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 ...

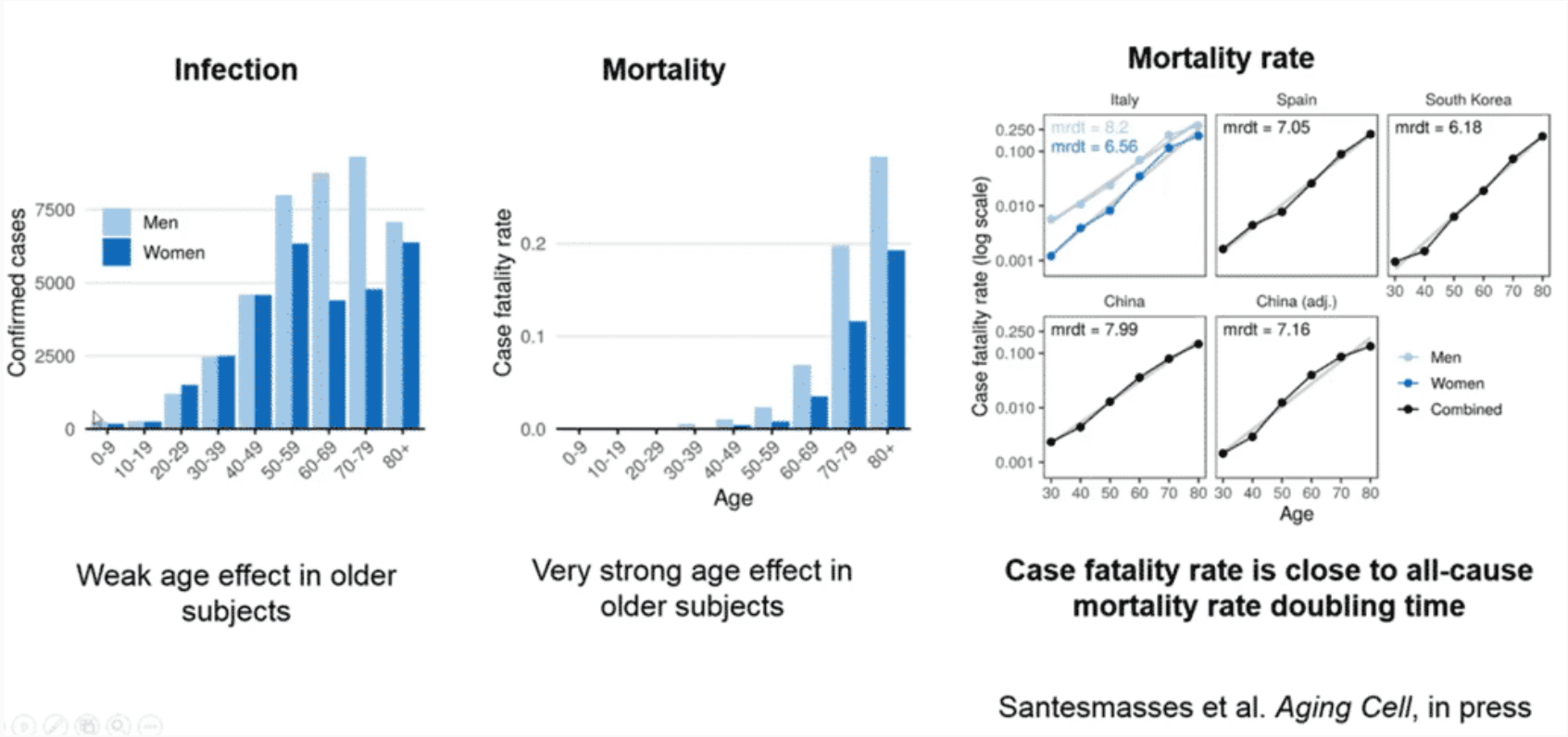
- What aging is
- Why it is a problem
- Why it is not necessary
- How it can be slowed down
- About personal anti-aging strategies
- How bioinformatics can help future research

Introduction

Why is Aging a Problem?

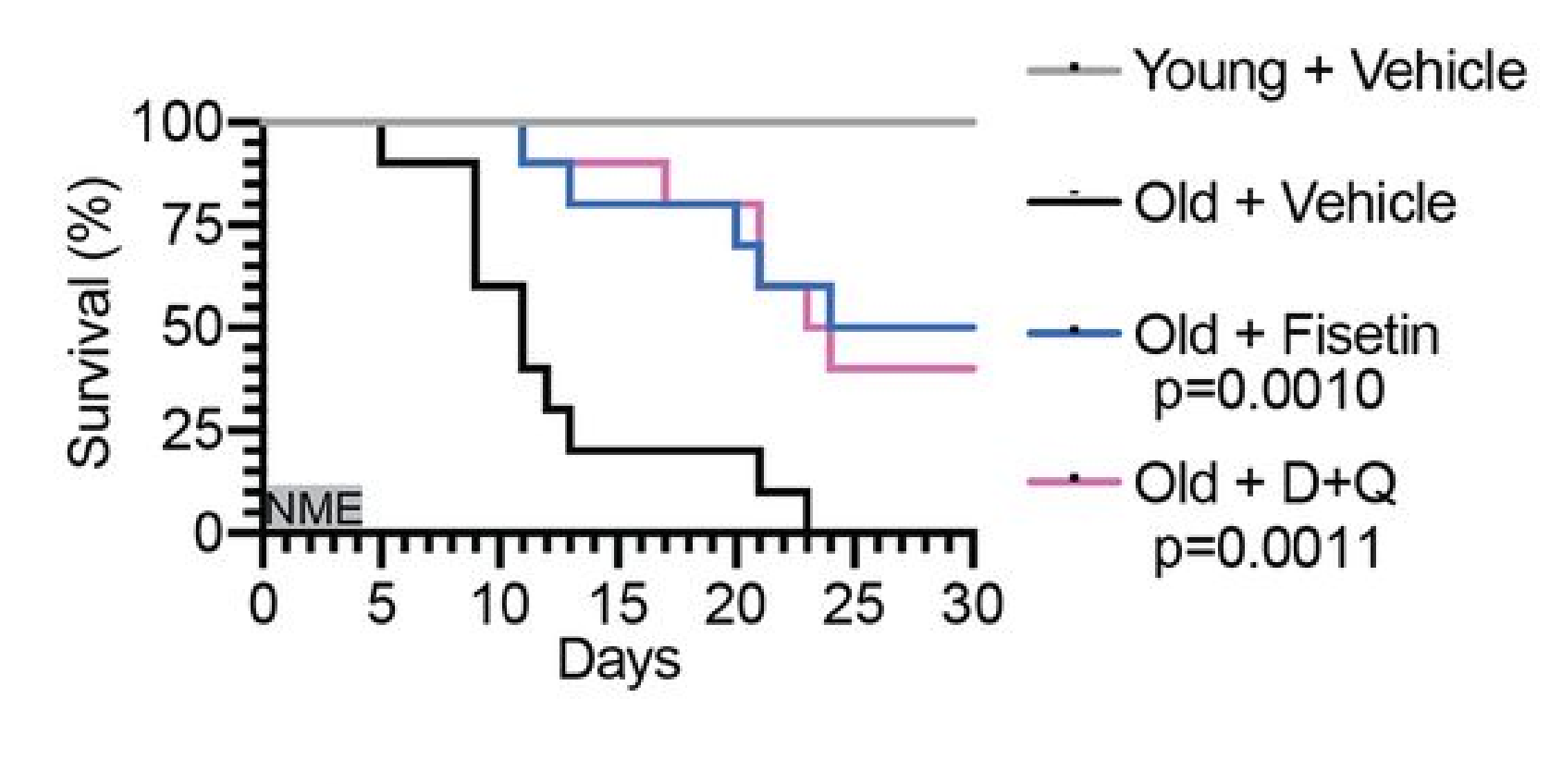
Is Aging Necessary?

