STIFEL | Healthcare

Aging:
Looking Forward

November 21, 2025

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Introduction

The Future of Aging Biology

This report reviews the status of aging biology and discusses areas where future progress is most likely. As will soon become apparent, our focus is on the practical. How might one go from an area that is science heavy and implement translational strategies that could really make a difference for humankind?

This, of course, is a long-standing dream of our species, outlined in our first report on aging biology (shown at right) published in March 2025.

You will get more out of this report if you have reviewed the first report. The most important parts are the introduction and the review of recent contributions to aging research that begins on page 160.

If your time is too constrained there is also a video summary of the original report. I have attempted to make the current report technically accessible to a generalist reader.

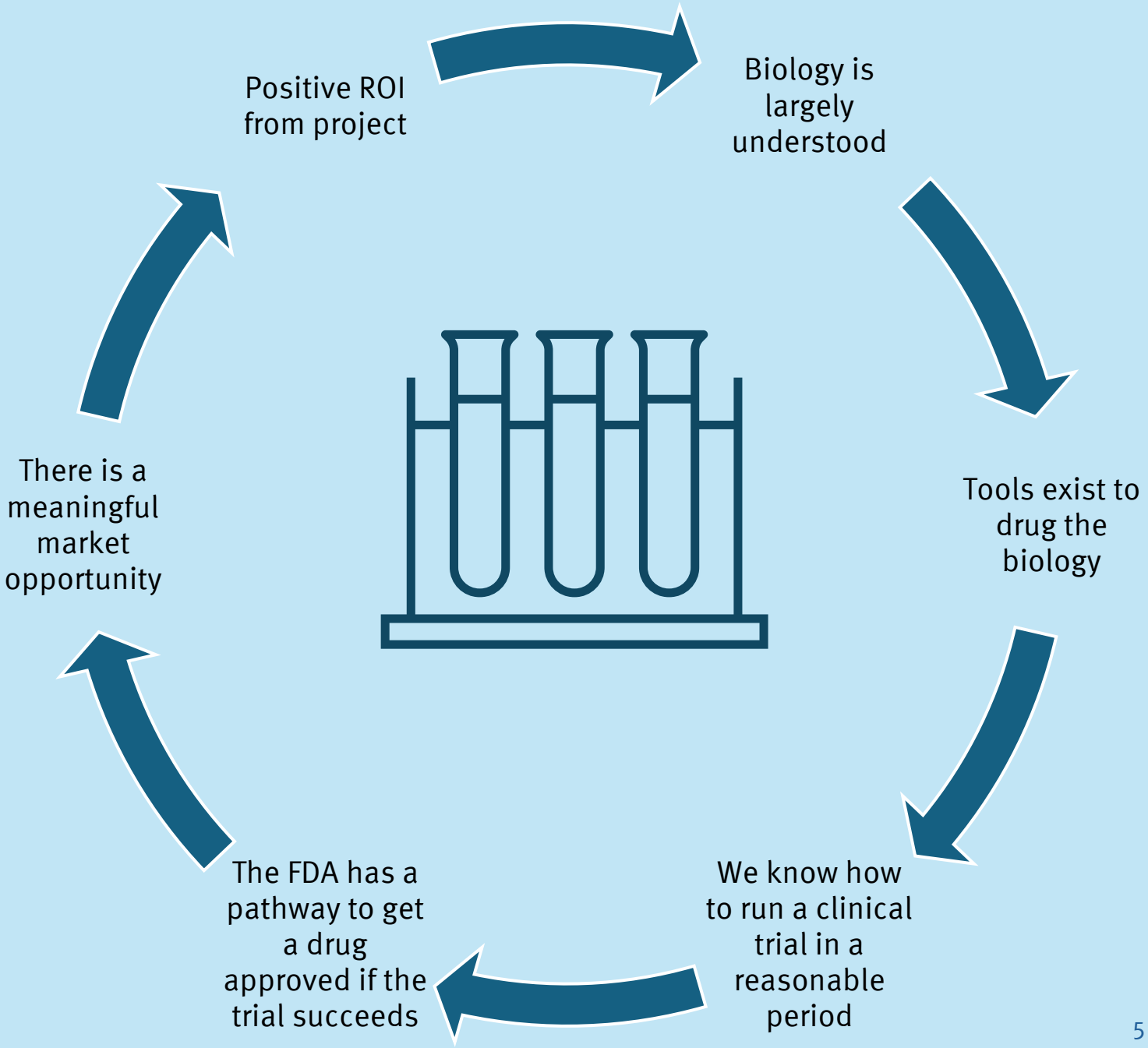
Best,

Tim Opler
Managing Director, Healthcare Investment Banking, Stifel
(oplert@stifel.com)

Download by clicking here.

What Makes a Biology Problem Translationally Ready?

The most important aspect of any drug discovery program is that it should involve a problem in biology that is understood and addressable with today's research tools.



Lifespan Extension is Translationally Ready for Drug Development:

1

Aging Biology is Fairly Well Understood

While aging is a complex multifactorial process leading to death of an organism it appears to have a central cause: oxidative stress that results from the mitochondrial respiration process. This stress creates cell damage and DNA damage that leads to eventual death. In a way, aging can be thought of as the ultimate mitochondrial disease.

2

Changing Cell Functions Leads to Aging

A variety of other cellular processes are impacted by oxidative stress, DNA damage and the time since birth of a cell. These include breakdown of autophagy and proteostasis and cessation of ability of a cell to replicate (senescence). The body's inability to make "young" cells also contributes and is affected by epigenetic factors.

3

Multiple Drug Targets Exist

There are a multitude of promising opportunities to rejuvenate cells and/or to reduce damage to cells. These involve management of oxidative stress damage (a well understood area), removal of senescent cells, reprogramming epigenetic factors (so-called "Yamanaka factors"), autophagy enhancers and much more.

4

Clinical Trials are Possible in Our Lifetime

One of the most remarkable developments of the last five years has been the advent of the ability to measure biological age from blood biomarkers. This means that it is possible to measure the effect of a drug on age using surrogate markers in a reasonable period. There are other ways as well to do trials in this area.

5

Regulatory Pathways are Available

The FDA has already approved trials to test aging drugs and is open to considering reduction of all-cause mortality in a time window as a clinical endpoint. Interestingly, while the FDCA requires that a drug be shown in trials to be effective to be approved it does not define effective against what. There are several other ways to introduce an aging drug.

Core Arguments in This Report

Aging Biology is Understood Well Enough to Support Drug Development

- Advances in the aging biology literature have been stunning in the last decade.
- Aging is a complex area, but genetic and biological insights point to two types of **cell damage** as central causes of aging.
- Even more surprisingly, at least to us, has been the discovery of age-reversal techniques including cell **reprogramming** (initiated by Yamanaka) and strategies to remove senescent cells
- These new techniques give us realistic hope that pharmacological interventions could substantially increase average human lifespans.

Clinical Development of Anti-Aging Drugs is Feasible

- We identify six strategies that can used in a reasonable time frame to run trials on aging drugs at a manageable cost.
- One idea is to focus on **older patients** where the probability of death is high. We believe it would be possible to run a true mortality trial on a drug that worked for less than $100 million.
- An alternative idea is to focus on **biomarkers**. In this report we spend quite a bit of time on this topic, showing that biomarkers are not only predictive of mortality but have specific informative biological context.
- A final idea would be to test aging drugs in **dogs** – which have much shorter lifespans. Loyal, a dog aging company, is doing just this now.

Regulatory Agencies Are Willing to Approve Anti-Aging Drugs

- We have spoken to FDA officials who indicate that the agency is **unequivocally willing to approve drugs for slowing aging.**
- FDA insiders note that the agency already approved the protocol for Nir Barzilai's as yet unfunded **TAME Trial**.
- This trial has a primary endpoint is a composite of events from cardiovascular disease, cancer, cognitive disease, and mortality. All-cause mortality is a secondary endpoint.
- The **Trump Administration** is particularly **receptive** to efforts to extend lifespan (a topic of high interest to HHS Secretary Kennedy).

The Remainder of This Report

- The remainder of this report provides the detail to support these arguments.
- In addition, we spend quite a bit of time talking about current efforts underway to develop aging interventions in the private sector and at various academic institutions.
- This report is a long read given the complexity of the issues involved.
- However, the underlying points are simple: We know why people die; we can develop translational hypotheses on how to delay their death; and we can test these hypotheses in a reasonable timeframe.
- Delay of aging is a science problem like any other. One needs to establish causes of a phenomenon and then run experiments based on reasonable hypotheses regarding interventions at appropriate time points.

Acknowledgements

In preparing this report I have benefitted from the advice and comments of many and am grateful for excellent suggestions along the way. I would particularly like to thank Johan Auwerx of EPFL for walking through a thoughtful set of ideas of how to carry out translational work in aging as has been embodied in the Healthspan Diversity Project; Vik Bajaj and Jim Tananbaum of Foresite Capital for conversation on biomarkers and aging strategy; Hal Barron, CEO, of Altos Labs; Marc Bernegger and Tobias Reichmuth of Maximon, an aging investor, for excellent suggestions; Frederick Beddingfield and Marco Quarta of Rubedo Therapeutics on translational ideas in aging science; Joe Betts-LaCroix, CEO of Retro Biosciences for a super interesting set of perspectives on aging; David Blaustein, physician and hedge fund analyst at BurkeHill for thoughts on the cell reprogramming literature and encouragement to look into aging in the first place; Andrew Brack of ARPA-H for explaining their initiatives in the aging field – particularly using longitudinal data; Andrew Dannenberg, of Emerald Bioventures, for linking the current proteomics literature to theories of aging and for providing detailed editorial comments; Vandon Duong of Stanford for introducing the work in Marius Wernig's lab; Jens Eckstein of Hevolution for a thoughtful discussion of aging theory; Robert Fried and Ozan Pamir of Niagen Bioscience for educating me on their strong commercial story; Cristina Ghenoiu of Mubadala Capital for some great thoughts on mitochondrial biology and detailed suggestions on improving this report; Bill Greene, Chief Investment Officer of the Hevolution Foundation, for making a fascinating and detailed presentation on their views on aging biology; Wa'el Hashad, CEO, of Longeveron for explaining their work on frailty; Antonio Henriques, CEO of Momentum Therapeutics for discussing some very interesting approaches to biomarkers for aging; Taro Inaba of Remiges Ventures for thoughts on mitochondrial disease, aging and interesting companies in the area; Hilmar Bragi Janusson of Kvika Asset Management for several constructive comments; Martin Borsch Jensen of Gordian for a very helpful phone conversation on aging biology and suggestions of biomarker approaches; Carina Kern and Serena Kern-Libera of Linkgevity for explaining their anti-necrosis approach to aging; James Kirkland of Cedars-Sinai for extensive comments on cell senescence and senolytics; Mark Kotter of Cambridge University for an extraordinary conversation on epigenetics and the work at Clock.Bio; Ann Kurth, President of the New York Academy of Medicine, for suggestions on the health span literature; Stephanie Leouzon of Stifel for numerous editorial suggestions; Art Levinson, CEO, Calico, for a series of suggestions; Ernest Li of Emerald Bioventures for making several good suggestions; Valter Longo of USC for walking through his fascinating ideas in aging

Acknowledgements (cont.)

and its reduction to practice in L-Nutra; Reenie McCarthy, CEO, Stealth Biotherapeutics, for walking me through their approach to mitochondrial disease drugs and aging biology; Tony Molina of UCSD for sharing insightful views on the role of mitochondrial damage in aging – and how it all might be picked up with biomarkers; Campbell Murray of DoublePoint Ventures for numerous helpful editorial suggestions; David Perlmutter, Dean of the School of Medicine at Washington University, St. Louis for generously guiding me through the recent aging literature; Dan Perry, Founder of the Alliance for Aging Research, for a number of suggestions; James Peyer of Cambrian Bio; Paul Ridker of the Brigham and Women's Hospital on aging biomarkers, public health and approaching the FDA on aging and novel approaches to extending lifespan; Nils Regge, General Partner, Apollo Health Ventures, for a broad-ranging conversation on aging biology and interesting companies in the field; Carlo Rizutto of Versant for suggesting an interesting mitochondrial disease biotech; Harry Robb of Lifespan Vision Ventures for identifying the importance of multi-morbidity and an interesting startup; Ed Schulak, Chairman of MetroBiotech, for walking me through a visionary strategy for showing the benefit of NAD+ for aging diseases; Vittorio Sebastiano, Associate Professor, Stanford University for thoughts and guidance on the cell reprogramming literature; Mani Subramaniam of OrsoBio for a wide range of comments on strategies for developing aging drugs;

Diederick van der Reigt, CEO of Celljevity, for explaining their partial cellular reprogramming approach and business model; Eric Verdin, Head of the Buck Institute for Aging, for suggestions on clinical trial strategy and Tal Zaks of Orbimed for pointing to some contemporary items including work on aging clocks. I would particularly like to thank the aging research group at the Mayo Clinic's Robert and Arlene Kogod Center for Aging for spending a half day talking me through their research and discussing a wide range of ideas. I visited with Darren Baker, Fernanda Bellolio, Tamir Chandra, Jorg Goronzy, Diana Jurk, Kristina Kirschner, Nathan LaBrasseur, Joao Passos, Marissa Schafer and Paul Tang. I appreciate the efforts of Gloria Olivier of Mayo to arrange the visit. Last but not least I would like to thank seven extraordinary interns who worked closely with me during the summer of 2024 to explore aging biology. Each researched an area of aging biology and made a detailed presentation on their findings. These were Nicholas Berbari (now at Goldman Sachs), Saanji Desai (finishing up at Rutgers), Tony Liu (finishing his degree at Penn), Michaela Murphy (working at her first job in an AI company in London), Alex Nailath (wrapping up his degree at Penn), Kiruthiga Shanmugananthan (doing work in lung biology at Cornell) and Eric Zhang (now at Centerview).

