mTOR inhibitors and aging – should we take account of their potential?

16th September 2024

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Longevity-19

3D – Current and future trends in life expectancy

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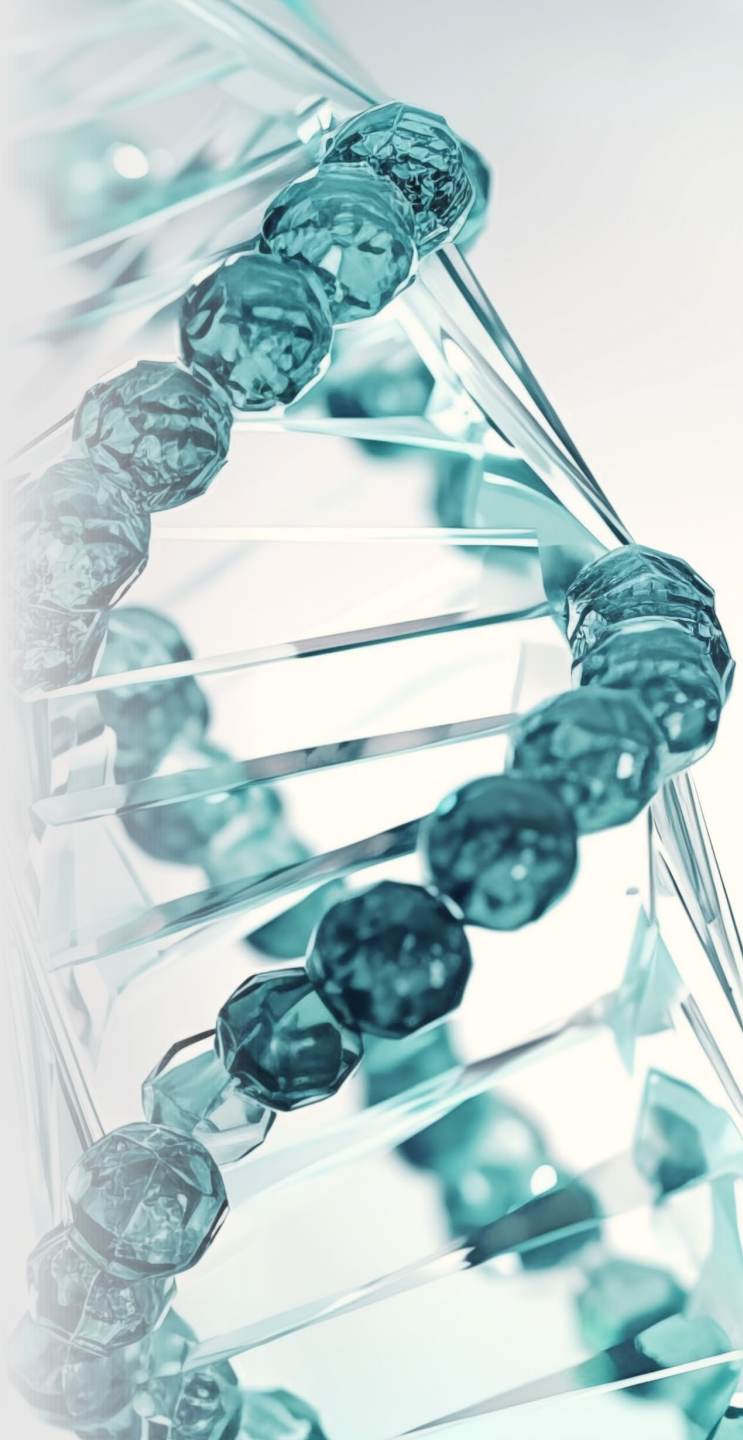
Mechanistic Target of Rapamycin (mTOR)

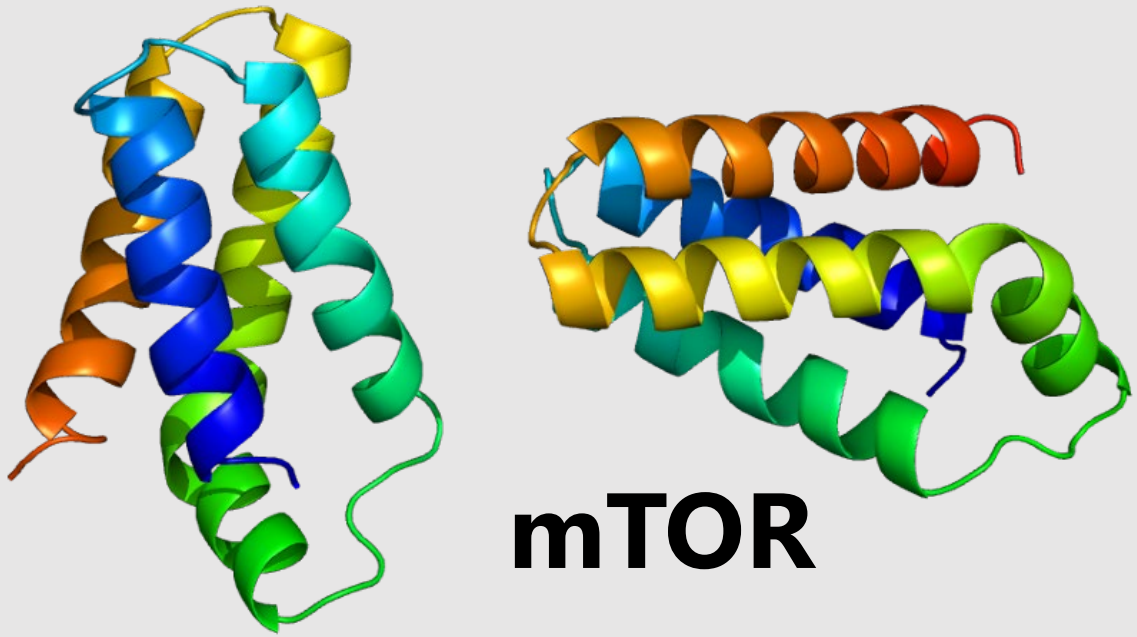


mTOR

mTOR = '**m**echanistic **t**arget **o**f **r**apamycin'

Previously '**m**ammalian', but was discovered to be conserved across animals – evolutionary ancient