Corona Deaths correlate with Age



Source: [Santesmasses et al., 2020]

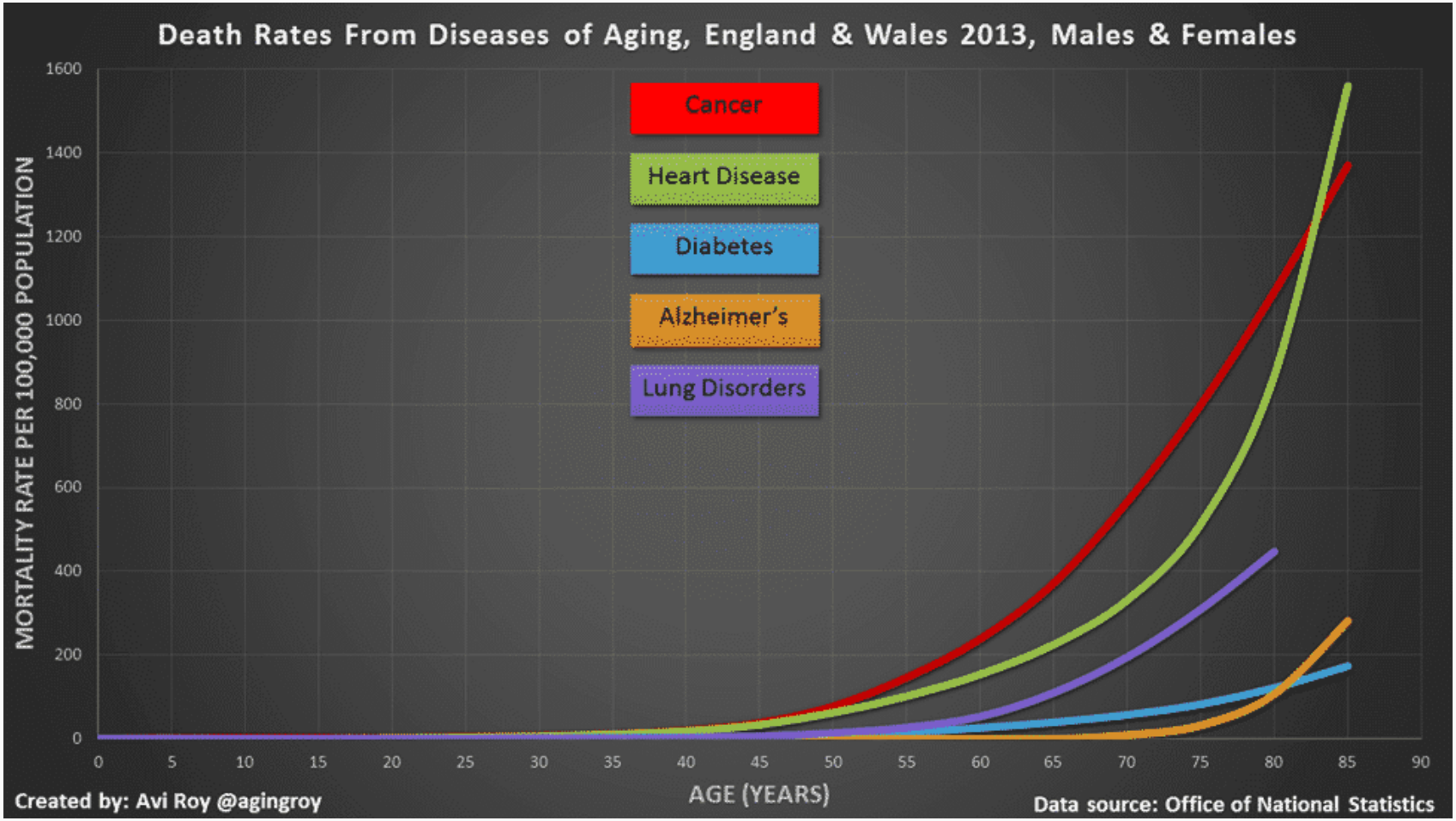
Treating Corona with Senolytics (anti-aging approach)



Source: [Camell et al., 2021]

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

Source: [Kaeberlein, 2019]

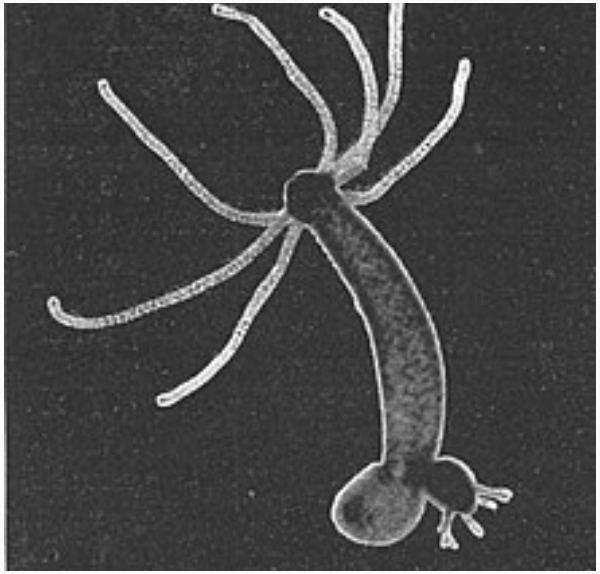
And yet it receives less than 1/100th of Funding!

Introduction

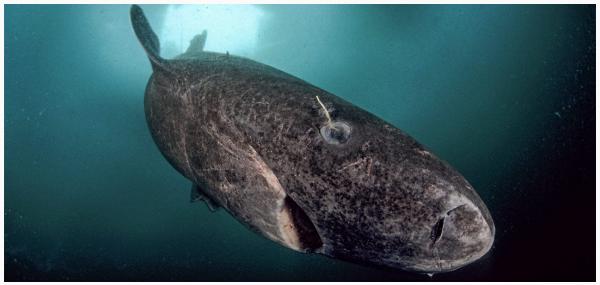
Why is Aging a Problem?

Is Aging Necessary?

Animals that do not senescence (age)



Hydra (biologically immortal) [Martıñez, 1998]