Going Forward with Aging Drug Development

Aging Research and Biotech

At a recent investor conference, I sat at a dinner table with some well-known biotech investors.

The conversation turned to the day's events, recent economic and political developments and people's thoughts about the future, particularly in neuroscience – an area that had featured prominently in that day's corporate conversations.

I announced that we were soon to publish a report on the future of aging research and indicated how interesting I thought this area could be. I argued that aging was a neglected area that seemed translationally ready and, potentially, quite lucrative for investment.

After a long pause one investor piped up: "you know that area is complete garbage".

Another said "why would you report on quacks and fraud when there is so much that is really interesting going on in our field?"

Another said "You might try obesity again. I really liked your work in that arena".

This was sort of like announcing to your parents that you were considering a career in sanitary engineering rather than something interesting like law or medicine.

Skepticism Abounds

Most people in the biotech ecosystem that we have spoken to in the last few years are pessimistic about the aging field.

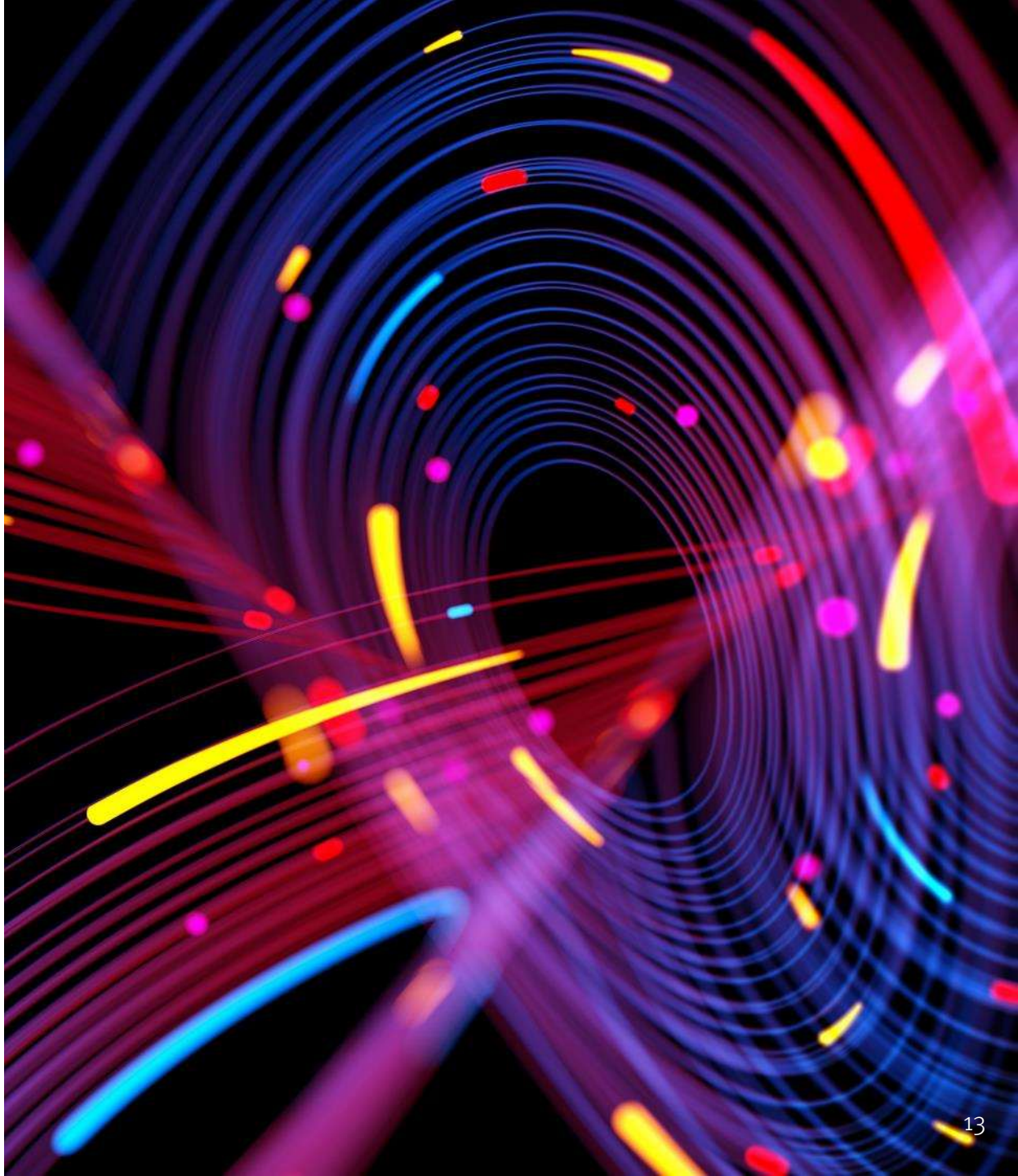
Aging biology is largely seen as not ready for prime time.

More the land of Silicon Valley billionaires, dreamers, kooks and snake oil salesmen than real scientists.

While there are hundreds of biotechs working on aging today, this area is definitely *not* in the mainstream.

There are numerous reasons that we have heard to not take the field seriously, including:

1. Lack of meaningful scientific progress on the causes of aging
2. No known evidence in humans that we might live meaningfully longer through pharmaceutical interventions
3. Minimal mainstream investor participation
4. No apparent way to test a theory of aging, even if there was a drug that might work



Biodiversionary Tactics

Perhaps the most frustrating aspect of meeting dozens of “aging” biotechs is how few are testing a drug to change lifespan.

What companies often do is go out and raise money on the promise of lifespan extension and then decide to test a drug for a disease associated with aging.

But not aging itself.

The argument that is typically made is that the FDA will not allow companies to test drugs for longevity itself – hence the reason for running trials of aging drugs in eye disease, knee disease, lung disease and the like.

This type of biodiversion confuses investors. As it is, the field of aging biology does not lack for false prophets.

As we meet CEOs of aging biotechs we frequently encourage them to, ahem, test their molecule’s effects on lifespan.

You would be surprised by (1) how few are doing it and (2) the fear of some when we explain that you can test your molecule for its effect on lifespan.

If there is a point to this report, it’s that you can test aging theories and that it’s high time we got serious about it.

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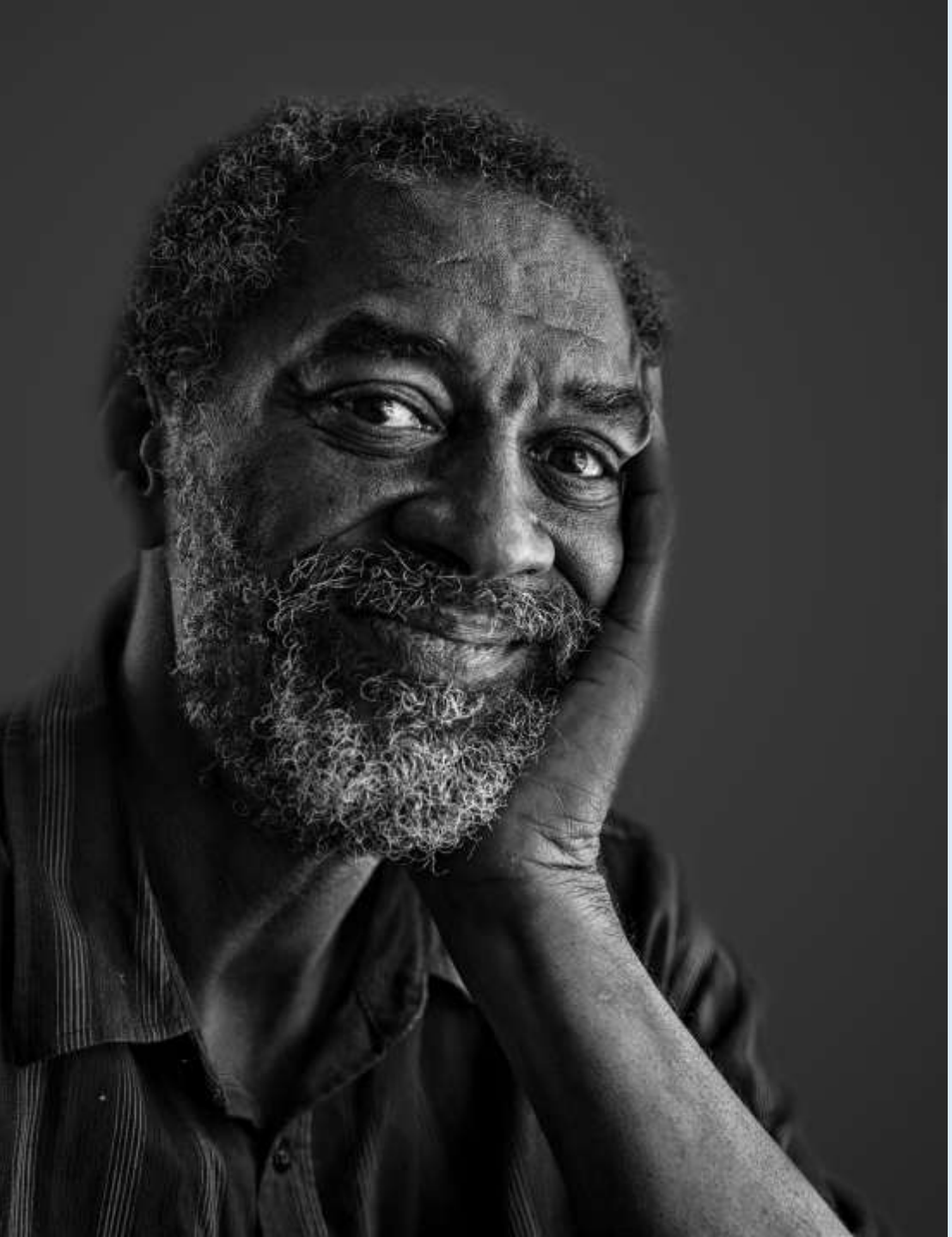


It’s Time to Get Real

Let’s stop dreaming. Before we take rapamycin pills, aging supplements, testosterone injections or shoot up with peptides let’s first work to get some hard data that these drugs matter. There is a paucity of empirical evidence supporting any of today’s aging interventions. It’s amazing how many well-educated humans will jump on the bandwagon for some drug without having good data that it matters in health or lifespan.

Our position is that we could and should test aging interventions to see if they actually work. If, for example, it turns out that NAD+ is the magic bullet, then great, let’s put the stuff in the water supply.

The first company to convincingly link a patent protected intervention to longer lifespan will be worth many billions. Probably the best shot that a healthcare company has to surpass the valuation of NVIDIA, Apple, etc.

It’s time to get real and start focusing on moving forward with aging science. Examples of recent excuses that might be better avoided:

(1) “Why would you ever actually test an aging drug? The FDA will never approve it.”

(2) “You know, there is no money for real aging companies. What I am doing is using aging theories to come back and treat chronic diseases like COPD. VCs love that.”

We Appreciate the Argument to Focus on Diseases of Aging

There is, of course, a perfectly reasonable argument for testing drugs on diseases of aging as opposed to aging itself.

Sometimes, certain drugs may be more relevant for specific conditions like cardiovascular disease associated with aging rather than all aging.

This point was made in a recent paper by Guido Kroemer and colleagues who noted that not all aging related genes have general effects. See the chart at right illustrating this point from their paper.

We completely get this point and don't want to argue that biotechs should *only* test their drugs for lifespan extension.

However, when you peruse the pipelines of biotechs working on aging later in this report, you will notice that essentially *none* of them are running trials of their drugs on extending lifespan and reducing mortality by attacking the various subclinical pathologies of aging.