A natural protein 'switch' that activates growth



mTOR

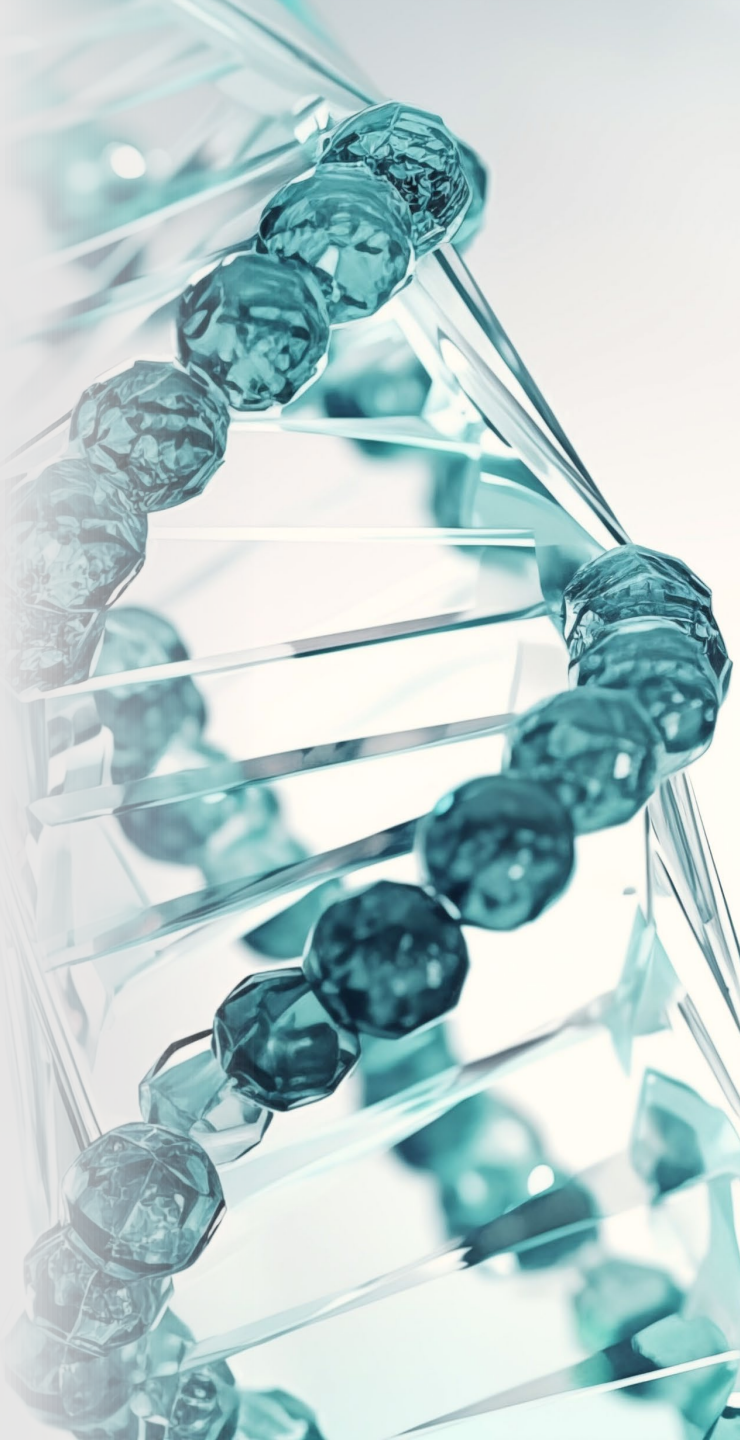
Actions of mTOR

mTOR plays a critical role in regulating growth. It has also been found to be important in the process of aging and aging-related diseases by influencing key cellular processes.

When food is plentiful, mTOR senses this abundance and signals cells to grow and multiply faster, producing more protein, fats and cholesterol.

Inhibition of mTOR reduces the size and quantity of cells, but promotes the function of quality control mechanisms, improving their efficiency.

mTOR inhibitors



Rapamycin

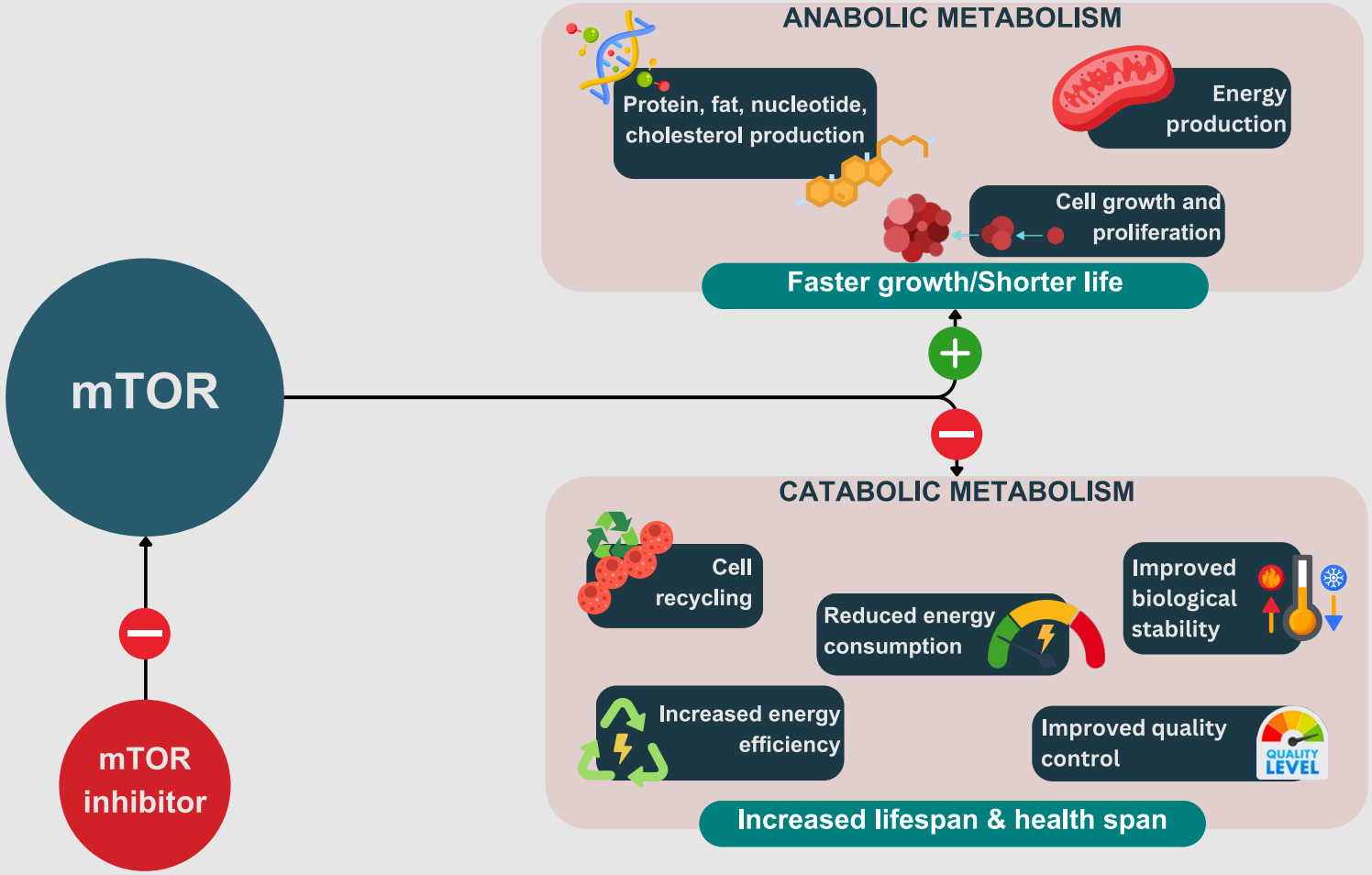
Rapamycin was first extracted from a bacteria called ***streptomyces hygroscopius*** that identified in the soil of Easter Island (Rapa Nui) in 1975. It was found to have potent antifungal properties.

Later it was found to have immunosuppressant and anti-cancer effects and has been developed as drug to suppress immunity, treat cancer and as a coating for coronary stents which can get blocked by overgrowth of cells. All these applications are possible because ***rapamycin reduces cell growth and proliferation***.

mTOR inhibition

Inhibiting the action of mTOR reduces cell proliferation and growth, but also stimulates the recycling of cells and cell components, removing dysfunctional elements and making cells more efficient.

In 2009 a study of yeast cells discovered that inhibiting mTOR with rapamycin extended lifespan.

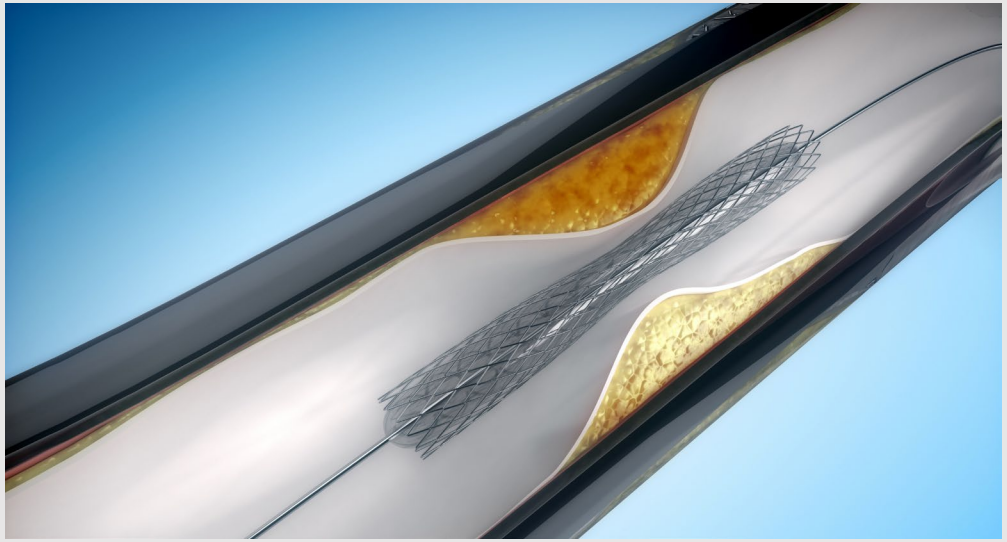


Harrison, D., Strong, R., Sharp, Z. et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 460, 392–395 (2009). https://doi.org/10.1038/nature08221