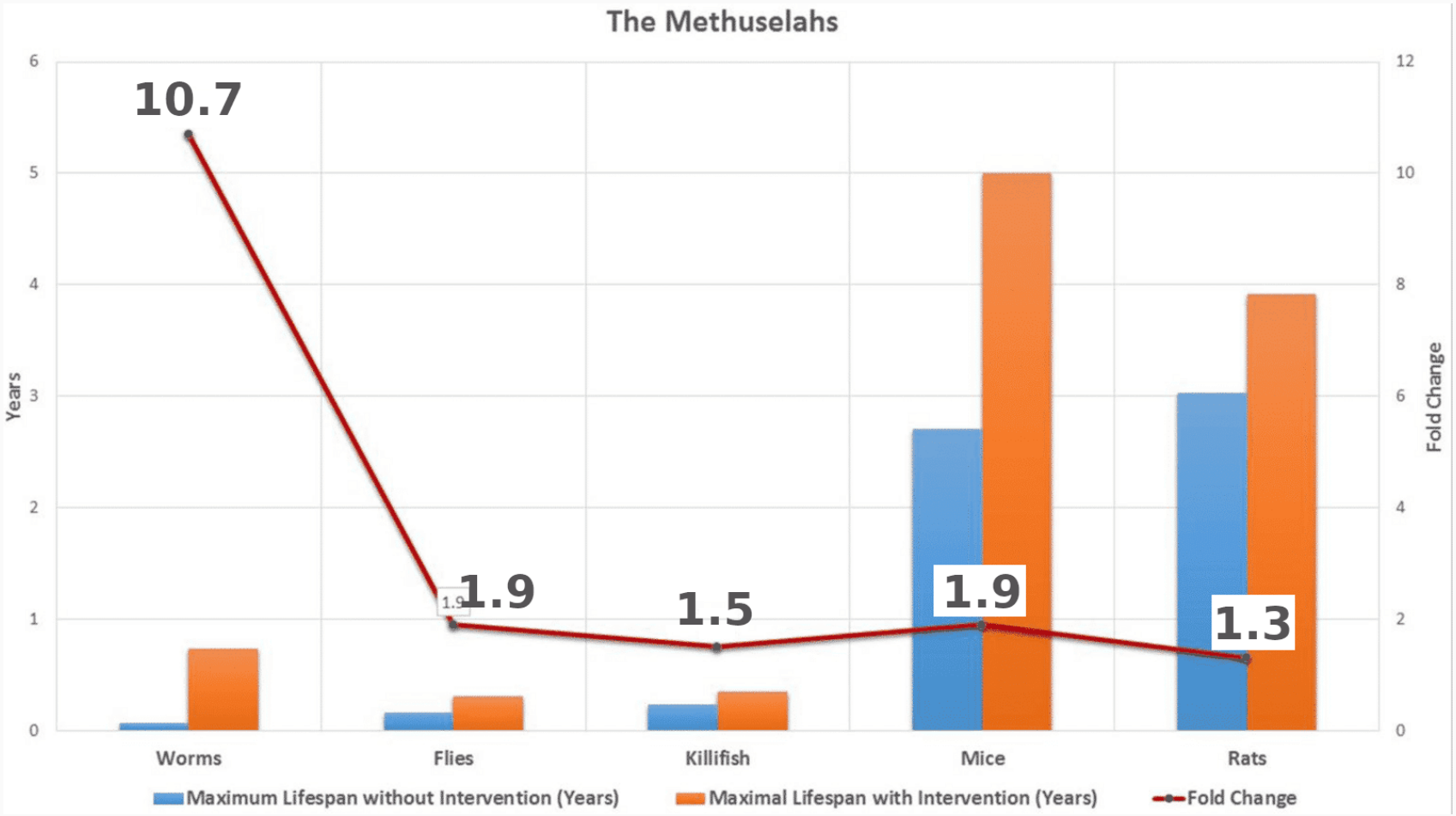
Greenland sharks: 400y [Pennisi, 2016]

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]

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What is Aging?

Definition and Hallmarks

Problematic: Many Unknowns

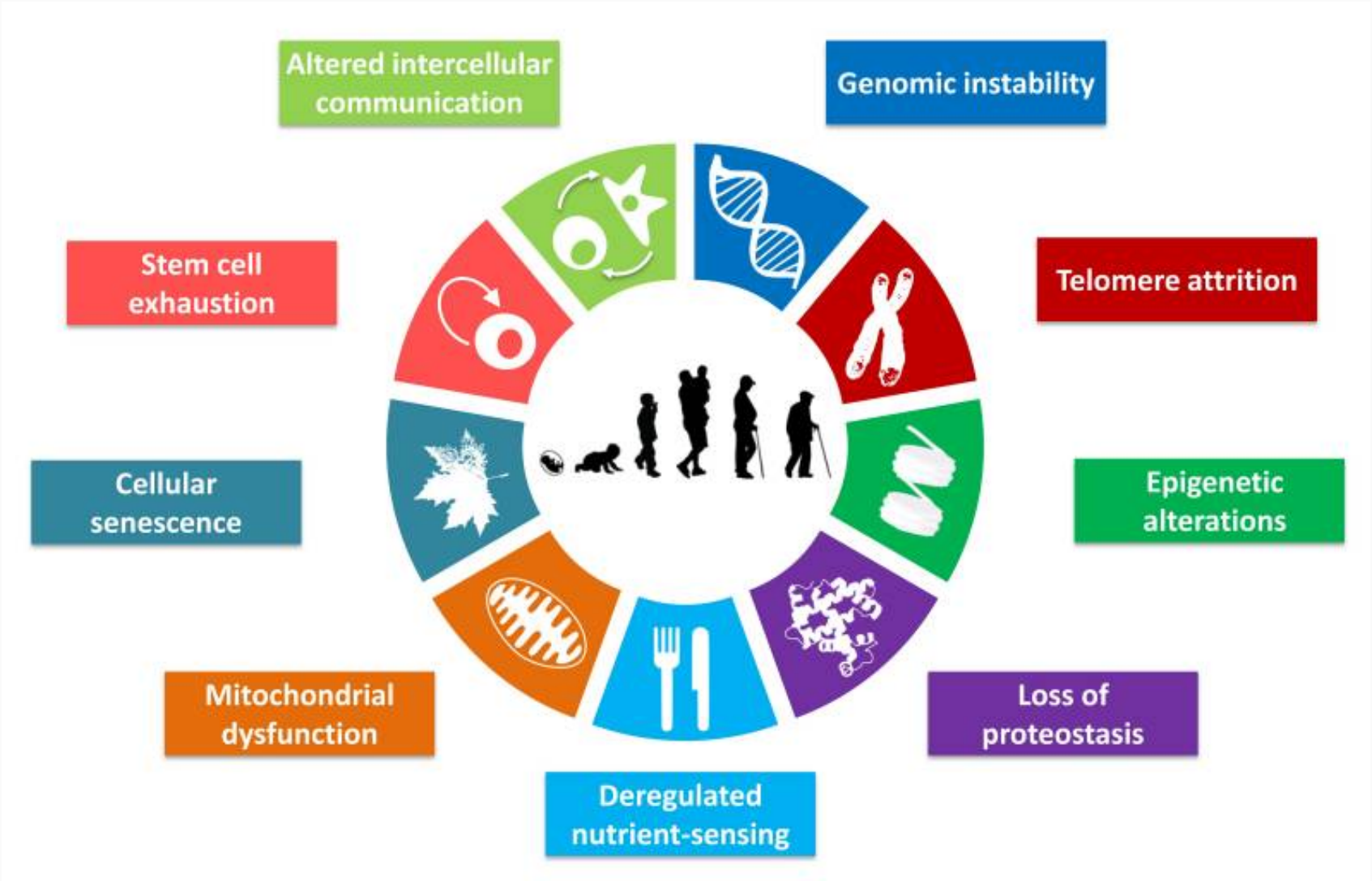
Aging

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



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 all 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

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How can we Slow down Aging?

Overview

Parabiosis

Metabolic Manipulation

Senolytics

Cellular Reprogramming

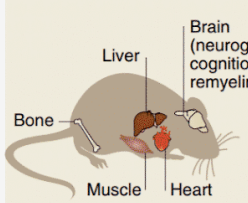
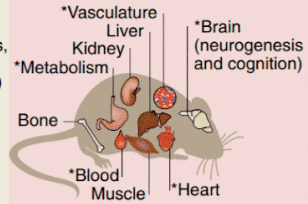
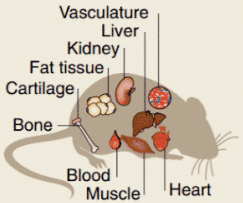
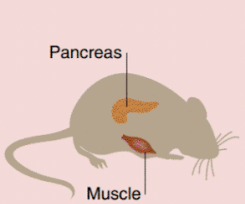
Other Approaches

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 neglegible senescence. Intermediate goals include slowing down aging, and increasing QUALYs (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
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

Source: [Mahmoudi et al., 2019]

How can we Slow down Aging?