Perhaps it's best to give an analogy. The field of obesity drugs has become really hot in the last decade and multiple biopharmas are testing novel strategies to show that various agents can induce weight loss. Others, however, are running trials to see if weight loss drugs can impact effects of obesity (like obstructive sleep apnea). This is a perfectly reasonable thing to do. But the big payoff is in going after obesity itself. Similarly, in the aging field, it might be perfectly reasonable to test whether a senolytic helps skin aging, but one shouldn't miss the opportunity to go after aging itself. Just as in the obesity field, we suspect that we will be amazed by how many diseases are impacted once people are on an effective aging drug. This is, of course, the *big* opportunity.

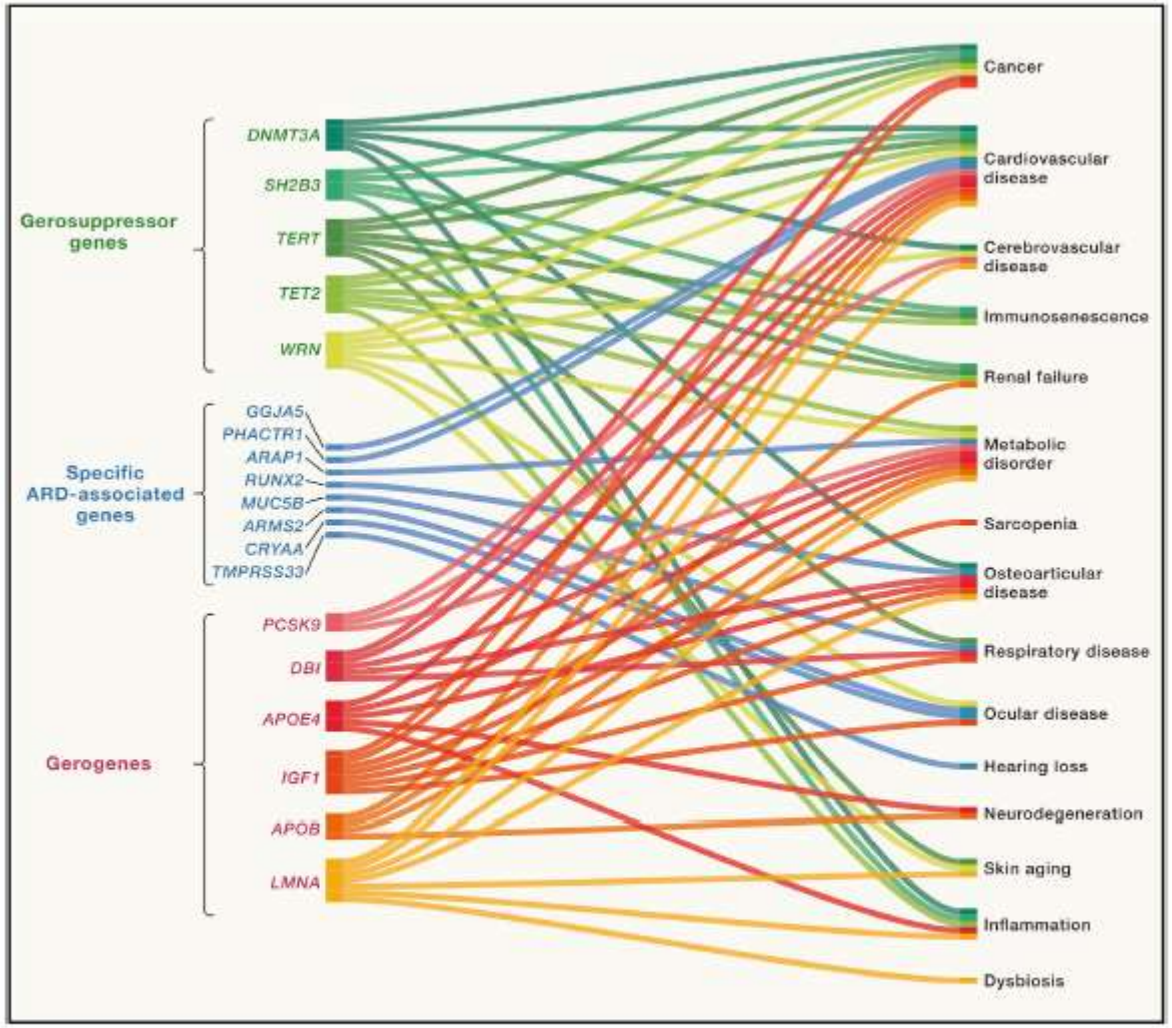


Figure 3. General versus disease-specific genotype-phenotype correlations

Gerogenes and gerosuppressor genes tend to affect multiple age-related diseases (ARDs), contrasting with specific ARD-associated genes that have a more reduced phenotypic impact. See Table 1 for a more exhaustive list of gerogenes and gerosuppressor genes. Note that this scheme provides examples of genotype-phenotype correlations and does not pretend to be comprehensive.

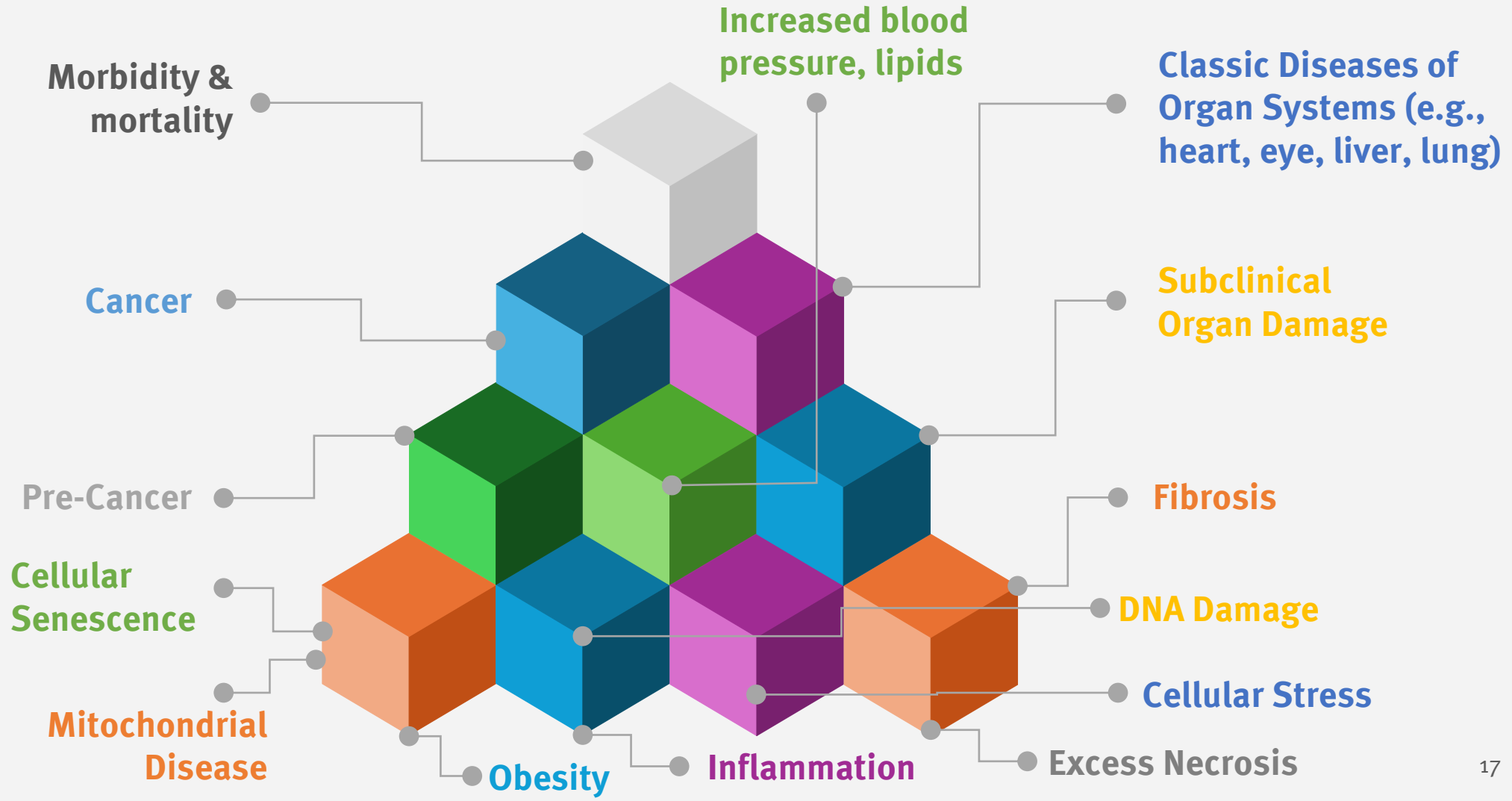
Major Opportunity in Addressing Subclinical Aging Pathologies

Traditional medicine spends relatively little time analyzing the underlying causes of disease and aging. Treating the subclinical causes of organismal aging may allow one to get labels for broad sets of disease as has happened with obesity drugs.

Consequences

Overt disease
Mid-stage phenotypic disease

Underlying Causes of Disease
Subclinical disease and aging pathologies



Let's Put Aging Theories to the Test

It's our goal to convince you that the aging field is going to become real. That is, we can develop drugs to extend lifespan and the major diseases of aging. To be clear, we have already done it. The SGLT2 inhibitor, for example, is associated with impressive reductions in all-cause mortality in a wide range of disease settings. More on this to come.

We believe that the aging field is going to be investable from a biopharma perspective. A lot sooner than one might guess. And we think one can do a lot better than the SGLT2 inhibitor.

We, of course, are not the only ones saying this. Deloitte recently issued a detailed report on longevity science and the exploding interest in the area. A recent report by *Longevity Technology* reviewed the growing investment in the field. A similar story was recently printed by the *Wall Street Journal*.

Our view is that aging biotechs should formulate testable, scientifically grounded hypotheses. And then, go out and test them. The key idea is that the field of aging should be pursued using the classical approaches of science: hypothesis formulation based on biology and the empirical method – where theories are confronted with data.

Francis Bacon is Waiting on Us

In this age of hyperinnovation coupled with politicized antiscience, we should all remember our debt to Francis Bacon – the Father of the Scientific Revolution. Everything about our lives – the electricity we have, the food we eat, the car we drive, the roof above our head – owes itself to the Scientific Revolution – which was started in 1620 by Bacon.

Francis Bacon (1561–1626) had a profound and immediate influence on thinkers who helped shape the Scientific Revolution. His advocacy of empirical observation, inductive reasoning, and systematic experimentation inspired an entire generation of natural philosophers who began to replace scholasticism with experimental inquiry. Contemporaries, including Boyle, Hooke, Newton, Wren and countless others were profoundly impacted by Bacon's ideas published in *Novum Organum* in 1620.

Fascinatingly, in his 1623 book *Historia Vitae et Mortis* (History of Life and Death), Bacon argued that the most important reason to adopt the scientific method was to use it in order that humanity could achieve immortality.

