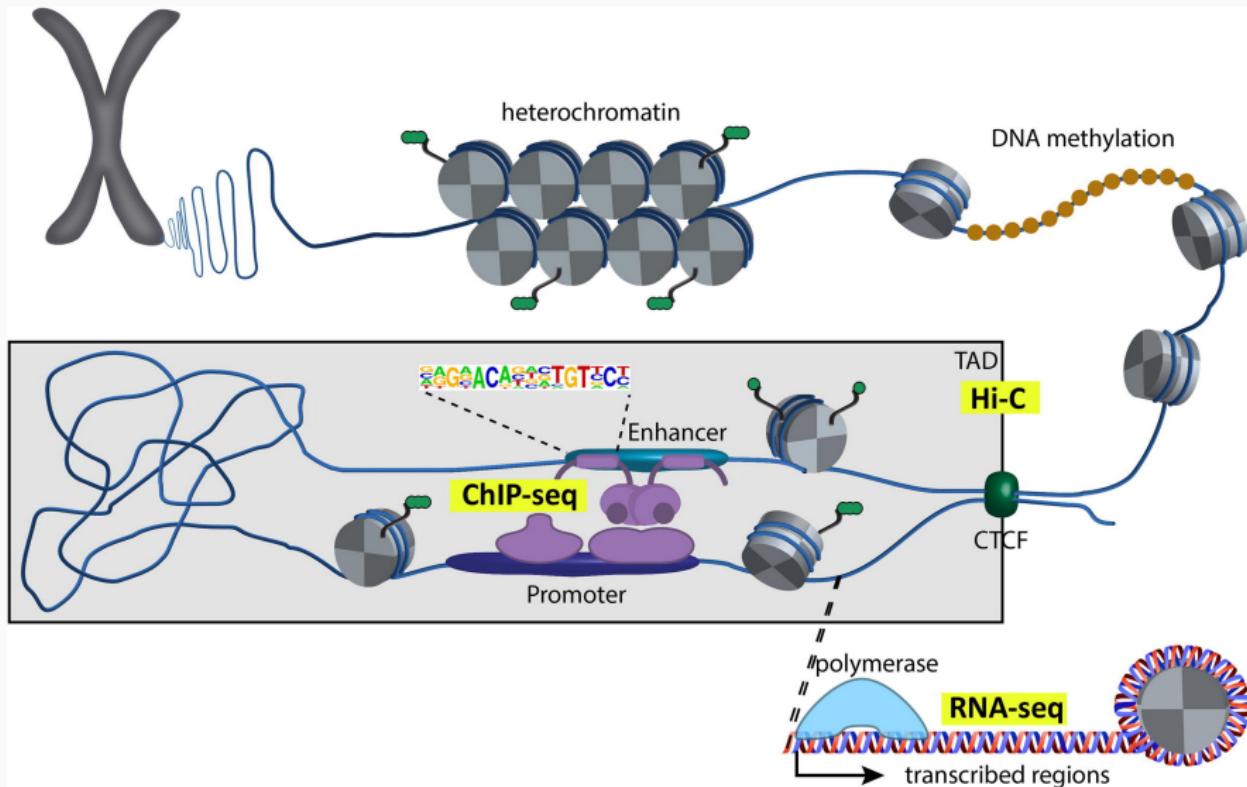
Senolytics

(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

Slowing down Aging (additional)

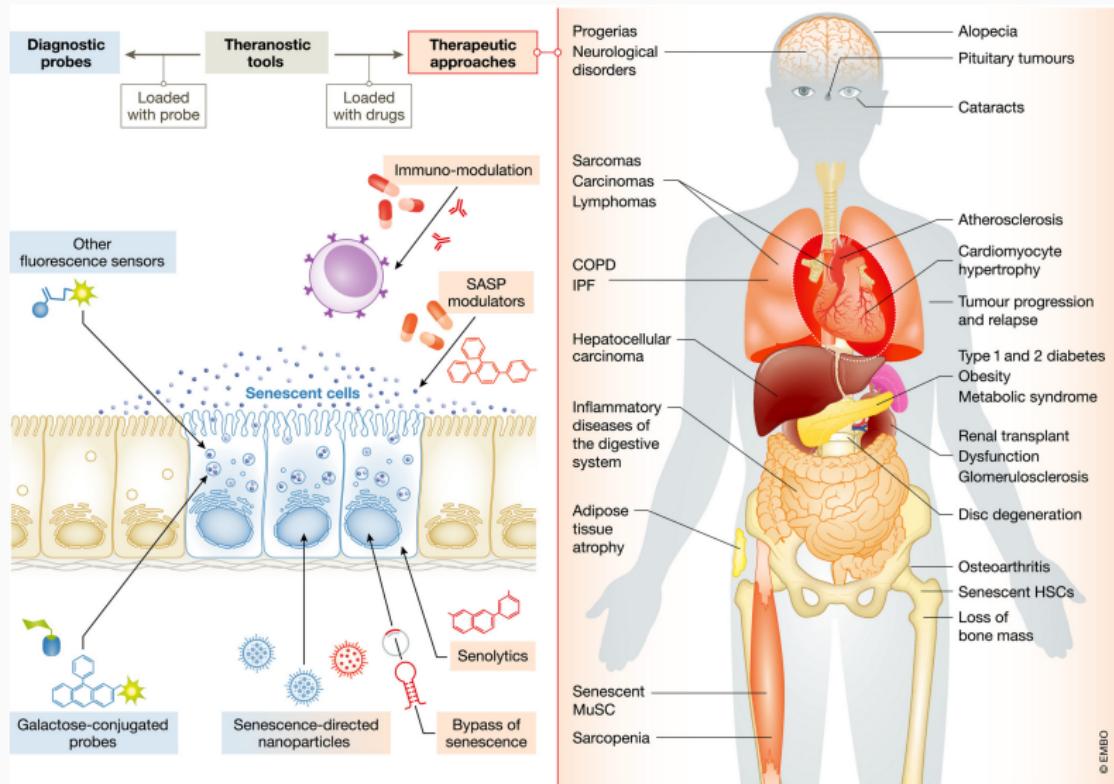
Parabiosis

Dietary Restriction

Cellular Reprogramming

Senolytics

Senolytics: Uses and Effects



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

Additional

Common Pathways

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Root Causes

Slowing down Aging (additional)

Misc

Misc

Problematic: Many Unknowns

Problem: Many Theories of Aging

- 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**