Overview

Parabiosis

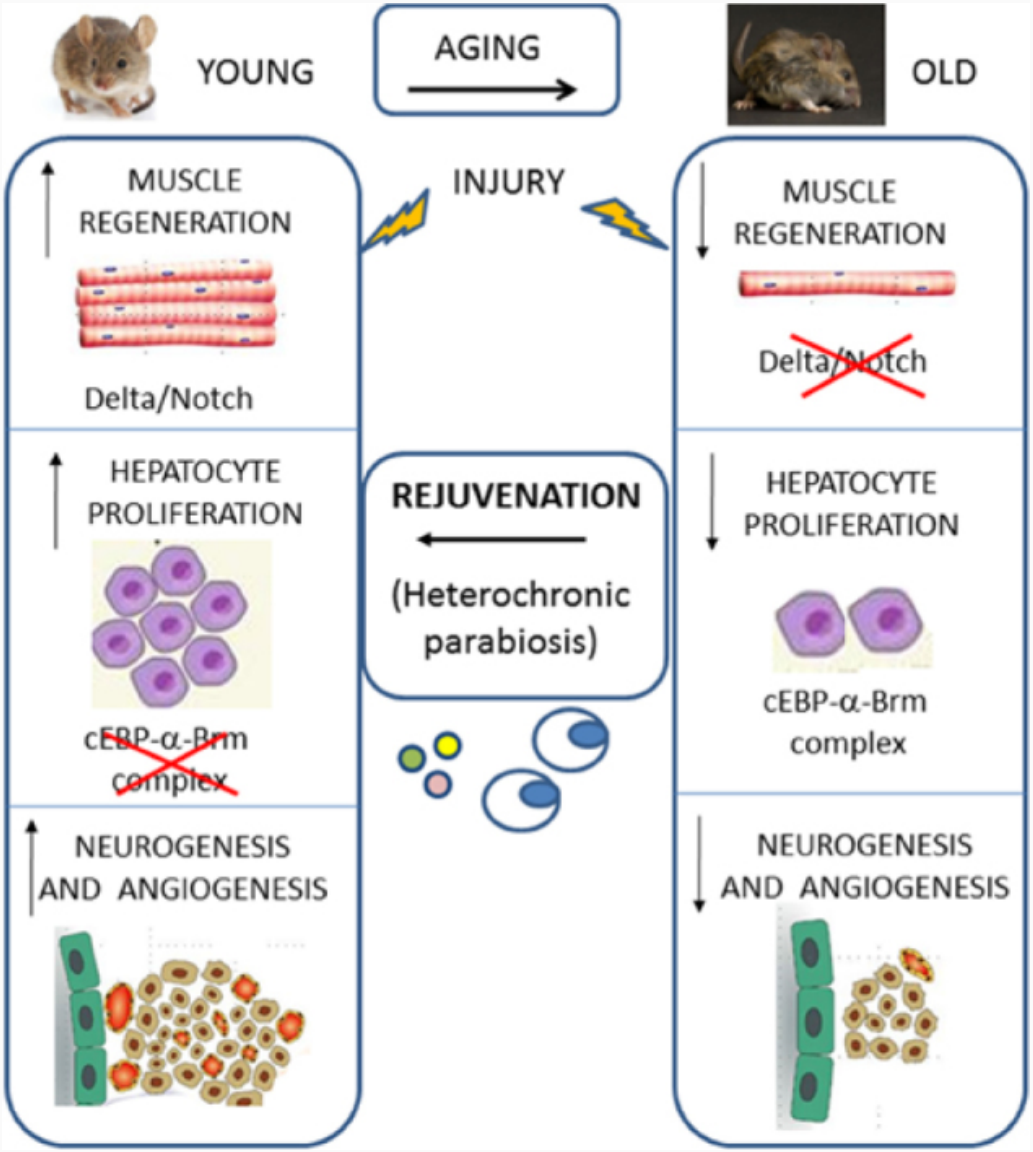
Metabolic Manipulation

Senolytics

Cellular Reprogramming

Other Approaches

Parabiosis (Blood Exchange)



Source: [Conese et al., 2017]

Method Evaluation: Parabiosis

Hallmarks affected:

> *'In principle, the heterochonic 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?