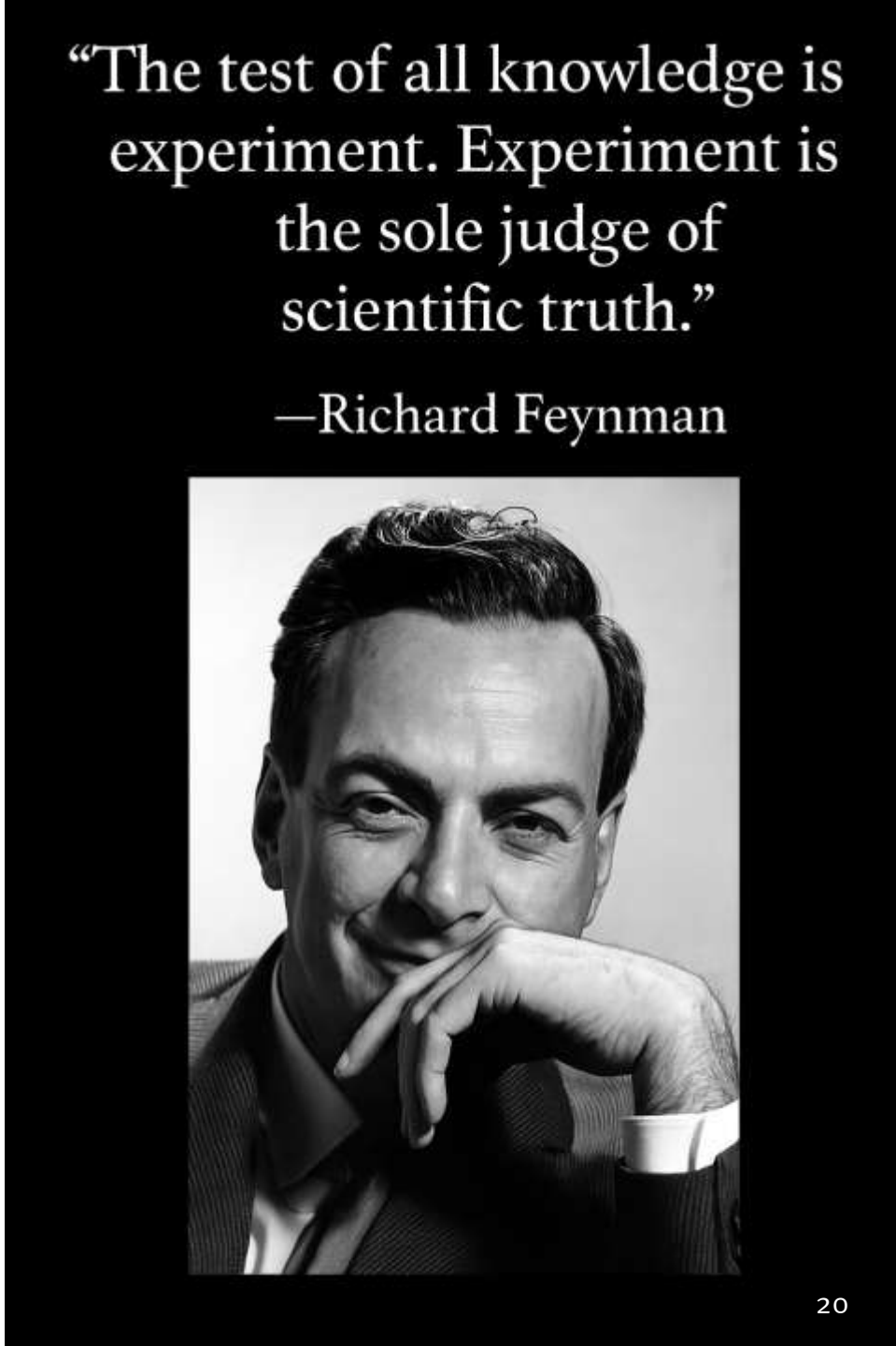
[Note: more on Bacon in our first report on pages 62 to 65].

Francis Bacon's entire philosophical program was designed to facilitate the growth of human knowledge so that immortality could be achieved.

Sticking to the Science

One might describe any scientific field where academics are rewarded for publications and citation counts as vulnerable to certain incentive issues. The aging field is worse than most because desperate people will pay money to stay alive and so there are financial and reputational incentives to promote theories of aging in ways that are not consistent with the underlying data. Already, we have seen several scientists suffer reputational loss for promoting aging ideas that were not consistent with the facts. The aging field begs for rigorous, iterative experimentation to discover the most fruitful avenues for lifespan extension. A further issue is that it is tempting to simplify quite complex areas with language conventions that are not consistent with the data. Science is not politics where one might wish to use language to arouse emotion in the receiver. Science thrives by the pursuit of truth through experimentation.

One of our pet peeves, for example, involves the phrase "aging clock". Well-meaning researchers noted that epigenetic factors predict cross-sectional variation in chronological age of humans reasonably well. Initial researchers decided to call statistical predictors of "biological age" an aging "clock". The concept of aging clocks then took off (PubMed now lists over 3,000 papers on aging clocks). The problem is that this phrase implies false precision and mechanism – very much in the tradition of René Descartes who saw man as controlled by physical mechanism in a clockwork universe. Specifically, when we humans see a phrase like "clock" we immediately analogize to a mechanical device that tells perfect time. But in no way does the work of aging clock researchers show that there is a determinative process in humans at work that is ticking off the time until death.



Avoiding Misleading Lingo

The evidence does not show this. Rather, the work on aging clocks demonstrates variables correlated with chronological age that have major stochastic components.

The idea of a clock is beguiling, of course, because we would all like to somehow slow down that clock. Further, it feels great, when we work out a lot, for example, to be able to say that our biological age is better than our chronological age. Now, we are learning that we also have *organ specific* clocks that can have different times on them. This turns what was initially a logical leap into an Olympic long jump with substantial methodological complexity. It's not obvious that human organ systems would have individual clocks, although it's well known that some organs might be in better shape than others.

To point out some issues with the clock literature: (1) there are more putative types of aging clocks than religions; presumably, if there really was a determinative clock counting down your time to death there should be only one; (2) clocks give results that aren't that correlated; and (3) epigenetic clocks are lousy predictors of all-cause mortality unless you include certain proteins that we will discuss later. We don't mean to pick on the clock researchers specifically but, rather, we encourage researchers and biotechs to use language that mirrors the data as closely as possible. We prefer the phrase "mortality risk predictor" to "aging clock", for example. There are other language conventions used, for example, like "digital twin" or "exercise in a pill" that can rapidly separate the real facts from the perception of those facts by the receiver.

Large Market Opportunity for an Anti-Aging Drug that Works

- What makes the aging market so interesting from a financial perspective is the confluence of payor incentives and personal incentives.
- The average person would prefer to stay alive longer and would pay for it.
- Our casual conversations with the populace show high interest in paying for life extension.
- Similarly, payors have powerful incentives for their insureds to be healthy and long-lived.
- A drug that extends the healthy human lifespan would very likely dwarf the obesity drug market, particularly if chronic use would be required to stay alive.
- It's hard to say how big the market would be.
- Our own view is that revenues in this market could run to $1 trillion or more.

Illustrative Market Sizing Exercise

Imagine a drug that gets you five extra good years of life. Suppose you need to start taking it at age forty and need to take it forever after. Assume that 500 million people take the drug at an average annual cost of $2000.

Revenue = Quantity Sold x Price = 500mm x $2000 = $1 trillion

This would be by far the largest drug product in the history of the world.

Compare this to the car market ($2.4 trillion a year), life insurance ($3 trillion a year in premia paid), residential real estate ($13 trillion a year).

We don't think we are off by an order of magnitude given the value of extra life to the customer.

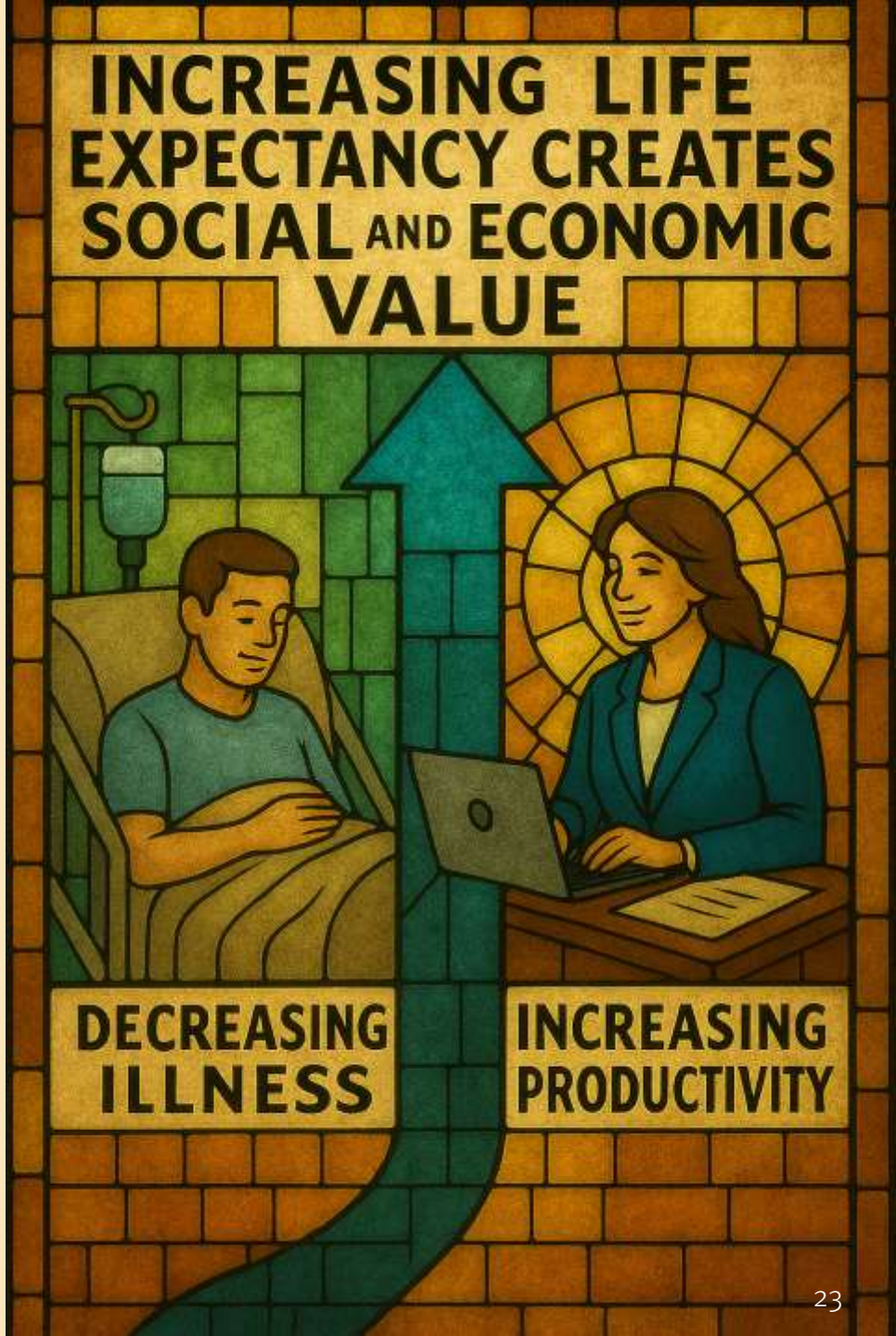
Key variables that will drive TAM include durability of benefit, safety implications, breadth of benefit (including reduction of aging-related diseases) and regulatory status.

Huge Economic Value to Society from Extending Lifespan

Andrew Scott et al., *Nature Aging*, Jul 5, 2021

Developments in life expectancy and the growing emphasis on biological and 'healthy' aging raise a number of important questions for health scientists and economists alike. Is it preferable to make lives healthier by compressing morbidity, or longer by extending life? What are the gains from targeting aging itself compared to efforts to eradicate specific diseases? Here we analyze existing data to evaluate the economic value of increases in life expectancy, improvements in health and treatments that target aging. We show that a compression of morbidity that improves health is more valuable than further increases in life expectancy, and that targeting aging offers potentially larger economic gains than eradicating individual diseases. **We show that a slowdown in aging that increases life expectancy by 1 year is worth US$38 trillion, and by 10 years, US$367 trillion**. Ultimately, the more progress that is made in improving how we age, the greater the value of further improvements.

Source: https://www.nature.com/articles/s43587-021-00080-0. Also see https://www.nature.com/articles/s43587-021-00074-y and https://nyaspubs.onlinelibrary.wiley.com/doi/epdf/10.1196/annals.1396.050.



Billionaire Interest in Anti-Aging Drugs is High

The tech billionaires trying to hack aging to extend their lives

Business Insider, Sep 5, 2025

By Lakshmi Varanasi + Follow

From Sam Altman to Peter Thiel many of the world's wealthiest billionaires seem to be on a quest for the fountain of youth. Lucy Nicholson/Reuters/Marco Bello/Getty Images/Evan Agostini/Invision/APDrew Angerer/Getty ImagesAnadolu Agency / Getty Images

Source: https://www.businessinsider.com/tech-billionaires-trying-to-hack-longevity-and-live-forever-2025-9

"When our time's up, it's up. All the money in the world won't buy you one more day."

Ted Turner

More Than Commercial Factors Are At Play

It's well understood that a lot would have to change if we introduced a commercially available drug that added, say 20 years of life expectancy to humans. We discussed some of this in our first report and Venki Ramakrishnan did a fantastic job of discussing the societal aspects and implications of the availability of drugs that would extend lifespan in his recent book *Why We Die*.

What is, perhaps, less discussed are the **distributional** aspects of such a drug.

If you had a monopoly on a drug that added 5 years to human lifespan, what would you charge? Would you make it available to everyone? Most likely you would charge a lot. Like a whole lot. And that's because billionaires and millionaires would pay up for it. One person we've spoken with has sounded out a few billionaires and found they would happily pay $1bn a year for another 5 years of life.

Given that there are over 3,000 billionaires worldwide, you could probably get to $100bn in sales just by hitting 100 people. Maybe more.

There are issues of equity and fairness to think about. The rich already live longer but what if it were immensely longer? This could accentuate inequality as physical and financial health go together.