Development of mTOR inhibitors

Current clinical uses of mTOR inhibitors include:

- Immunosuppressants to prevent rejection of organ transplants
- Anti-cancer treatments
- Prevention of re-stenosis of coronary stents



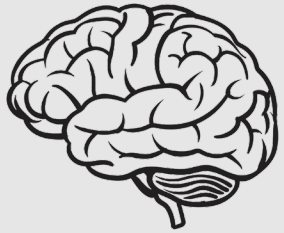
Dog Aging Project

Under investigation as a 'gero-therapeutic':

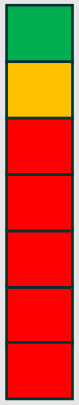
- 15 years of studies showing mTOR inhibitors extend lifespan in mice
- TRIAD trial (**t**est of **r**apamycin **i**n **a**ging **d**ogs)
- Meta-analysis of investigating the effect of mTOR inhibitors on markers of aging

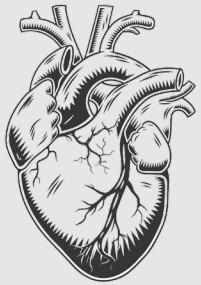
Mannick, J.B., & Lamming, D. (2023). Targeting the biology of aging with mTOR inhibitors. Nature Aging, 3, 642 - 660.
https://dogagingproject.org/triad
Lee DJW, Hodzic Kuerec A, Maier AB. Targeting ageing with rapamycin and its derivatives in humans: a systematic review. Lancet Healthy Longev. 2024;5(2):e152–62.

Trials of mTOR inhibitors on markers of aging

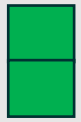


Nervous system

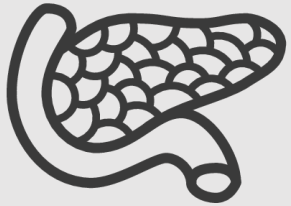




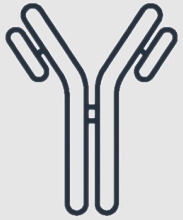
Cardiovascular



Skin

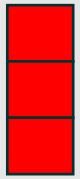


Endocrine system



Immune system

Muscles



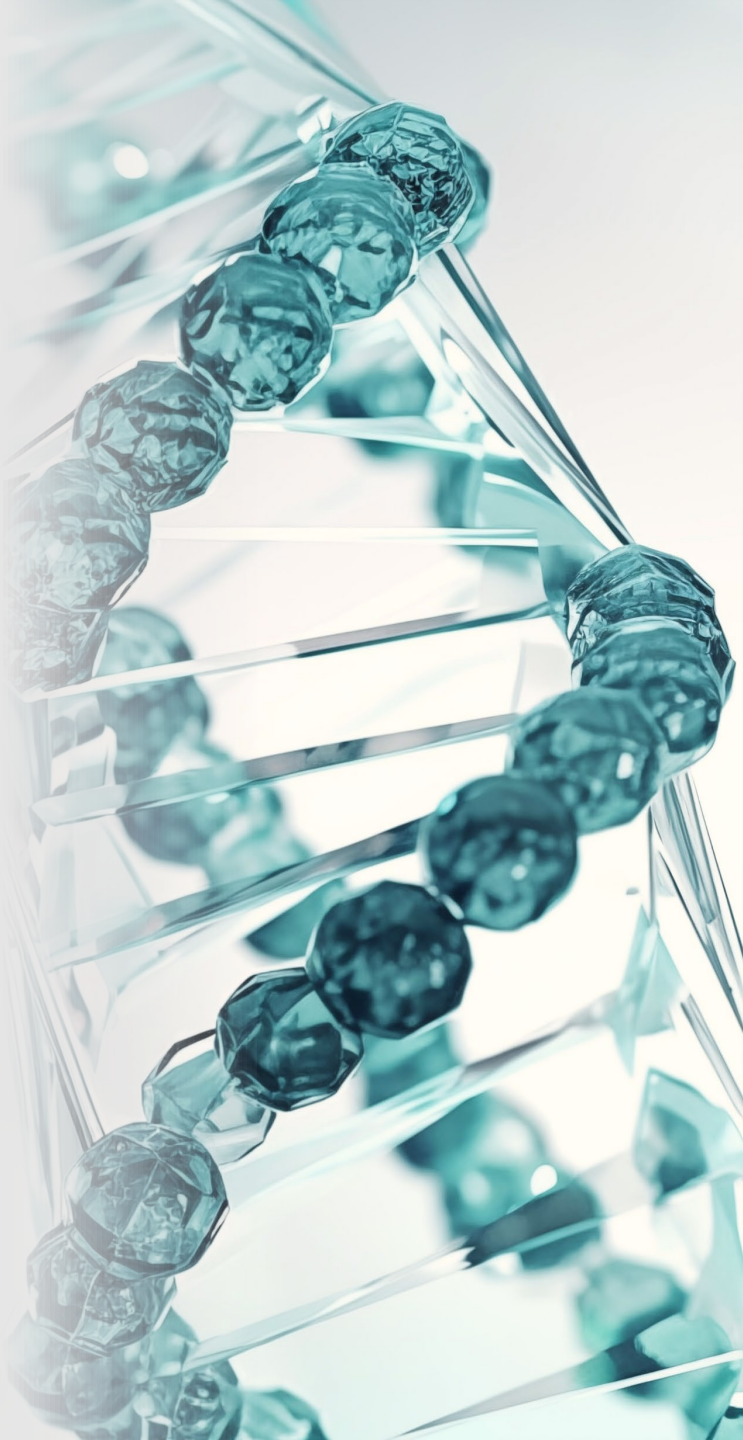
Positive trial

Partially positive trial

No effect trial

Lee DJW, Hodzic Kuerec A, Maier AB. Targeting ageing with rapamycin and its derivatives in humans: a systematic review. Lancet Healthy Longev. 2024;5(2):e152–62.

Hallmarks of aging



The Hallmarks of aging

Primary
The initial triggers of cellular damage.

Antagonistic
These hallmarks act as responses to the damage caused by the primary hallmarks. Initially, they may be beneficial, but over time they can become harmful and contribute to aging.

Integrative
These are the hallmarks that arise from the damage and responses from the primary and antagonistic hallmarks, leading to the functional decline observed in aging.