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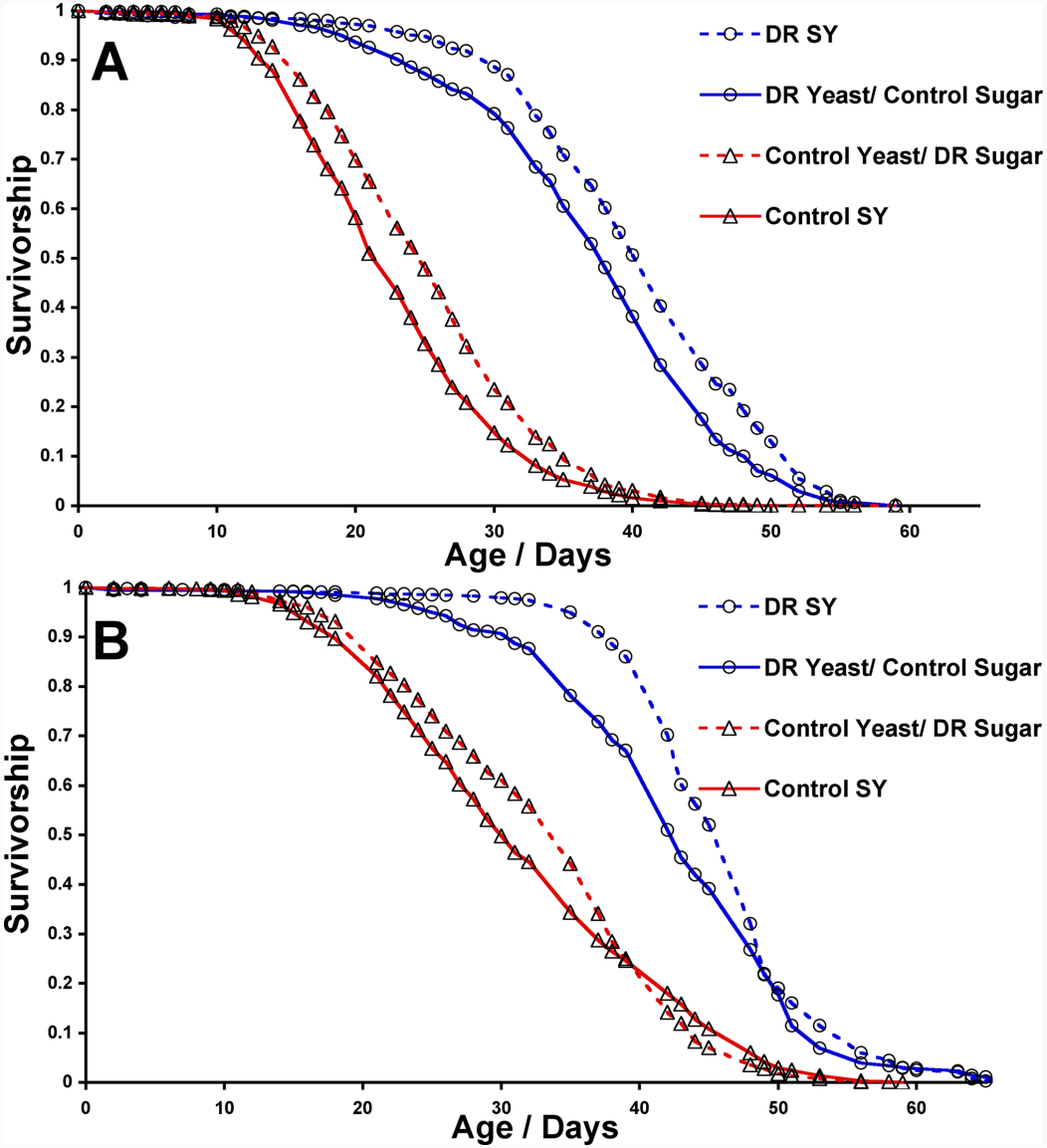
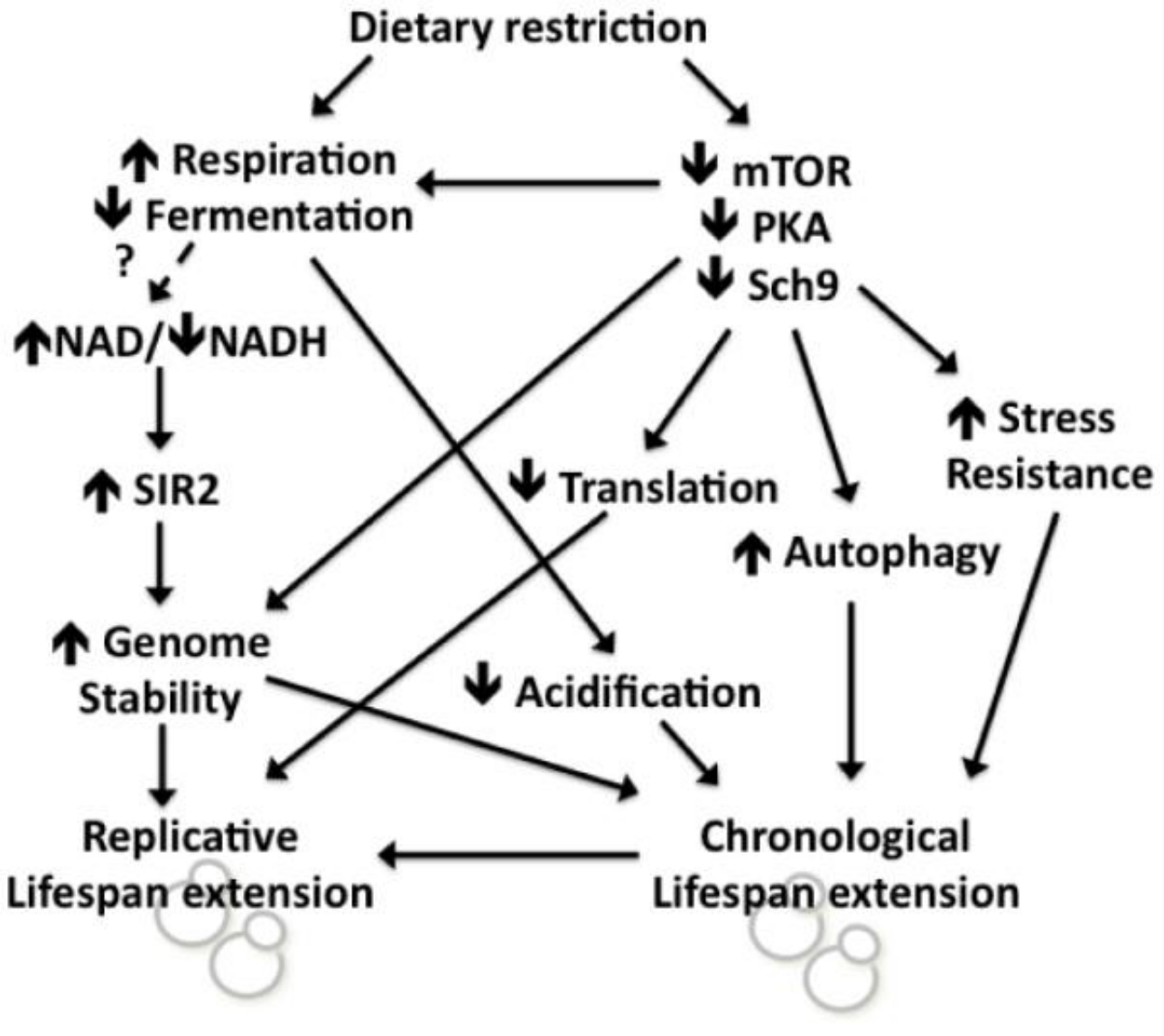
Dietary Restriction in D. melanogaster (Fruit Fly)



Source: [Mair et al., 2005]

Dietary Restriction Pathways in Yeast



Source: [Kapahi et al., 2017]

Dietary Restriction Effects

- 'Different' mitochondrial energy production (less ROS)
- 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:

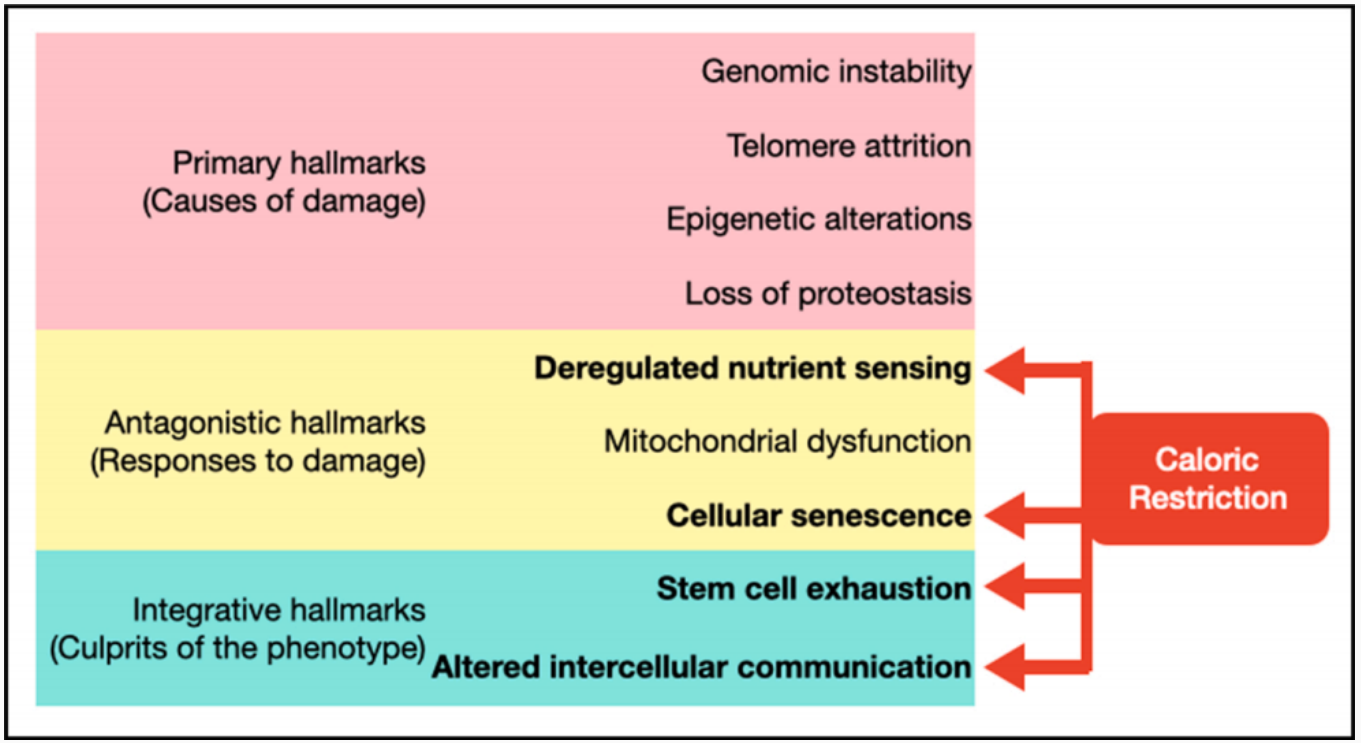
- AMPK
- mTOR
- IGF-1

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% QUALY [Swindell, 2012]

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

How can we Slow down Aging?