Further, what if it weren't billionaires who got the drugs but instead **politicians**? As noted on the next page, China's Premier and Russia's President recently had exactly this conversation. Premier Xi appears to be well briefed on the science that is underway in his country. It is not a crazy idea at all that an individual could go through a process of organ reconditioning via transplants. The number of high-quality publications coming out of China on aging science is growing fast. Despite NIA and ARPA-H efforts, the U.S. government has not made life extension research a priority. The NIA is going through budget cuts and ARPA-H spending on aging is small. Aging could become an area of national security interest as it would be very odd if the Chinese had access to life extension technology and the West did not. Of all the areas in biosciences research where the West would not want to fall behind, life extension technology is arguably one of the most important.

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What China and Russia Are Thinking

Jennifer Jett, *NBC News*, September 4, 2025 (expert)

HONG KONG — What do autocratic leaders talk about when they get together? Maybe how to live forever.

The exchange between Chinese President Xi Jinping and Russian President Vladimir Putin was caught on a hot mic Wednesday as the duo and North Korean leader Kim Jong Un, in their first joint public appearance, led a delegation of 27 world leaders attending a massive military parade in Beijing.

As they ascended the rostrum at Tiananmen Square to watch the parade, Putin and Xi, who are both 72, appeared to be discussing the world's strides in life expectancy.

While it used to be rare for people to reach age 70, "now they say that at 70 you are only a child," a translator for Xi can be heard telling Putin in Russian.

With advances in biotechnology, people will be able to "transplant human organs continuously, grow younger with age and perhaps even achieve immortality," Putin's translator responds in Mandarin.

Xi, who at that point was off-camera, can then be heard saying, "Some have predicted that by the end of this century, humans could potentially live up to 150 years."

Source: https://www.nbcnews.com/world/asia/xi-putin-organ-transplants-immortality-hot-mic-china-parade-rcna228996

China is Pouring Billions Into Longevity

Andrew Higgins, *New York Times*, November 8, 2025 (excerpt)

China, eager to catch up with and, whenever possible, surpass the West in biotech, artificial intelligence and other advanced technologies, has made the longevity industry a national priority, **pouring billions into research** and related commercial spinoffs.

"They have improved very rapidly. A few years ago, there was nothing here and the West was still far ahead," said Vadim Gladyshev, a Harvard Medical School professor who has done pioneering work on longevity, including an experiment that extended the expected life span of old mice by connecting their circulatory systems to young mice. Chinese researchers, he said during a recent trip to China to attend two scientific conferences, "are rapidly catching up."

China's average life expectancy last year reached 79 years, five years higher than the global average, according to *The People's Daily*, the Communist Party's mouthpiece. But that, achieved through steady improvements in health care and lifestyle, is still behind Japan's average of nearly 85 years and a long way from the 150 years mentioned by Mr. Xi.

Mr. Xi and Mr. Putin, both 72, may have just been making small talk. But they were taken seriously by exiled opponents of the Communist Party, who pointed to a 2019 video that appeared on Chinese social media purporting to be a promotional pitch by an elite military hospital in Beijing, 301, which treats senior officials. The video, which was quickly scrubbed by Chinese censors, boasted that the hospital was doing pioneering work for the "981 Leaders' Health Project" — and aimed to extend the life span of senior party figures to 150 years.

Comment Emailed to Us From One of the World's Best Known Aging Researchers on Nov 19, 2025:

"Just came back from two meetings (Toronto and Guangzhou). From these meetings it became clear that China will become "a", but most likely "the", predominant player in the aging arena. The government is having a big vision and building the infrastructure to tackle a wide range of original approaches to understand aging. "

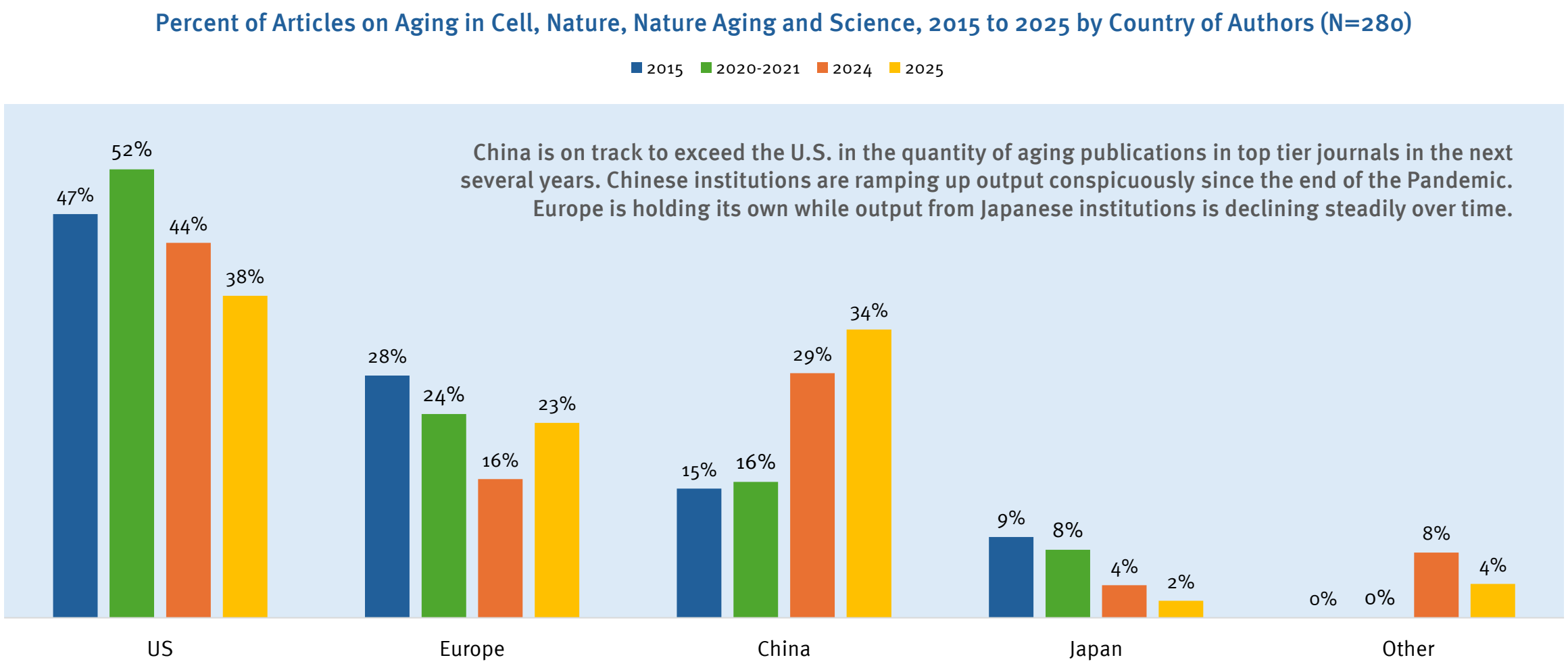
Source: https://www.nytimes.com/2025/11/08/world/asia/china-aging-longevity-science.html

Illustrative Chinese Efforts in Aging Research

Institution	Focus areas for aging	Example labs / programs	Representative mechanistic outputs
Fudan University	DNA damage/repair; human phenomics & cohorts; clinical geriatrics	Xu Lab (DNA damage response & repair); Human Phenome Institute; Huashan Hospital gerontology teams	DDR/repair program page (ATM/ATR, FA, DNA-PKcs); participation in Rugao Longevity & Ageing Study; university-level Fudan Institute on Ageing for interdisciplinary aging work.
Tsinghua University	Healthy-aging epidemiology & policy; UX/assistive tech for the elderly; basic epigenetics platforms; cell reprogramming	Ding Lab work on cell reprogramming; Future Lab AeX (aging user-experience & assistive tech); Life Sciences (DNA methylation / epigenetic state transitions)	Cohort-based studies on functional/cognitive impairments; AeX center designing tech solutions for aging at home; recent campus-news on DNA methylation programs in development.
Chinese Academy of Sciences	In vivo partial cellular reprogramming; epigenetic rejuvenation; stem-cell aging	Guang-Hui Liu lab (reprogramming/regeneration)	IOZ profile highlights partial reprogramming that enhances liver plasticity; related national releases on immune/aging interfaces from Liu's group.
NIBS Beijing	Lysosome/longevity pathways; proteostasis (C. elegans & mammalian)	Xiaochen Wang lab (lysosomal degradation, lifespan control)	eLife paper: lysosome activity as a node for multiple longevity pathways; profiles detailing the lab's aging focus.
Westlake University	Aging clocks; reprogramming & stem-cell meetings; multi-omics	Westlake–Cell Press Aging Conference series; groups building single-cell aging clocks	University & meeting pages; 2024–25 reviews mention Westlake single-cell aging clock work.
Peking University	Reprogramming; Large-scale healthy-aging cohorts and longitudinal surveys; methods for aging indices	Deng Lab / small molecule reprogramming; Center for Healthy Aging & Development Studies	Small molecules for reprogramming; Longitudinal/healthy-aging surveys (e.g., CLHLS/derivatives) with emphasis on functional outcomes and trajectories.

Source: Stifel Investment Banking Department.

Percent of Articles on Aging From Chinese Researchers in Top Tier Journals is Rising Quickly



Source/Note: Stifel Investment Banking Department review of journals for the relevant years. To be included articles needed to be on an aspect of aging with some general applicability. For example, an article on tau's role in Alzheimer's would not be included. In the case of articles where authors were from multiple countries, we classified an article based on the location of the lead author at the time the article was published.

Argument 1: Aging Biology is Fairly Well Understood

First Point:

The Right Metric to Focus on is Lifespan

Human Lifespan is Well-Defined

- It is a remarkable fact of human life that we all die by the age of 125.
- Despite the biblical tale of Methuselah, there is no known record of a human who has made it to age 125.
- Notwithstanding some claims of fraud, there is strong evidence that the French woman Jeanne Calment lived for 122 years before dying in 1997 at a nursing home.
- She reported eating chocolate often and to have been a regular cigarette smoker.
- A Japanese male lived to the age of 119.
- Humans clearly have a biological age limit.
- We find it quite interesting that a human who lives a healthy life (not smoking nor eating tons of junk food) can reasonably expect to die between the ages of 85 and 105 - a relatively narrow band.
- To give a detail on the upper end of the age band, the 2022 U.S. Social Security Life Table notes that 99% of American females die by the age of 102 and 99.9% of American females die by the age of 106. For males the 99th percentile mark is age 99 and the 99.9th percentile mark is age 104.

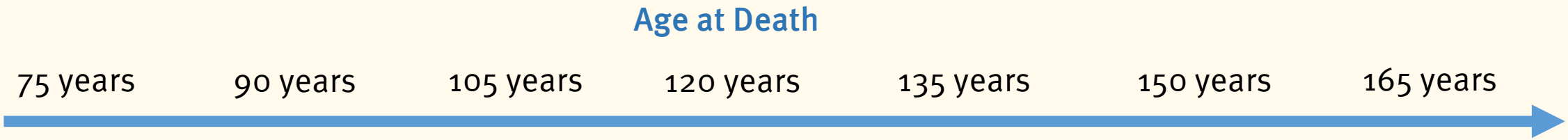
Jeanne Louise Calment, the world's longest living person (who died at the age of 122) was born in Arles, France on February 21, 1875. She claims to have met Vincent Van Gogh. “I've waited 110 years to be famous, I count on taking advantage of it,” she quipped at her 120th birthday party.

Lifespan is the Critical Metric

- We argue that we can realistically expect progress in developing therapies that will meaningfully alter human lifespan.
- Lifespan and **healthspan** are not the same thing, although the two go hand in hand. The correlation between the two in practice in a recent study using UK Biobank data was strikingly high.
- There are thousands of books and articles that talk about how we can live healthier lives and make it to age 100 – or even 105 if we are lucky.
- This is referred to as “compression of morbidity”.
- Rather, from the day we’re born, we age. The look of our bodies changes rapidly – initially showing rapid growth and youth. And later, gray hair, wrinkles and the like.
- Our focus in this report is on whether it is possible to change maximum human lifespan by biological interventions. This should have the effect, also, of increasing healthspan.
- We recently reviewed popular articles in the press and listed on X.com that contained the words “aging” or “longevity”. Almost universally, they were focused on interventions and habits that could help humans increase healthspan but not change humanity’s maximal lifespan.

Classifying “Aging” Interventions by Their Intended Effect

Observers on aging and longevity can mean vastly different things when they speak of pharmaceutical interventions and lifestyle changes for aging. Overwhelmingly, the discussion tends to focus on efforts to extend age *within* existing human age limits. While a perfectly reasonable thing to do, our focus in this report will be on steps that could be taken to change those limits – that is to extend maximal human lifespan.



Healthspan: Stay healthier within normal age bounds by attacking age-related disease.

Longevity: Change your date of death from its expected time (e.g., age 80) to a date inside maximal lifespan.