Primary hallmarks and mTOR inhibitors

Telomere Shortening	Not directly affected
Epigenetic Alterations	Not directly affected
Loss of Proteostasis	**mTOR inhibitors decrease protein production**
Disabled Macro-autophagy	**Cell recycling is increased with mTOR inhibition**
Genomic Instability	Unaffected by mTOR inhibitors

Antagonistic hallmarks and mTOR inhibitors

Mitochondrial Dysfunction

mTOR inhibition promotes recycling of inefficient mitochondria

Cellular Senescence

mTOR inhibition slows down the development of senescent cells

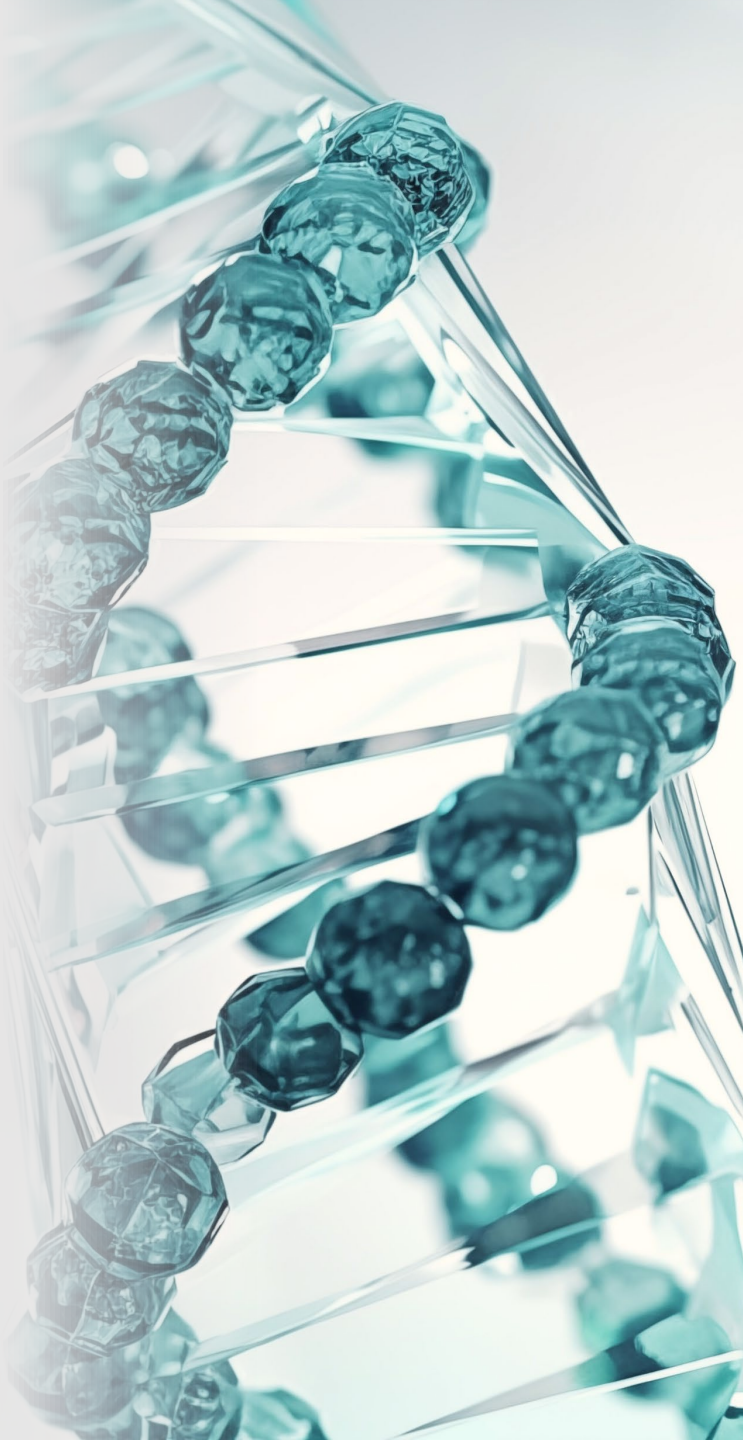
Deregulate Nutrient-sensing

mTOR inhibitors pushes metabolic function to reduced energy consumption and greater energy efficiency

Integrative hallmarks and mTOR inhibitors

 **Chronic Inflammation**	**mTOR inhibitors reduce chronic inflammation.**
 **Altered intercellular Communication**	**Not directly affected**
 **Dysbiosis**	**Not directly affected**
 **Stem Cell Exhaustion**	**mTOR inhibition increases stem cell numbers and function.**

The effect



Effect size in mice - longevity

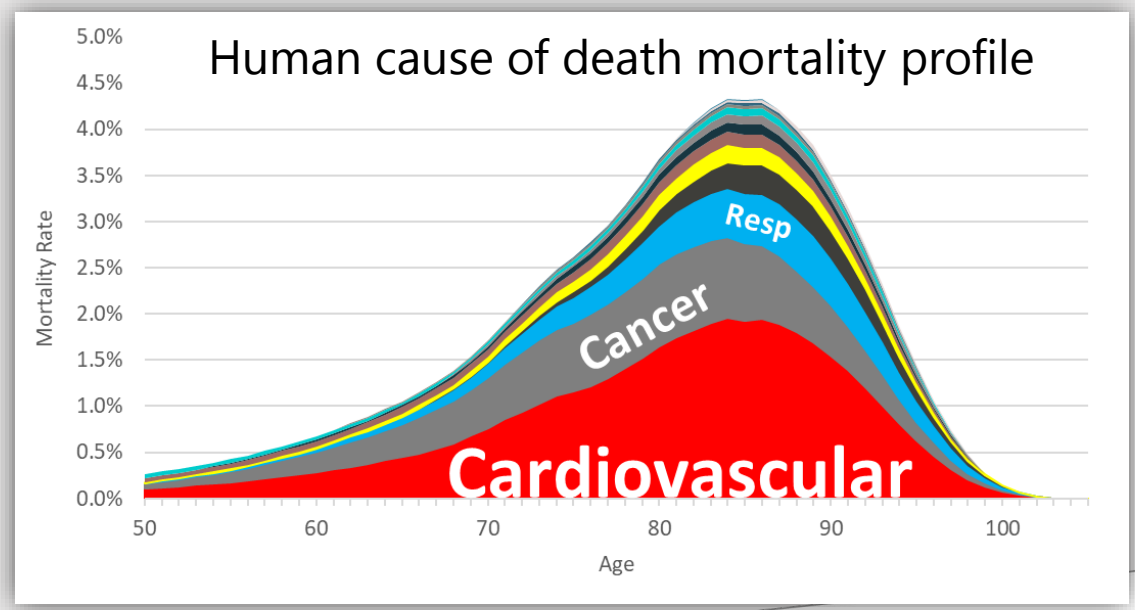
- Meta-analysis of **18 trials** of **rapamycin** on the lifespan of mice. Average of a **12% increase in lifespan** across the studies.
- **15 trials** with sufficient data to estimate the effect on the **rate of aging itself**.
- Fitting mortality models to the data suggest the **rate of aging** is reduced by about **37%**.

Image generated by ChatGPT, August 23, 2024, OpenAI

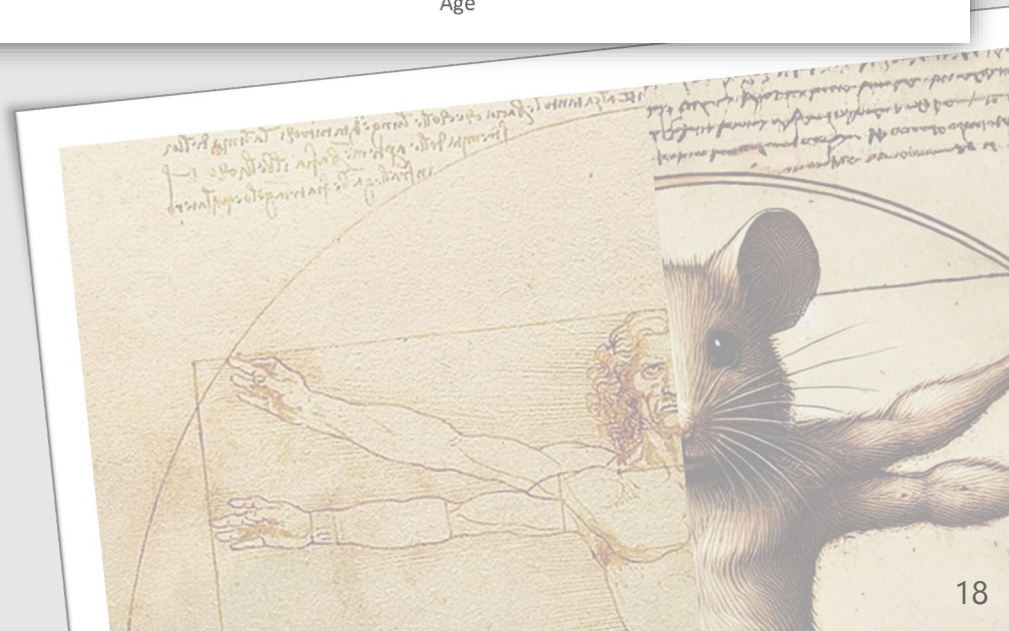
Mannick JB, Lamming DW. Targeting the biology of aging with mTOR inhibitors. Nat Aging. 2023;3:642–60.