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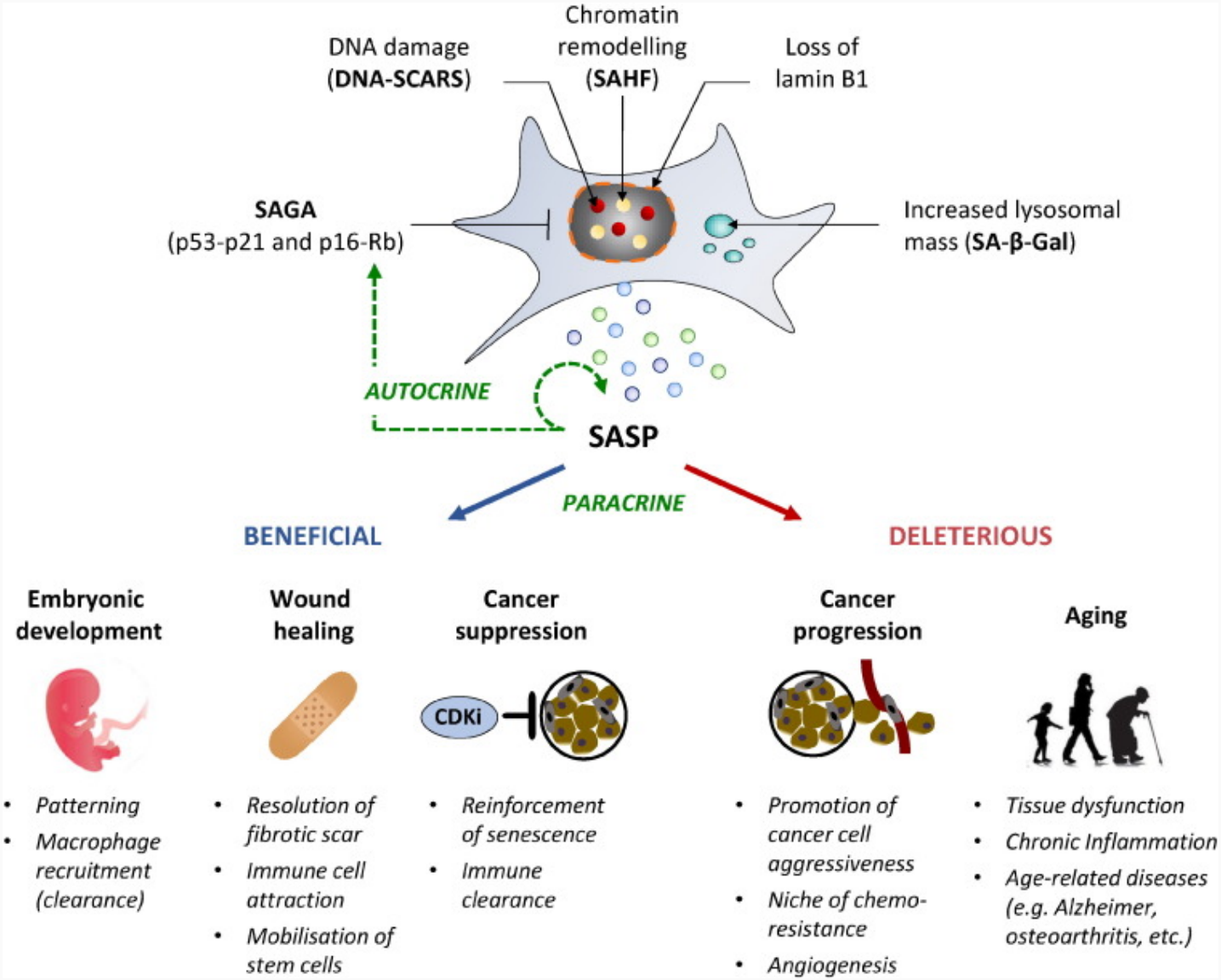
Other Approaches

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



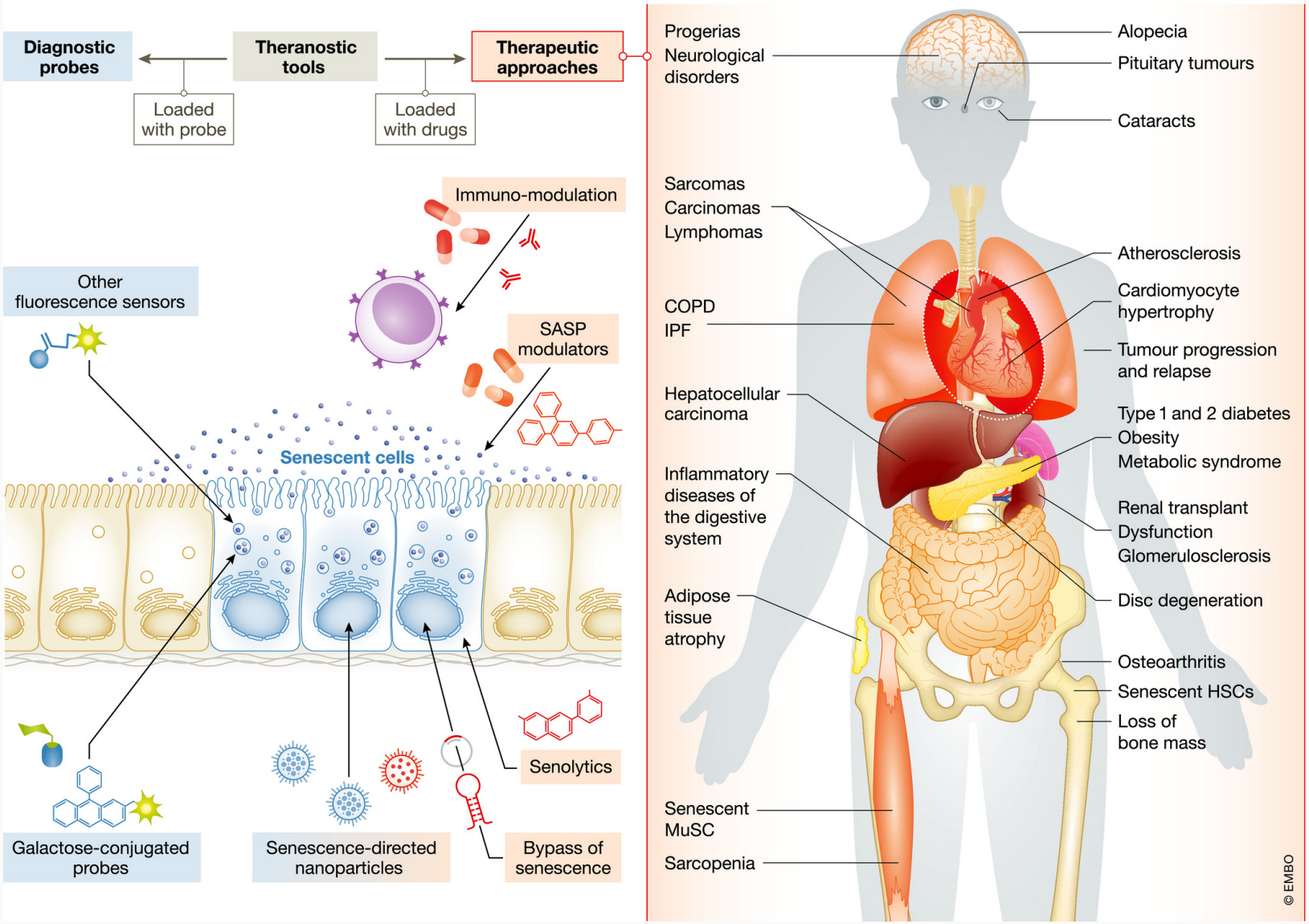
Source: [Malaquin et al., 2016]