Recent stories such as those classifying GLP-1’s as longevity drugs are largely focused on measures to extend healthspan or longevity but not to extend maximal lifespan. By definition, lifestyle changes, caloric restriction or interventions involving biology where monogenic mutations are known to shift humanity’s date of death (e.g., mTOR, IGF-1) are not lifespan altering because there are numerous examples of humans who have the characteristics associated with those interventions that do not live beyond normal age boundaries.

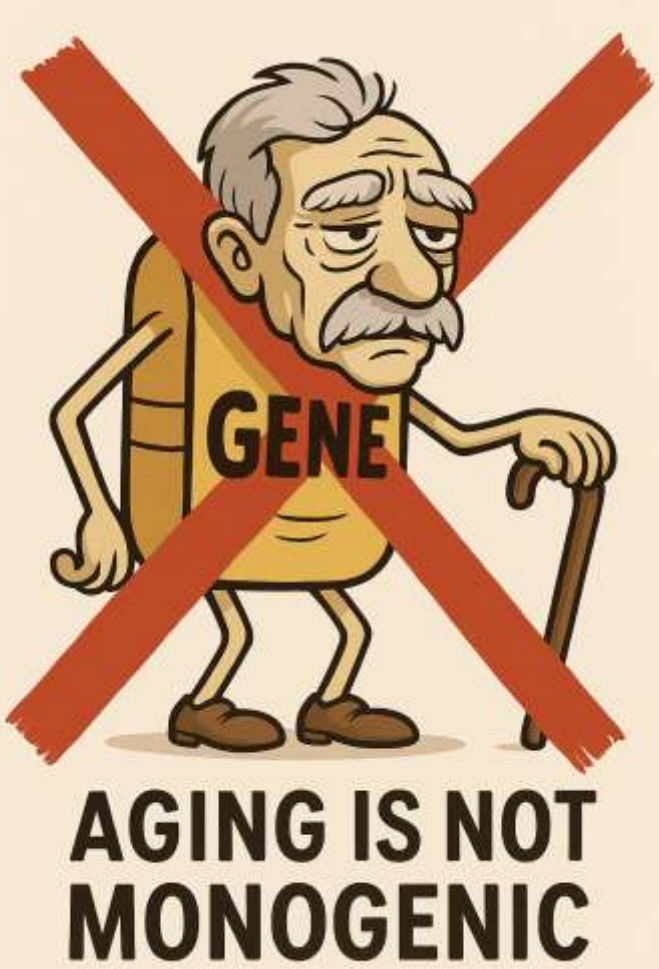
Altering Maximal Lifespan: Change your date of death from its expected time (e g, age 80) to a later time that would fall outside of normal age bounds.

Point Two:

It is Unlikely that the Explanation of Humanity's Limited Lifespan Comes Down to a Single Gene

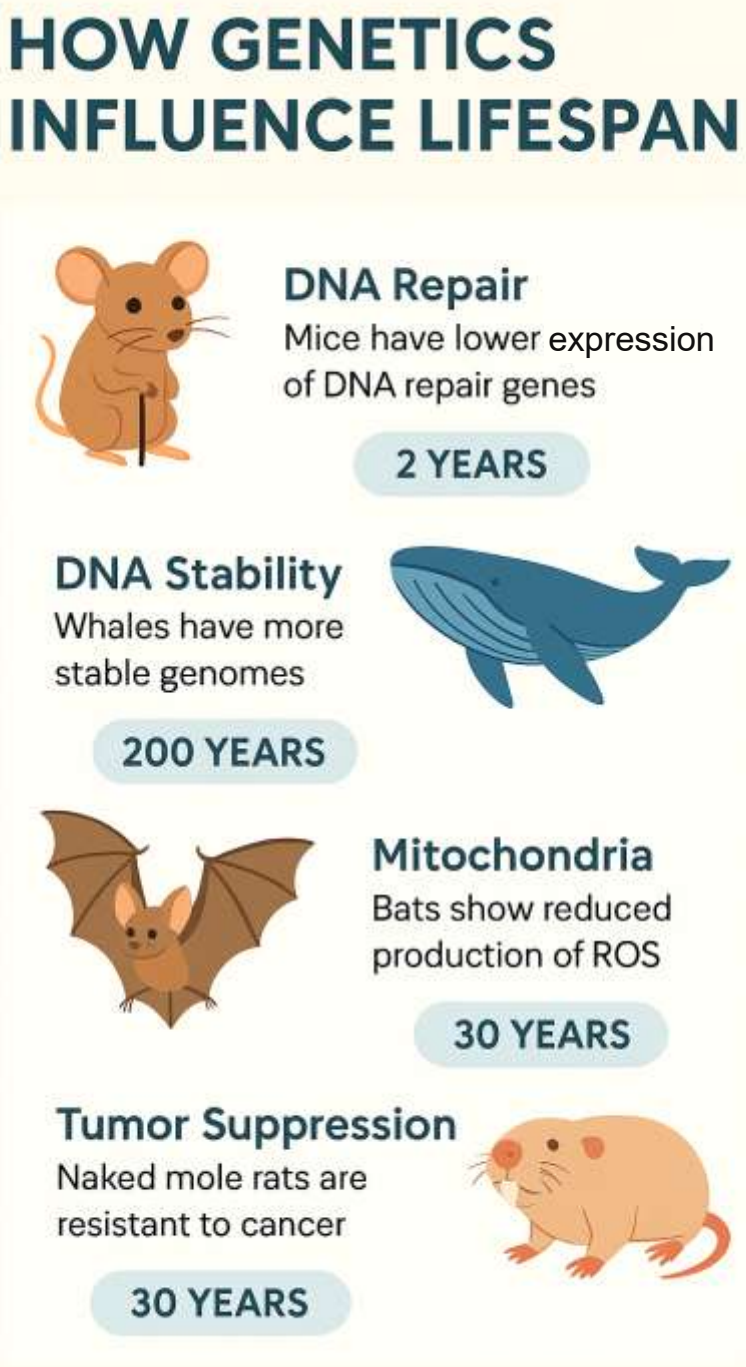
Why Aging is Unlikely to be Monogenic

- Almost all genes mutate at one point or another – this is part of the evolutionary process.
- Were there a single gene change that could lead to much longer lifespans we should have seen that play out already.
- That is, there should be a few humans wandering around that are 150 years of age or older – that have had the lucky gene mutations because all genes get mutated eventually.
- We don't see that and there is no verifiable record of a human ever living past age 125.
- This tells us that it is extremely unlikely that a single gene controls lifespan.
- We suspect that there are at least several underlying physiological processes that control human lifespan.
- Interestingly, there are a number of gene mutations that can lead to unusually short lifespans (progeria).
- And a team using Regeneron data has recently shown that there are some gain of function protective mutations that can make it more likely that we would get to be centenarians. But not double centenarians.



Aging Must be Genetic

- Even though aging is very unlikely to be caused by a single gene, we also argue that it is certainly genetic.
- This might be a bit controversial to some as there are quite a few papers that point out that differences in genes among humans are only associated with roughly 20% of the variation in aging. Others have argued it's much less.
- We, of course, agree that environmental factors matter. If I lead the life of a cave man, without adequate shelter, food, healthcare, protection from predators and the like, there is a good chance that you, with the normal protections of modern humans, will outlive me. Studies of identical twins also show this. The average difference in date of death of identical twins is 14 years. Bad things happen to twins that have adverse lifestyles.
- But we know that some species have lives that run for less than a week whereas others live for 400 years or more. Most species are somewhere in between, and all have rather tight mortality timing bands.
- These aging differentials must be genetic because differences in maximum lifespans of animals are defined wholly by their genes. We don't think you could take a butterfly, for example, which lives on average for two weeks, and get it to live for twenty years by putting it in one of those nice indoor butterfly gardens with abundant food and a lack of predators.
- Key differences in lifespan can be attributed to differences in DNA repair genes, DNA stability genes, tumor suppressor genes and the like.



Note: ROS = reactive oxygen species

Point Three:

There are Many Theories of Aging and a Large Associated Literature

Tens of thousands of papers are published each year on aging biology.

Research on Biological Aging is Exploding

- The interesting question given the tight upper line on human lifespan is why do we all die at a certain time. Why aren't there a few exceptional individuals, for example, who make it to age 150 or age 200?
- To this end, there has been an outpouring of research on biological aging in the last decade. Our understanding of how organisms age and why is accelerating.
- As spelled out in our first report, initial theories developed between 1930 and 1980 noted that caloric restriction could extend life, that mutational burden was associated with lifespan and that the length of chromosomal telomeres put a limit on how many times a specific cell could divide (called the Hayflick Limit).
- But, for various reasons, each of these initial biological theories of aging have in some way been less than satisfactory.
- Research efforts in the period from 1980 to 2019 focused on several novel areas including sirtuin activators, the TOR pathway and senolytics.
- Since then, in less than five years the field has grown rapidly, and novel insights have accumulated with ever more translational potential.
- Aging research has truly come into its own and there are, by now, increasingly credible, well documented theories that can explain the human age limit.

We are all prisoners to the clock. Humans appear programmed to die within 85 to 105 years from birth. Despite billions of births no one has yet made it past 125.

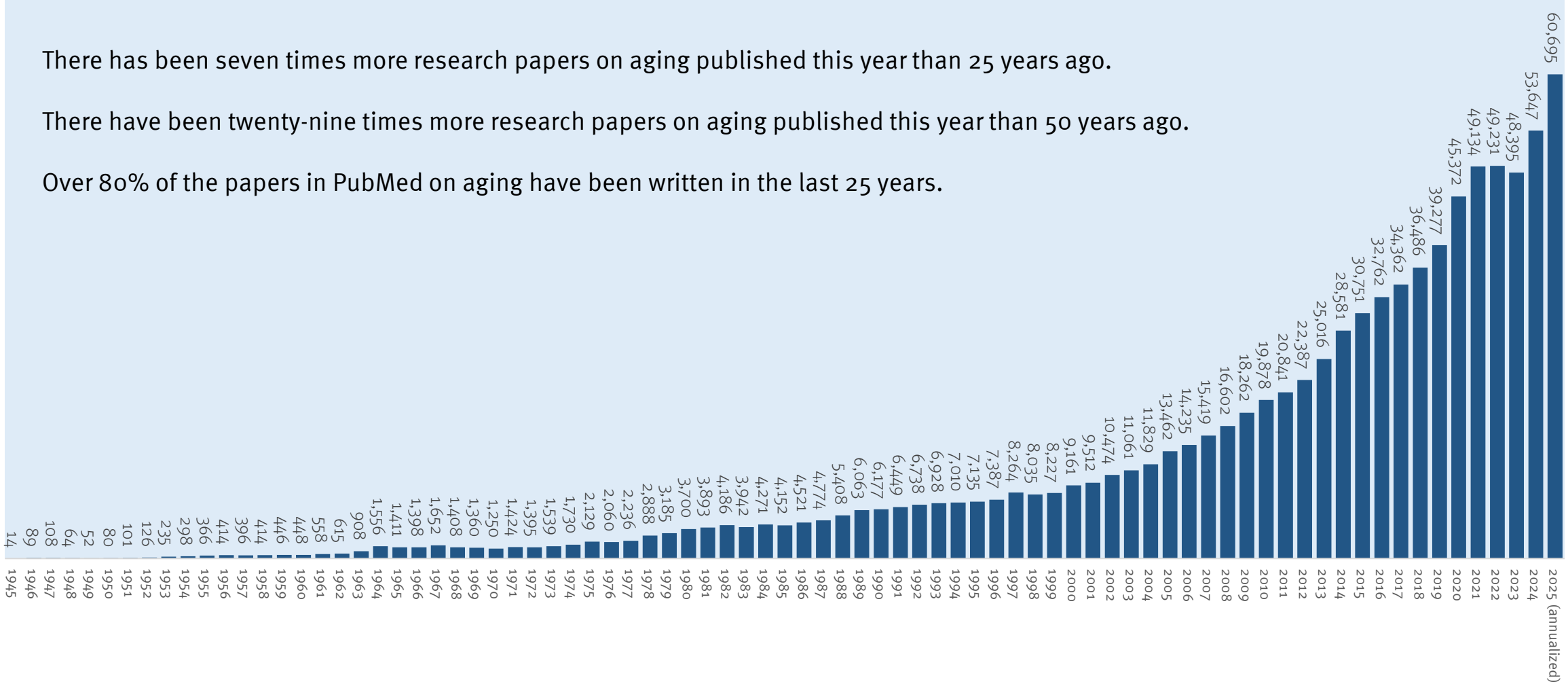
Explosion in Aging Research Over Last Century

Number of Papers in Pubmed Mentioning the Phrases "aging" or "longevity“, 1925 to 2025

There has been seven times more research papers on aging published this year than 25 years ago.

There have been twenty-nine times more research papers on aging published this year than 50 years ago.

Over 80% of the papers in PubMed on aging have been written in the last 25 years.