Effect size in humans?

- Human are not mice
  - Our last common ancestor would have been a snack for a dinosaur
  - Mice are small, develop fast, breed fast, have **short lifespans**
  - Mice tend to die of **cancers**, humans of **cardiovascular diseases**
    - **different hallmarks** involved
    - **different effect sizes** from interventions



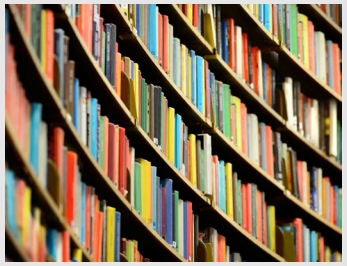
- Human lifespan trials are not a route to quick answers!



Leonardo da Vinci - Leonardo Da Vinci - Photo from www.lucnix.be / Image generated by ChatGPT, August 23, 2024, OpenAI

Modelling effect in humans – diseases and hallmarks

Fraser HC, Kuan V, Johnen R, Zwierzyna M, Hingorani AD, Beyer A, et al. Biological mechanisms of aging predict age-related disease co-occurrence in patients. Aging Cell. 2022 Apr;21(4):e13524



Mined nearly one million scientific articles and identified associations between mentions of **hallmarks of aging** and specific **human aging related diseases** to build a **map of associations**.

Mined 3 million patient health records for **associations between aging-related disease co-occurrence**.

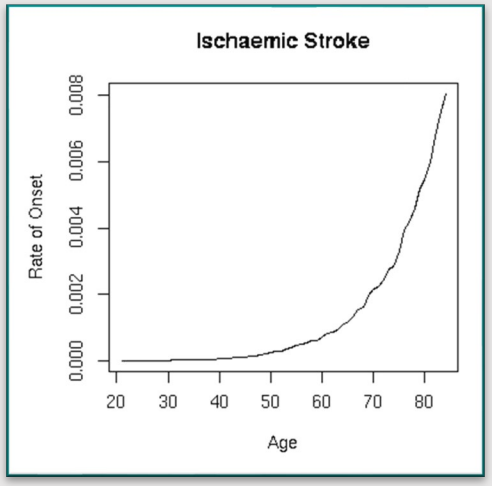
Mined a database of genome-wide associations to identify **genes linked to the top aging-related diseases and aging hallmarks**.

What hallmarks are associated with which human diseases?

Modelling effect in humans – diseases and aging

Kuan, V., Fraser, H.C., Hingorani, M. et al. Data-driven identification of ageing-related diseases from electronic health records. Sci Rep 11, 2938 (2021). https://doi.org/10.1038/s41598-021-82459-y

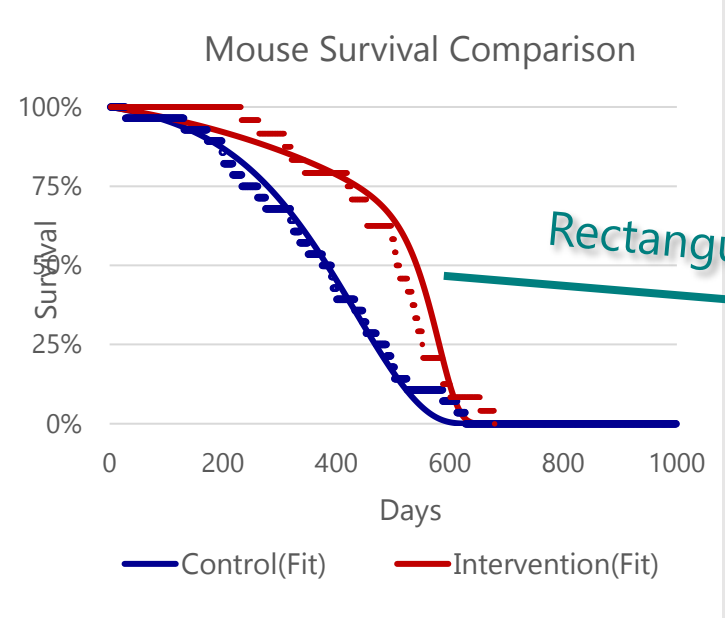
Mined 3 million patient health records for **age of onset** of high-burden diseases.



Fit to a **Gompertz-Makeham (GM) model**

We use **goodness of fit** (R^2) as a proxy measure of aging-relatedness of the disease – **"How much might progression of this disease be amenable to gerotherapeutics?"**

A longevity limit?



Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, et al. Naturally occurring p16Ink4a-positive cells shorten healthy lifespan. Nature. 2016 Feb;530(7589):184–9.

- In very old humans, mortality is increasingly **multimorbid** and/or **cryptic**
- ICD R00-R99 codes increasingly used – **unknown** and **unspecific**

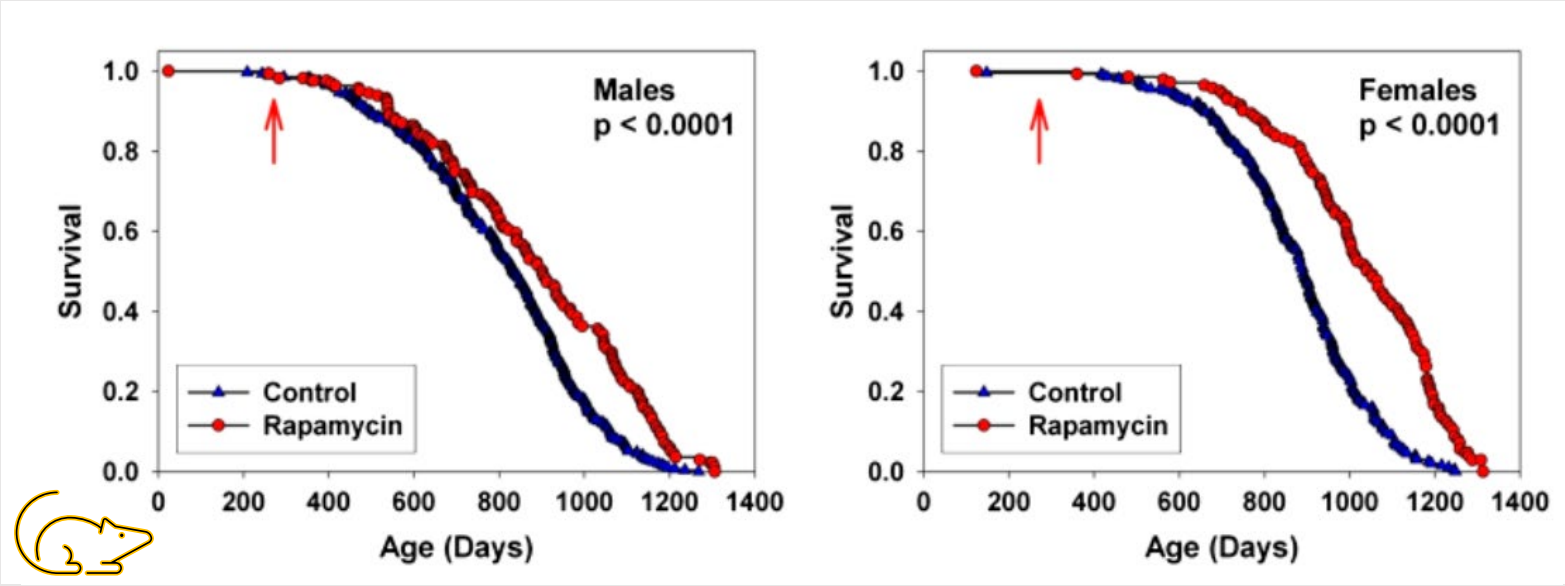
Rectangularisation

Supports a **limit** to aging interventions

- Coverage of aging processes by hallmarks and interventions is **incomplete**
- A ballooning list of damage and disorder will eventually **overwhelm any intervention**
- Thus, **very old ages are modeled with a separate Gompertz function**, regardless of aging rates up to this point