Inflammation Effects

'Also, the environment that inflammation creates is one that is *meant to increase cell turnover* (More apoptosis, but also more cell growth to replace lost cells), with granulocytes secreting toxic agents (Including ROS) to make the area affected less hospitable (But also increases damage to DNA), and specific cytokines like the *tumor necrosis factor that induce cell death, and growth factors that promote cell growth.*'

[Ricón, 2020]

Senolytics: Uses and Effects



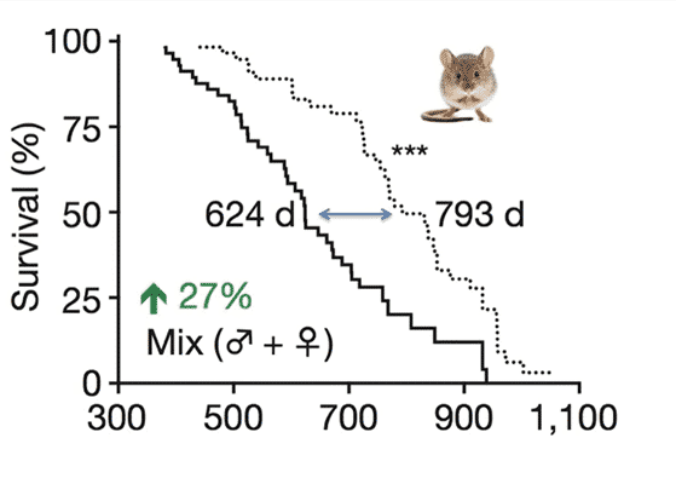
Source: [Paez-Ribes et al., 2019]

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?

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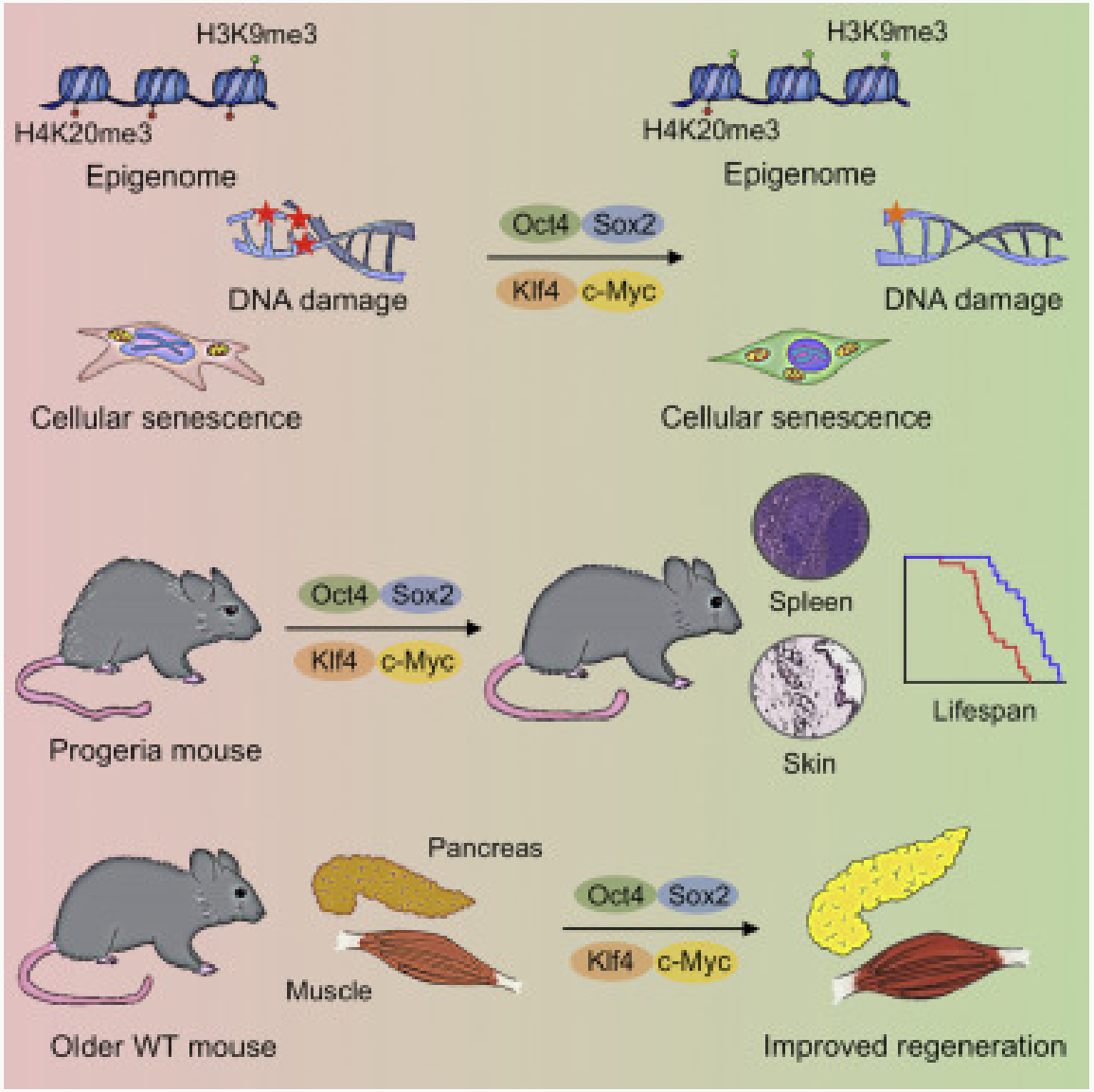
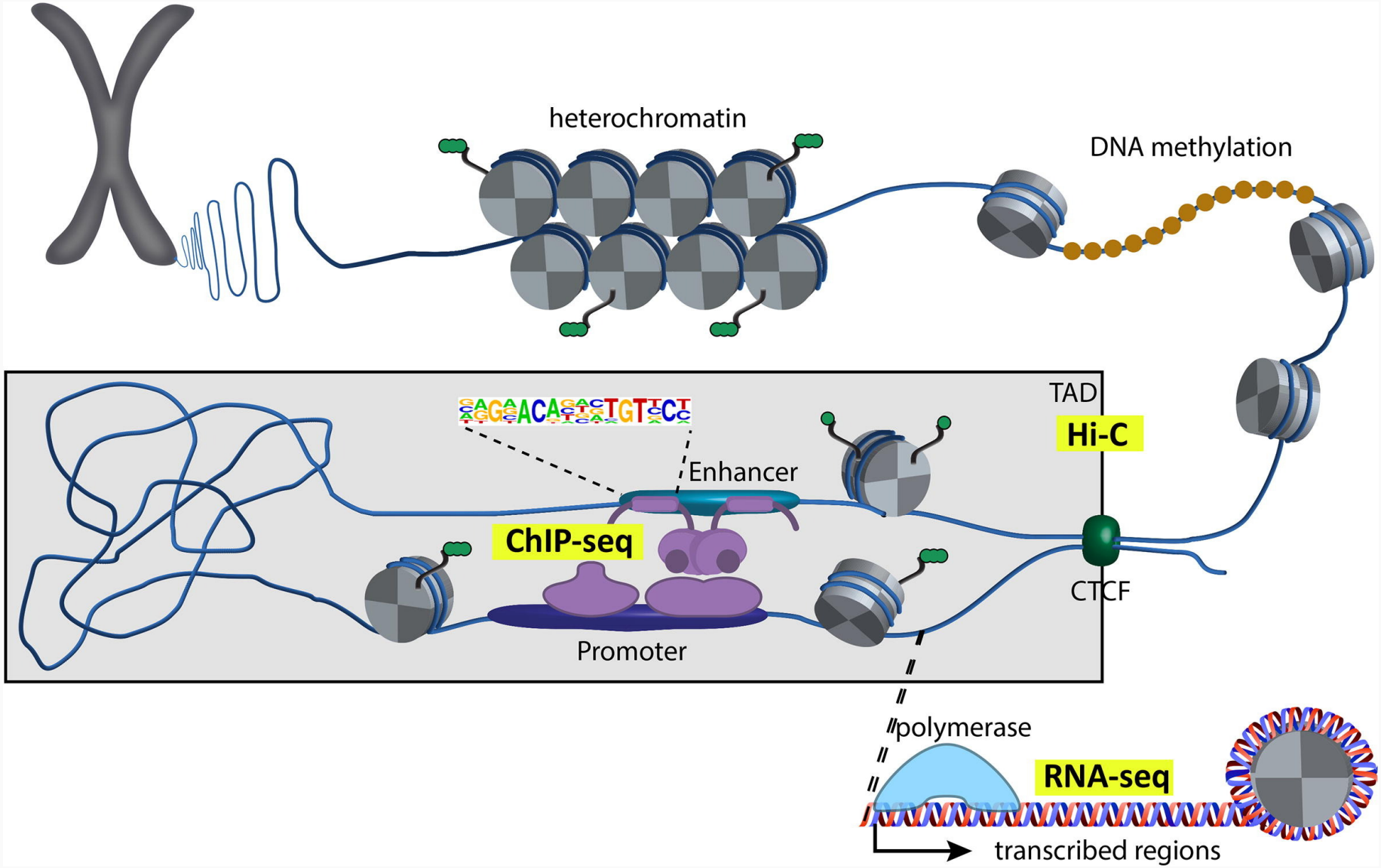
Other Approaches