Source: PubMed. Count of papers as of Nov 11, 2025 was multiplied by 1.18 to annualize the total count.

There are Dozens of Theories of Aging in the Literature

Telomere shortening	Replicative senescence	Metabolic rate of living	Free radical theory	Mitochondrial theory	Yamanaka factors
Autophagy breakdown	DNA damage	Protein misfolding theory	Loss of proteostasis	Immunosenescence	Inflammaging
Vascular permeability	Endocrine theory	Reduced IGF-1 / insulin signaling	Neuroendocrine theory	Brain-centered theories	Disposable soma theory
Antagonistic pleiotropy	Mutation accumulation	Stem cell exhaustion	Epigenetic alteration theory	Sirtuin theory	Cell enlargement
Impaired lipid metabolism	Dysregulated RNA processing	Altered ECM dynamics	Dysbiosis	Deregulated nutrient sensing	Orgel theory / errors

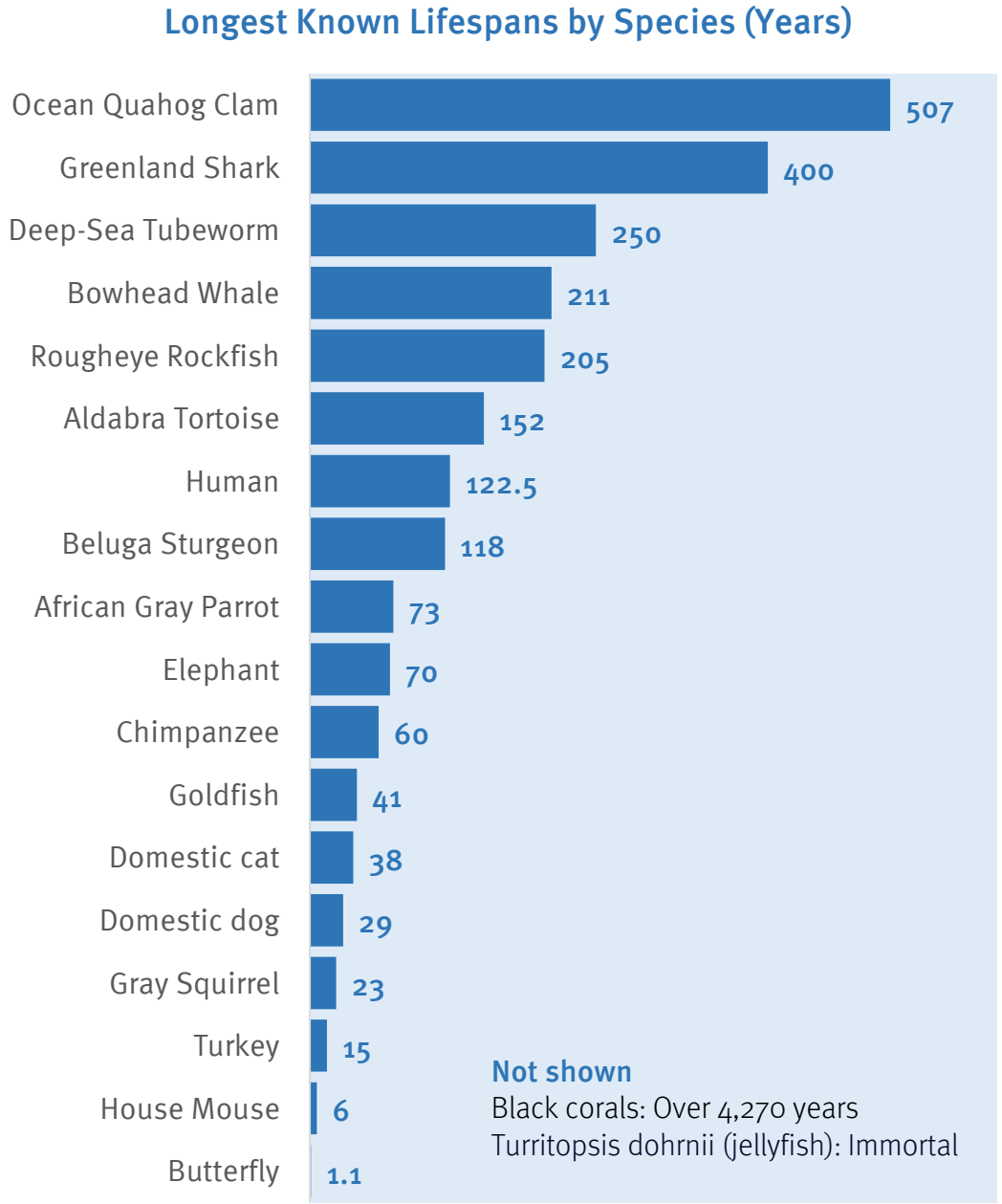
Point Four:

The Study of Interspecies Variation in Lifespan is Highly Informative

Some species live for a very long time while others don’t survive a week. Understanding why is likely to help us identify the core causes of aging.

Comparative Zoology of Aging

- Interspecies variation in maximum lifespan offers important clues as to the underlying biology of aging itself.
- A Mayfly might only live for a day. The butterfly typically has a life of two weeks.
- In contrast, certain species (some sharks, mollusks and corals) live substantially longer than us humans. There is one species (*turritopsis dohrnii*), a jellyfish, that is immortal.
- We are not aware of a credible scientific explanation that can unify the many observations about humans and other species in the aging literature to explain why we generally don't make it past 105 years of age.
- It turns out that there are a number of factors that explain interspecies variation in lifespan – and much to learn from this diversity. In general, the differences among species are highly informative about the underlying causes of aging.



Source: Stifel research

Factors that Explain Interspecies Variation in Lifespan

Metabolic Rate

Species with higher metabolic rates tend to have shorter lifespans. High metabolism leads to more energy production, which increases the generation of reactive oxygen species and oxidative damage, contributing to aging. Consistently, smaller animals have higher metabolic rates than larger ones.

Body Size

Generally, larger animals tend to live longer than smaller ones. This relationship is known as the "rate of living" theory, which suggests that larger animals have slower metabolic rates, thus producing less oxidative stress over time. Further, larger animals have a lower mass-specific metabolic rates.

Resting Heart Rate

There is an inverse relationship between resting heart rate and lifespan. Species with slower heart rates generally live longer because a slower heart rate reduces wear and tear on the cardiovascular system. For example, the resting heart rate of the long-lived blue whale is around 10 beats per minute.

Diet

Caloric restriction has been shown to extend lifespan in various species. Some species have evolved to have specialized diets that reduce oxidative stress or inflammation. For example, some species of tortoises have diets that are low in protein and high in fiber, which may contribute to their long lifespans.

DNA Repair Capacity

All species experience mutagenesis in their DNA as a natural part of cell replication – which is required for organismal growth. Some long-lived species, like the Bowhead Whale and the Naked Mole Rat, turn out to be a lot better than others at repairing these double-stranded breaks in DNA.

Aquatic Adaptations

Marine animals often have longer lifespans compared to terrestrial animals of similar size. The stable and cold environments of the deep sea reduce metabolic rates, and buoyancy in water can decrease the energy expenditure associated with maintaining body structure. The Greenland shark can live for over 400 years in part due to cold.

Epigenetics

Epigenetic mechanisms, such as DNA methylation and histone modification, play a crucial role in aging by regulating gene expression over time. Species with more robust epigenetic mechanisms that protect against DNA damage or maintain cellular function tend to have longer lifespans.

Reproductive Timing

Species that reproduce later in life tend to have longer lifespans. This is because late reproduction is often associated with longer periods of growth and development, which can be linked to slower aging processes. For example, animals like the Greenland shark reach sexual maturity at around 150 years old.

Point Five:

The Right Thing to Focus on is Cause and Effect

That is, what part of the aging process would you have to change to increase lifespan? Presumably, there are initial causes of aging that can be changed with positive effect. Based on our review of the literature, cellular damage theories appear to be a good place to start.

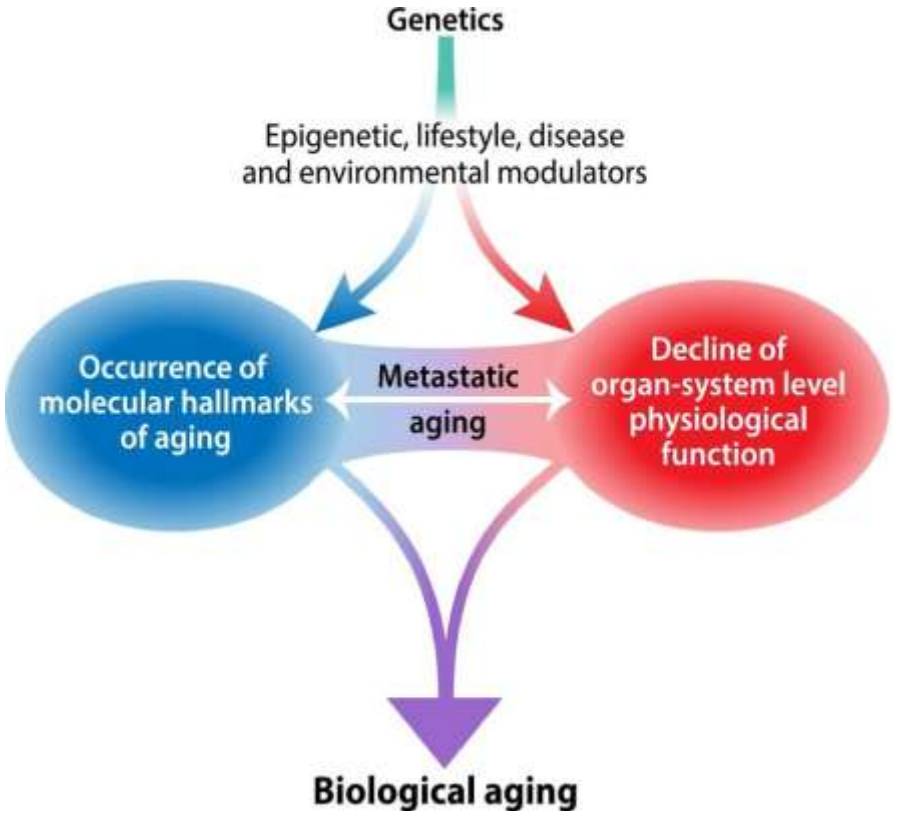
The Etiology of Aging

- As we have already seen, there are dozens of theories of aging. Some attribute aging to immune system decline while others point to vascular decline – you name it – there are as many theories of aging as sports teams.
- Our view is that it is very likely that a hierarchy of systems contribute to the lifespan of an organism.
- Humans die for multiple reasons much like cars do: most gasoline cars fail in 200,000 miles or less because of head gasket damage, but if you make the head gasket unusually durable, the transaxle will eventually fail, but if that can be prevented, they finally succumb to undercarriage rust, and so on.
- Thus, one would very likely need to change at least a half dozen things about how a car works to get it to last meaningfully longer. Or radically restructure how it works (e.g, use an electric engine approach).
- Think of long life then as requiring multiple changes to human systems. Long life is unlikely to be achievable with one single ingenious change to physiology.