A longevity limit – mouse data, human model

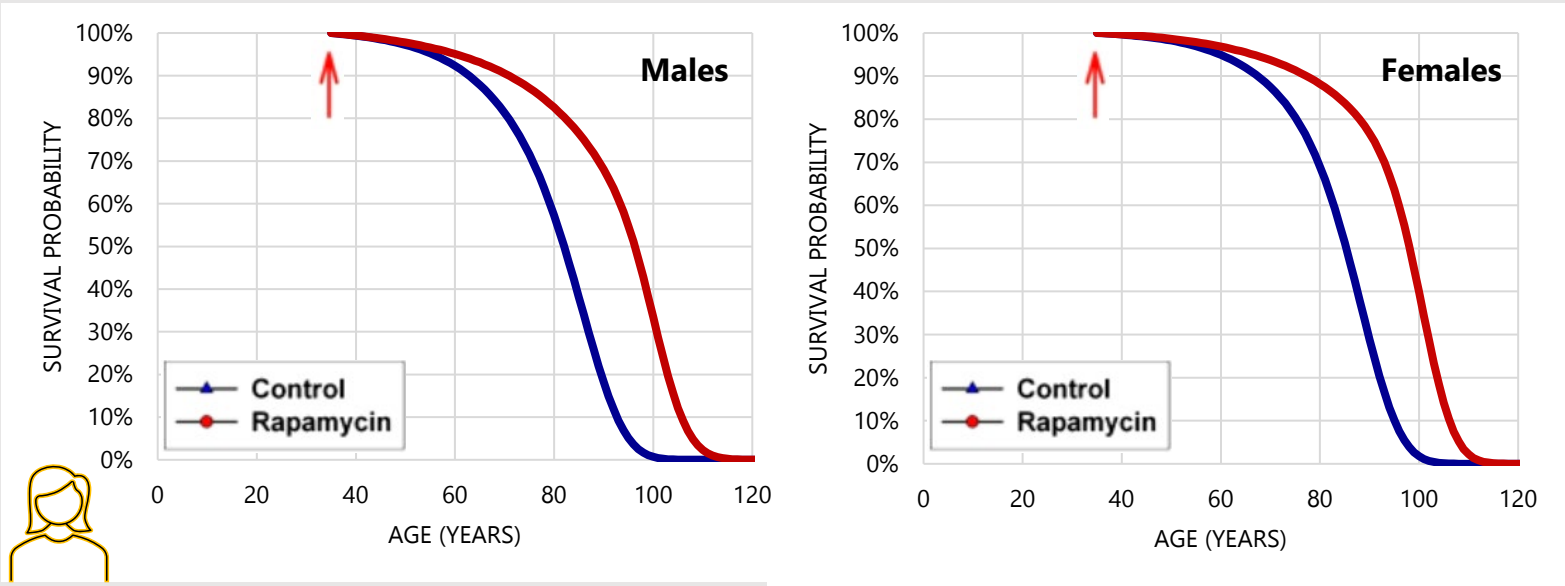
- **Mouse** experiment
- Rapamycin from 9 months



Miller RA, et al. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. J Gerontol A Biol Sci Med Sci. 2011 Feb;66(2):191-201. doi: 10.1093/gerona/glq178.

Figure 1.

- **Human** modelling
- Rapamycin from age 35 (similar life-phase)
- Double Gompertz



What limits the impact?

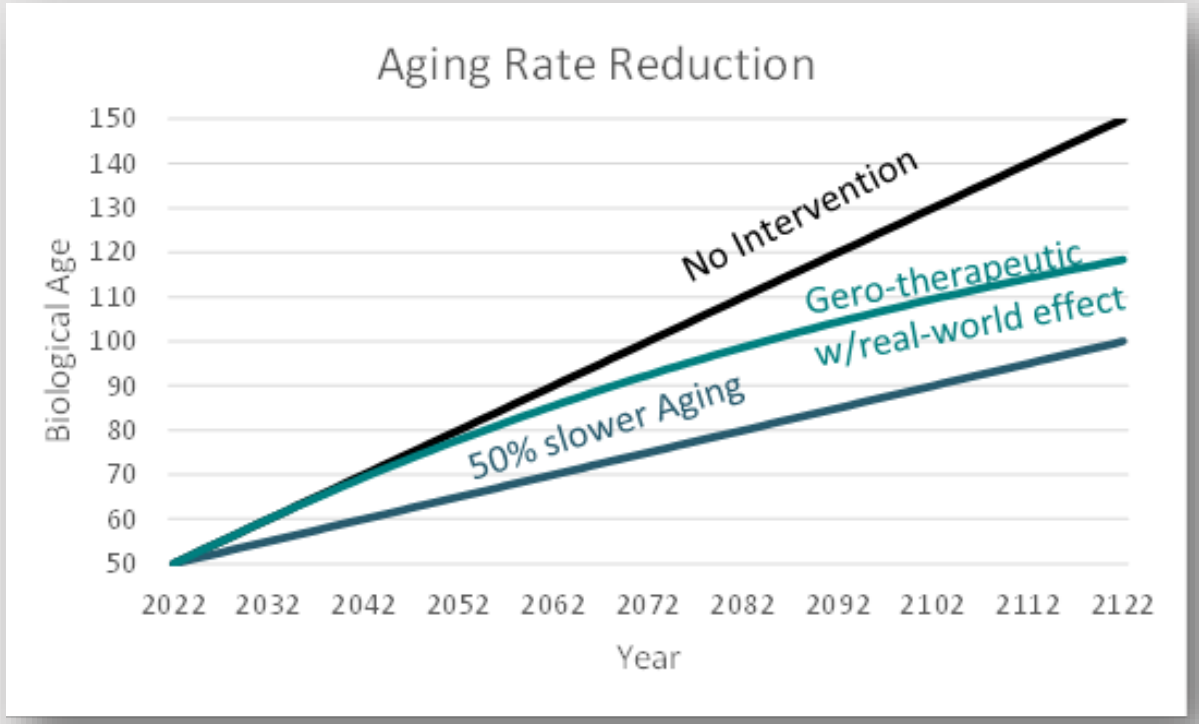
Estimating Future Biological Age

Aging Rate Reduction
- Gero-therapeutic Aging Rate Reduction from rodent studies

Disease-specific Aging Rate
- Currently observed disease-specific mortality rates by age/gender
- Proportion of disease likely to be affected (aging relatedness)
- Evidence of link to hallmark of aging