(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 (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?

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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: ???

State: Active research, some are in clinical trials

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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 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

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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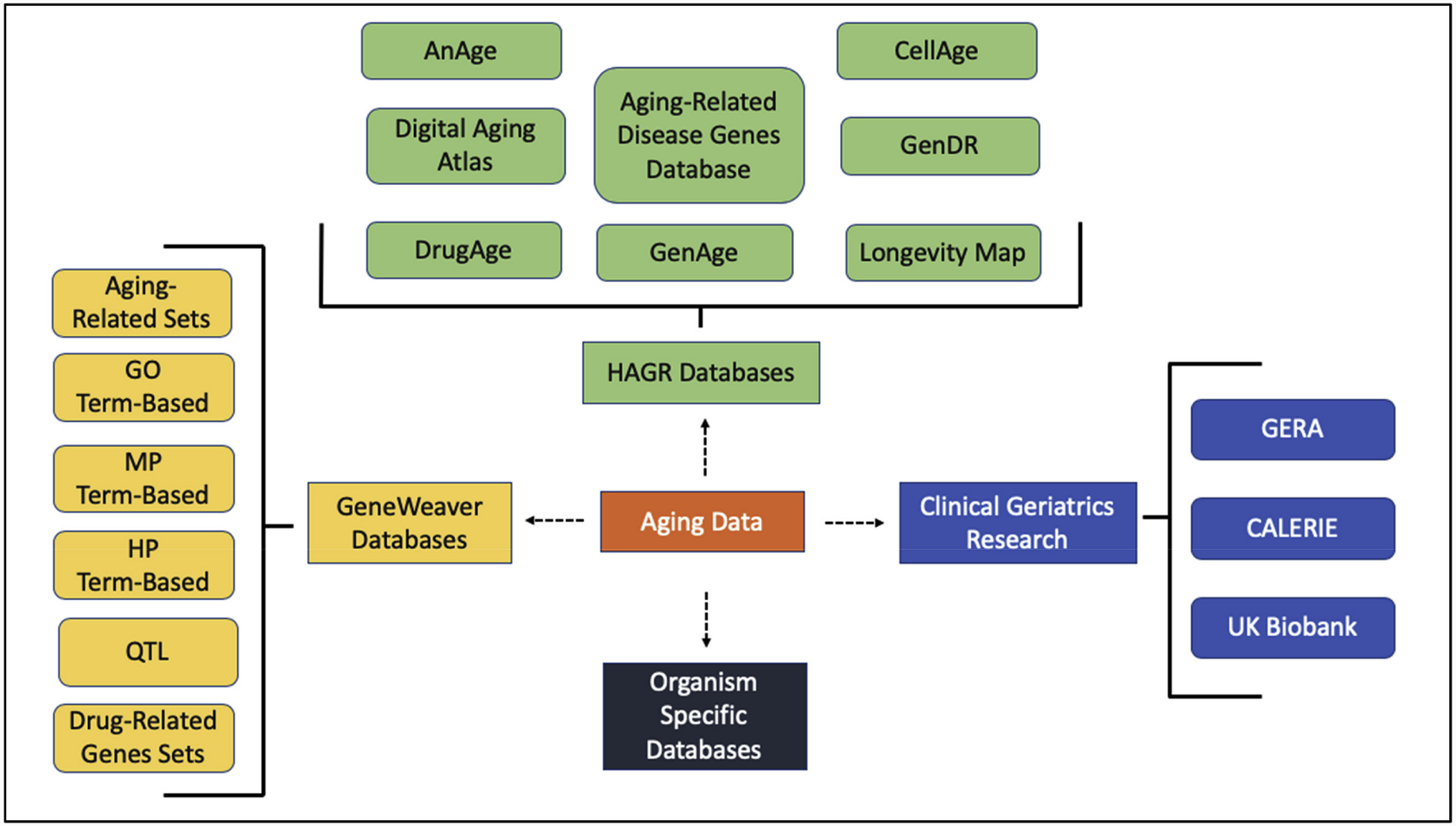
Where can Bioinformatics Help?

Databases and Tools for Analysis

Machine Learning

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
- Classifying genes in model organisms as pro- or anti-longevity
- Prediction of aging-related genes
- Identification of improved biomarkers for aging in humans
- Establishing aging- and mortality-related gene expression profiles in humans

According to [Kruempel et al., 2019], [Putin et al., 2016], [Townes et al., 2020], [Kerber et al., 2009], [Nakamura and Miyao, 2007]

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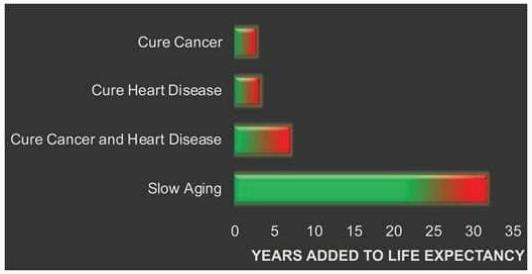

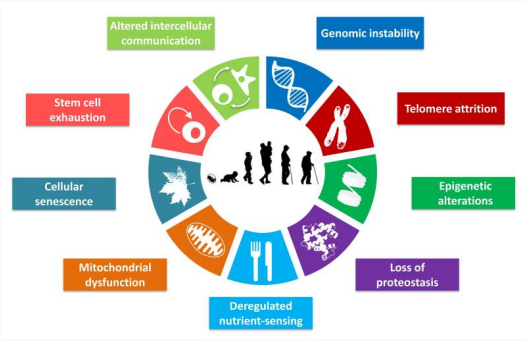

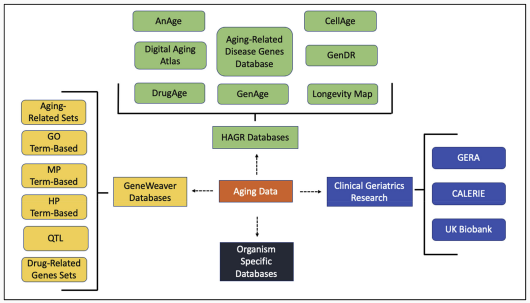

- There is a lot to do, and steady progress happening!
- We already know a lot!
- The first large-scale studies are starting!
- We will learn a lot in the next few years!

What are your Questions?

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