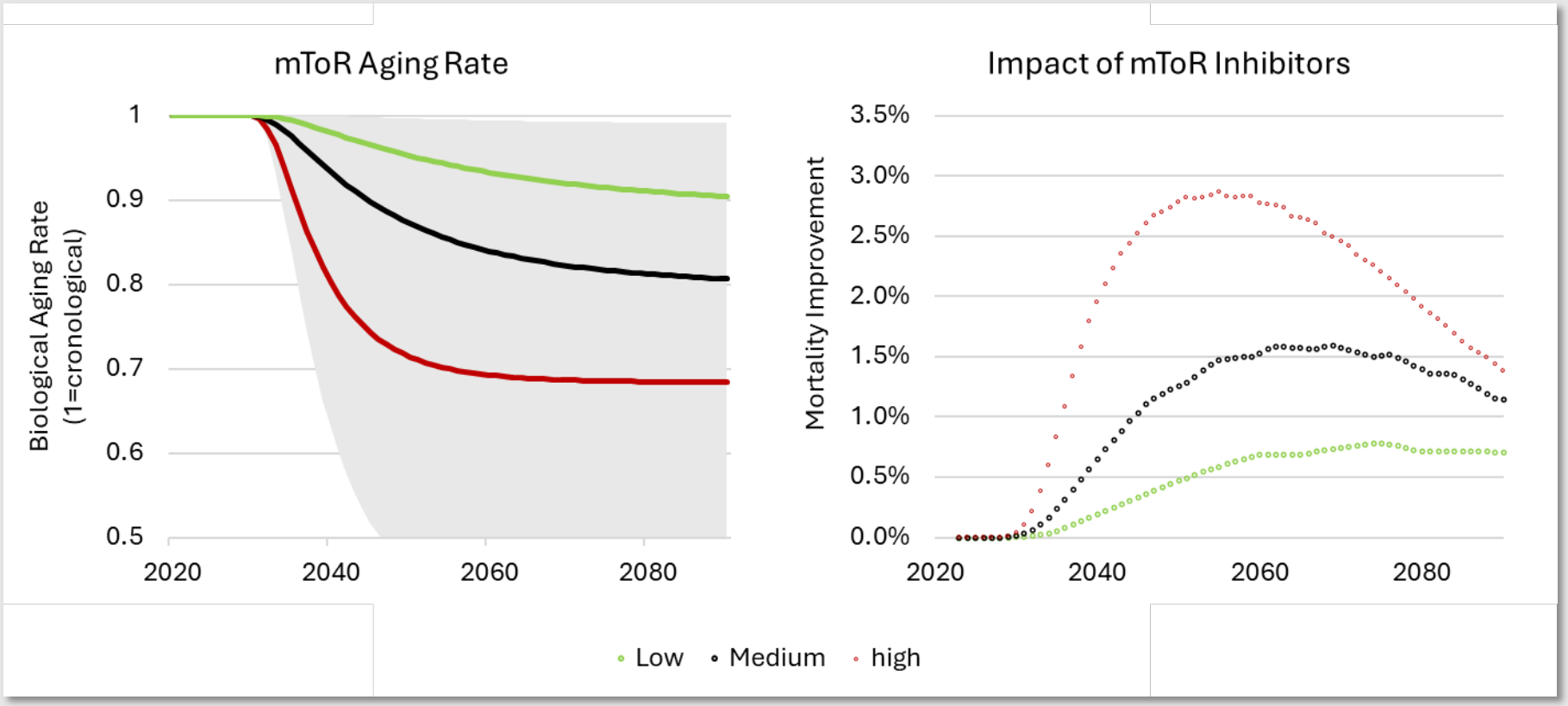
Take-up Transition
- Delay due to drug development pipeline
- Take-up transition

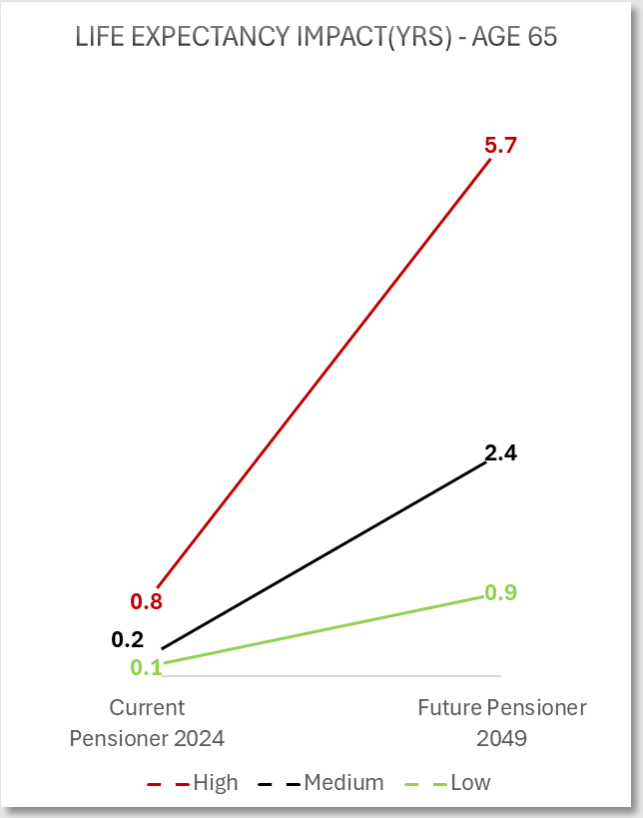
Access & Compliance
- Access to healthcare
- Compliance with intervention



A range of impact scenarios

Impact scenarios are highly sensitive to **take-up transition**, **access**, and **compliance**





Current Pensioner: age 65 now
Future Pensioner: age 65 in 25 years

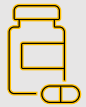
Key questions going forward

- How does gerotherapeutic effect **translate** between mice and humans?

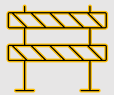
- What other **existing interventions** show promising gerotherapeutic effect?

- How will **clinical trial** design and regulatory approval **adapt** to assessing aging outcomes?
  - **Incidence** of diseases of aging?
  - Aging **biomarkers**?

- Which hallmarks and biochemical pathways represent the **best targets**?



- What can we expect from **gerotherapeutic polypharmacy**?



- Where might we expect **access** and **compliance** barriers?

Acknowledgements

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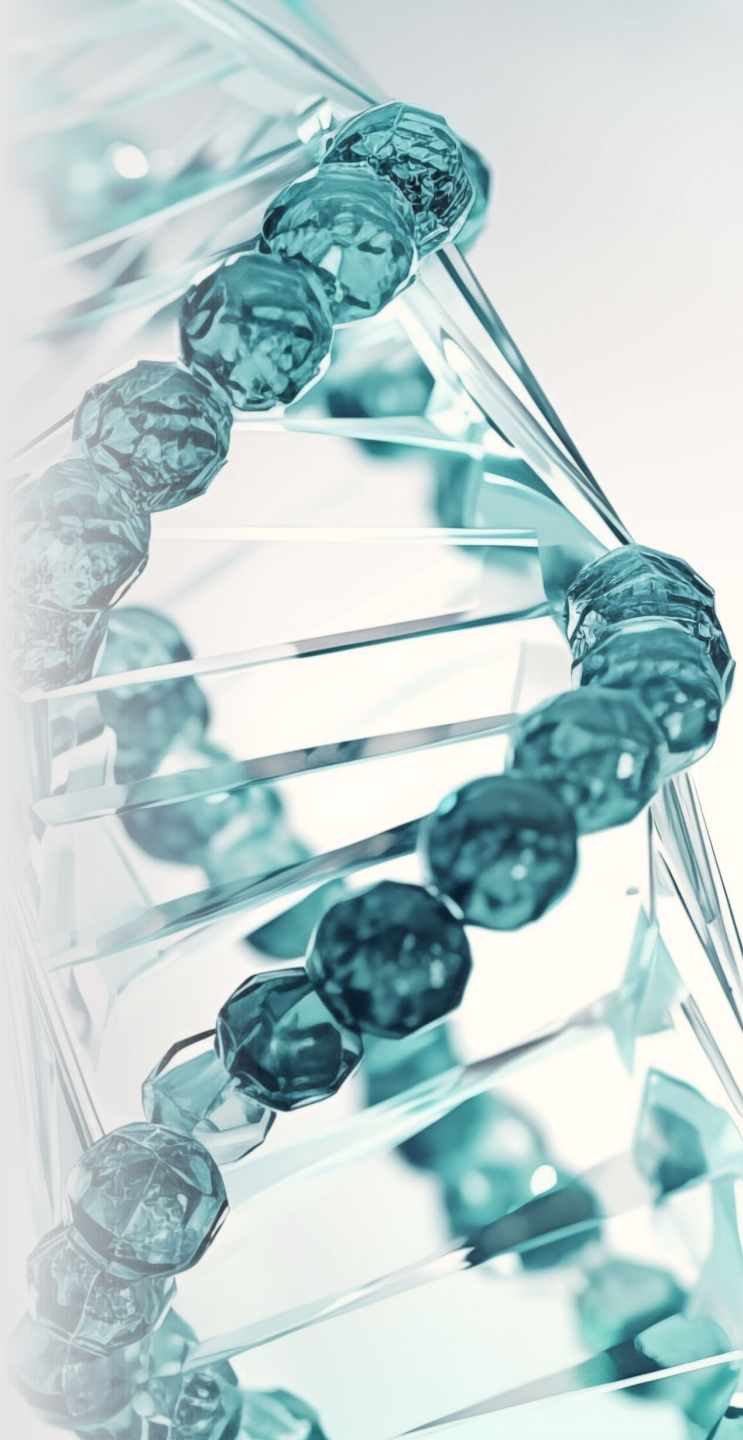
- **Uli Stengele**, FSA
- **Fred Slater**, FSA
- **Richard Faragher**, Professor of Biological Gerontology at the University of Brighton
- **Joseph Lu**, FIA
- The work was, in part, commissioned by the Longevity Science Panel and is currently being reviewed by them.



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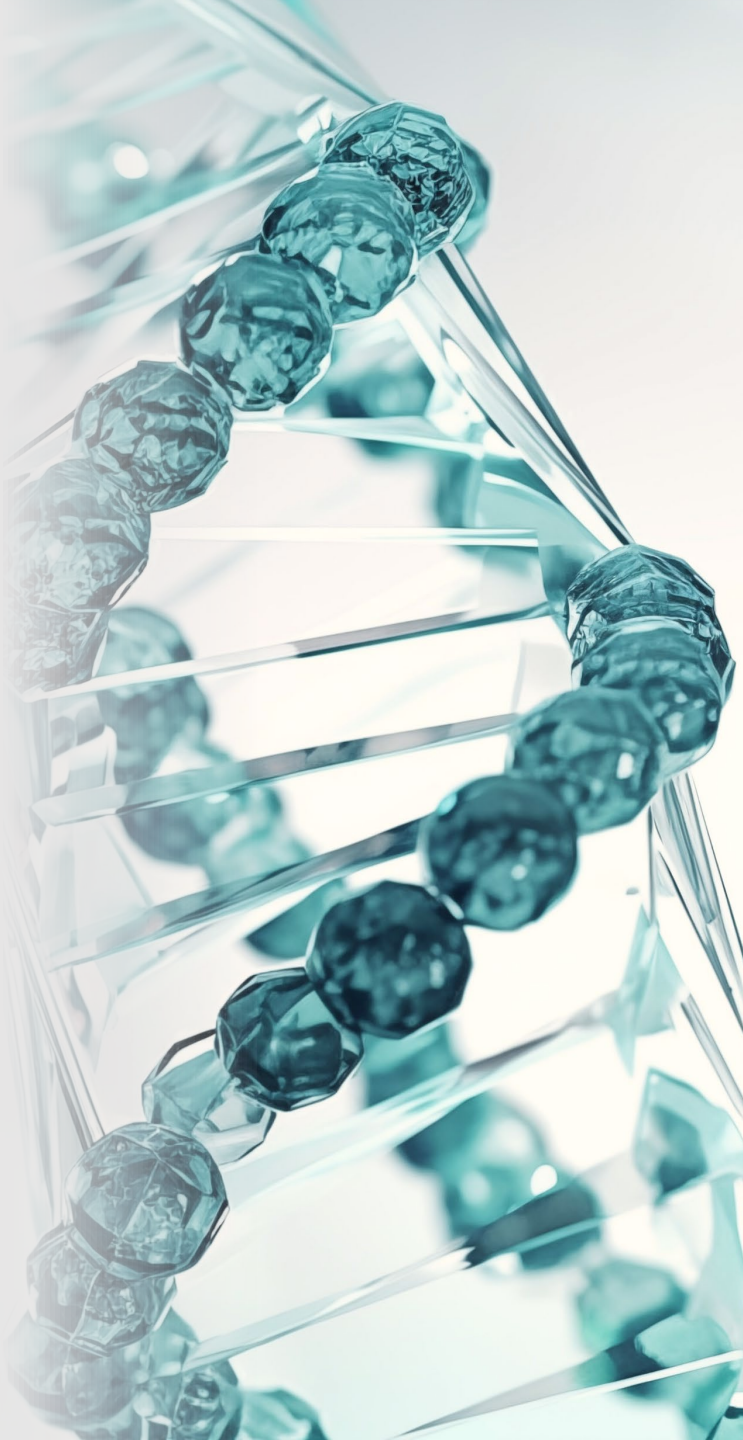

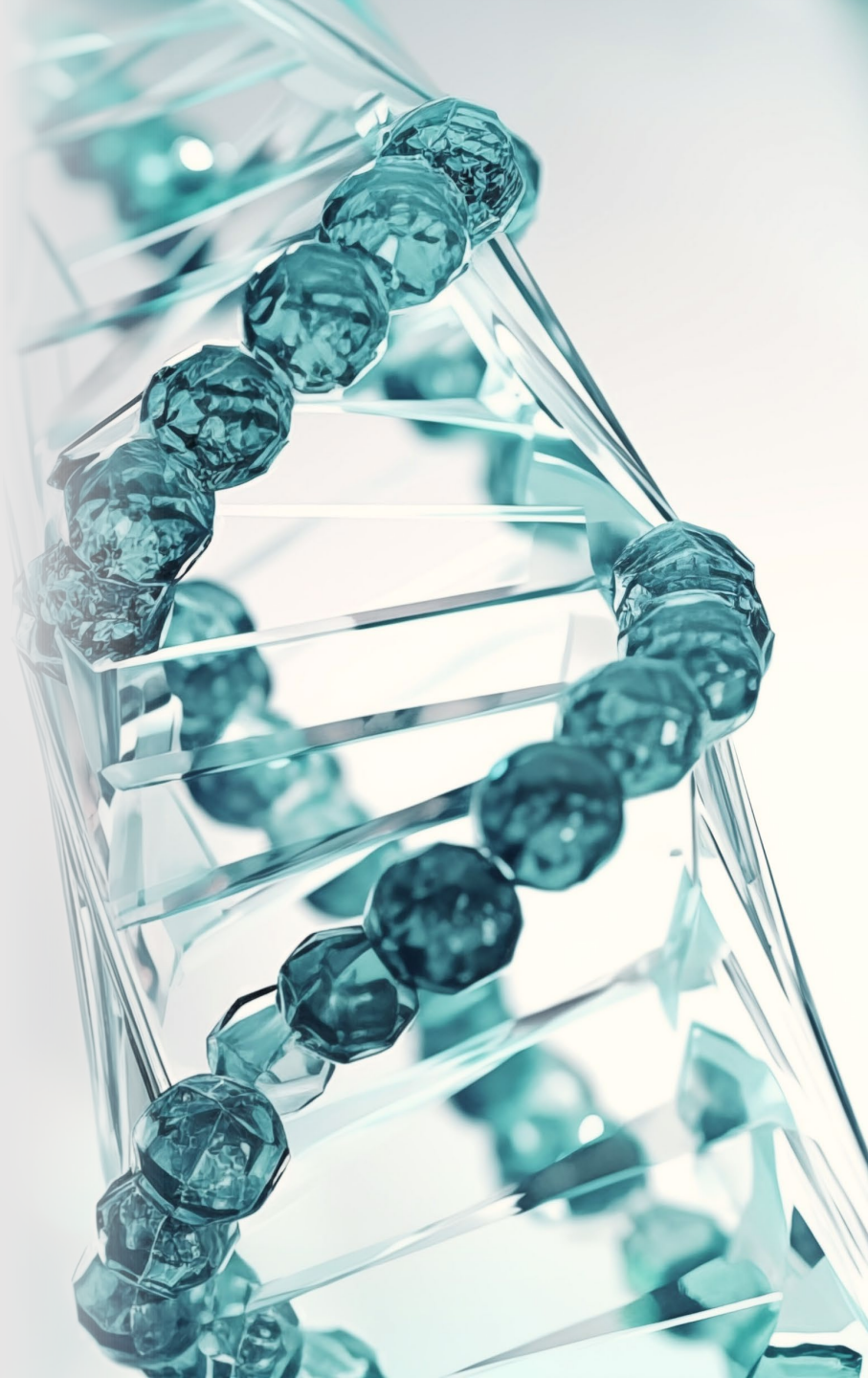

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