Important to Disentangle Causes and Effects of Aging

Putative Causes of Aging

Metabolism
Oxidative stress
DNA damage
Epigenetics
Impaired autophagy



Putative Effects of Aging

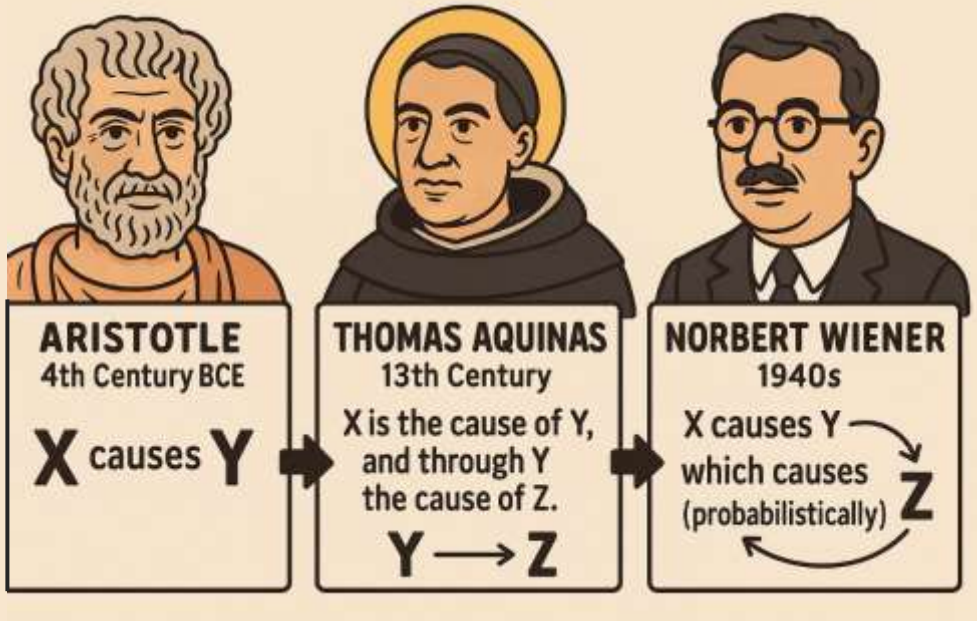
Mutation Accumulation
Protein misfolding
Aberrant Chromosomes
Organ system decline
Cancer
Immune dysfunction
Impaired metabolism

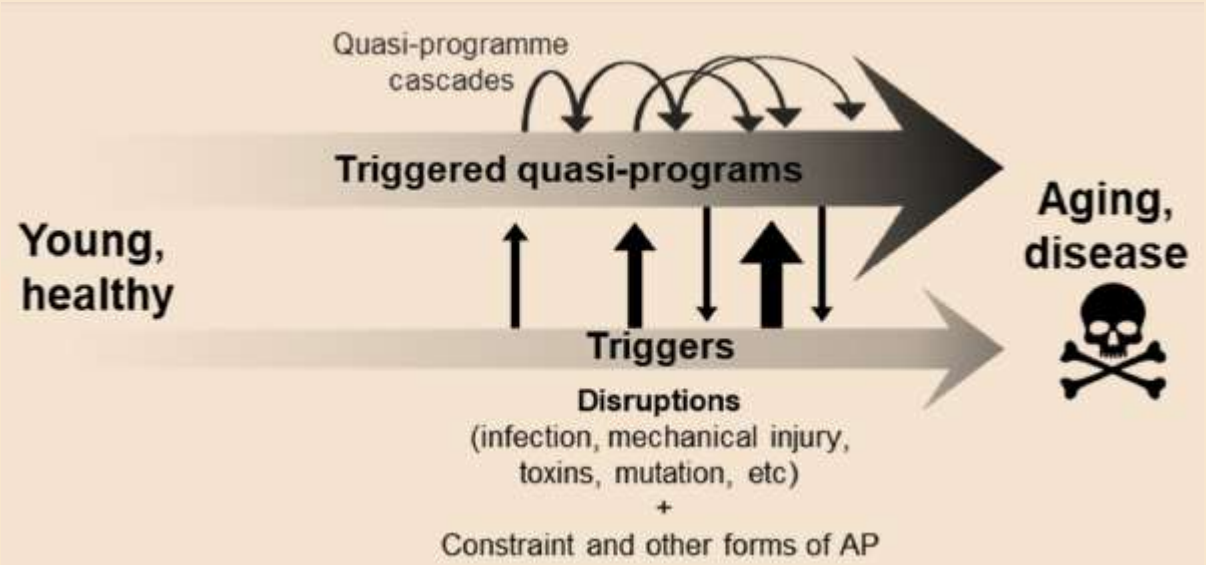
Source of image: https://onlinelibrary.wiley.com/doi/10.1111/acel.12601

Important to Recognize that Chains of Causality Can Involve Cascades, Loops and Probabilistic Forks

In our effort to sort out theories of aging, we may be oversimplifying matters because it is likely that simple causal relationships may be insufficient to explain the timing of human mortality. Carina Kern, for example, has argued that aging and ultimate death is associated with pathological processes that play out in causal cascades. She writes: "…the consequent pre-pathological and pathological changes may in some cases trigger further changes, leading to futile and destructive cascades of quasi-programmes and pathology." This thought process versus our more simplistic search for cause and effect of human death mirrors the progression of logic theory noted in the cartoon below at left.

Aristotle described simple causality while Thomas Aquinas noted the potential for multi-step causality. Later, John Stuart Mill and, ultimately, Norbert Wiener described a more modern view: complex cascading causal chains can have probabilistic elements with feedback. This is not, of course, an argument for scientific nihilism in aging research – but merely a call for recognition of the complexity of causal chains. Kern's chart taken from her "Blueprint of Aging" paper (below right) highlights this notion.





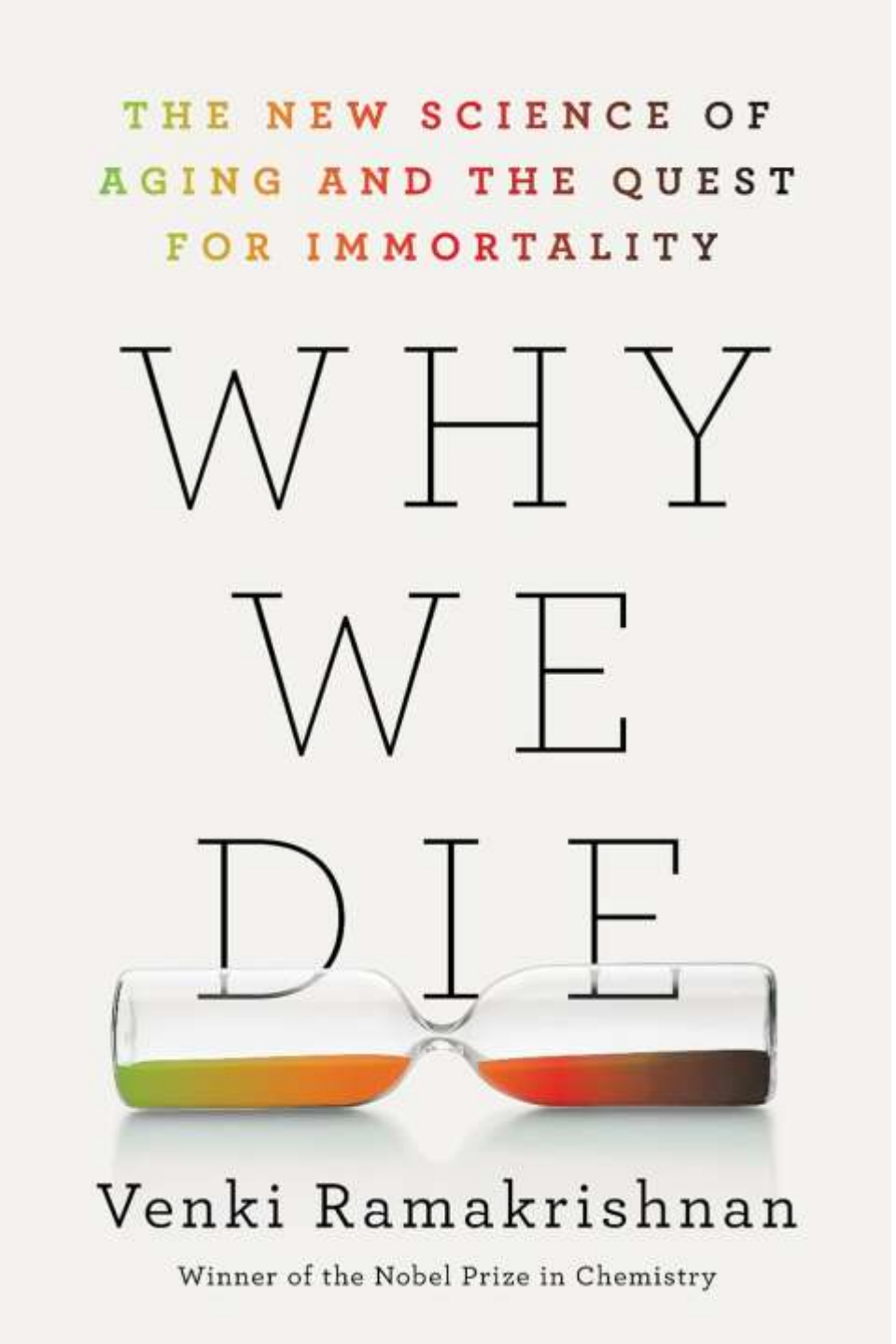
An Alternative View: Systems Biology

We spoke at some length to one aging expert who does not love our focus on cause and effect. He thinks a systems biology framework is more appropriate than either an Aristotelian or Weinerian perspective on aging biology.

The expert spoke by metaphor. Imagine that you're life involves navigating over a three-dimensional map. You are trying get into a beautiful lush green valley that is called long life. You spent plenty of time there when you were young. Unfortunately, random things happen all the time that keep you from getting back into that valley. Perhaps a fallen tree blocks the path into the valley. Or a windstorm sweeps you away. The expert's point is that there is a lot of chance events, particularly involving environment, that make it more difficult to get on the path to an optimal long life as we age.

But there are many ways to get into the valley and there are just as many ways to get out. There is not a single path. Aging and, ultimately, death are seen as multicausal and overall system integrity matters as much as any one biological pathway. Aging can be seen as involving changes in a multi-node network that has many points of redundancy. The expert encourages all of us to listen to Peter Attia's interview of Brian Kennedy (minutes 23 to 30) who describes this systems approach from the perspective of a mathematician. We liked the interview too. Kennedy is a deep thinker.

The expert particularly likes the idea of resilience. As we age, the biological system that protects us from cataclysm weakens randomly and we become more vulnerable to physiological damage. A key point is that reversal of causal factors that get us into biological trouble may not get us out as aging may involve irreversible biological changes that trigger new harmful programs. Our own view is that it is important to understand both proximate causes and distal effects of aging processes. Yet, causal complexity should not be a reason to abandon empiricism nor to take a nihilistic view of aging science. We like Carina Kern's viewpoint which acknowledges the complexity of aging and yet does not abandon the search for causal chains and hypothesis-driven interventions.



Our Approach to Thinking About Aging

1. We reviewed the literature extensively, looking at hundreds of papers on aging biology published since 2020 (to update the review done for our previous history of aging report)
2. We spoke to over twenty academic and industry experts while simultaneously meeting with over a dozen aging-focused biotech companies
3. We worked with seven bright interns to review the aging literature in the Summer of 2024
4. We read multiple books on aging including Ramakrishnan's excellent synthesis of the literature shown at left (published in 2024)
5. We focused heavily on "clues" to the underlying causes of aging:
   (a) What proteins are most predictive of longitudinal variation in when people die? What biology is associated with such proteins?
   (b) Which animal species live especially long or short lives and why?
   (c) What genetic mutations are associated with short or longer life and what biology is associated with these genes?
   (d) What are the effect sizes of the genetic, proteomic and interspecies aging differentials?

We synthesize the literature with a focus on the underlying core causes of aging. Our focus is on the translational machinery that would be required to develop and test hypotheses of lifespan extension.

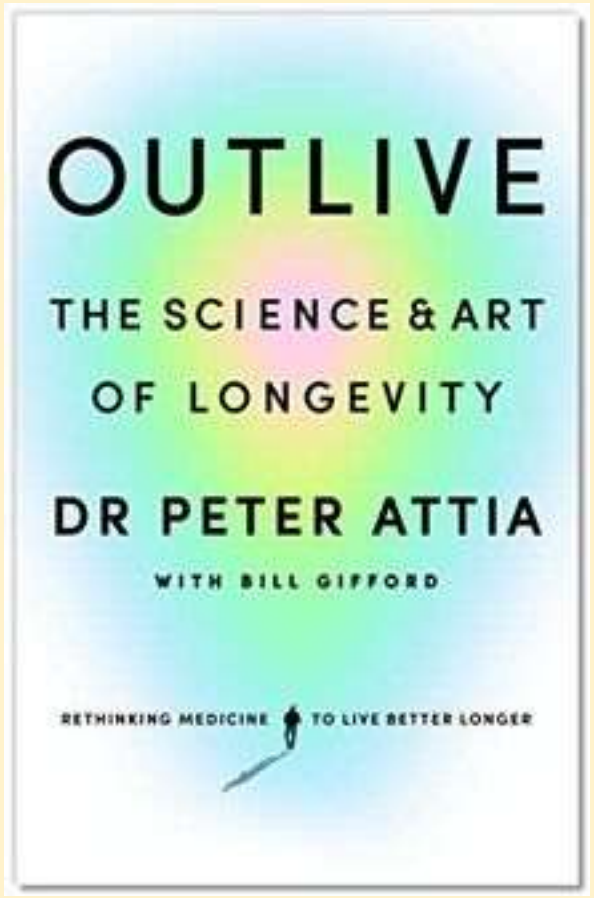
Aging is Caused by the Accumulation of Cellular Damage

“I would say, broadly speaking, you can think of ageing as an accumulation of damage with time. This is a damage to our molecules, which in turn affects our cells and our organelles, and then that in turn affects our tissues. So, this damage gradually builds up over time, and it reaches the point where you get loss of function. …if the loss of function is critical — for example, if your heart stops beating or your brain stops working — then you can no longer function as an individual. And that’s when you die.”

Venki Ramakrishnan

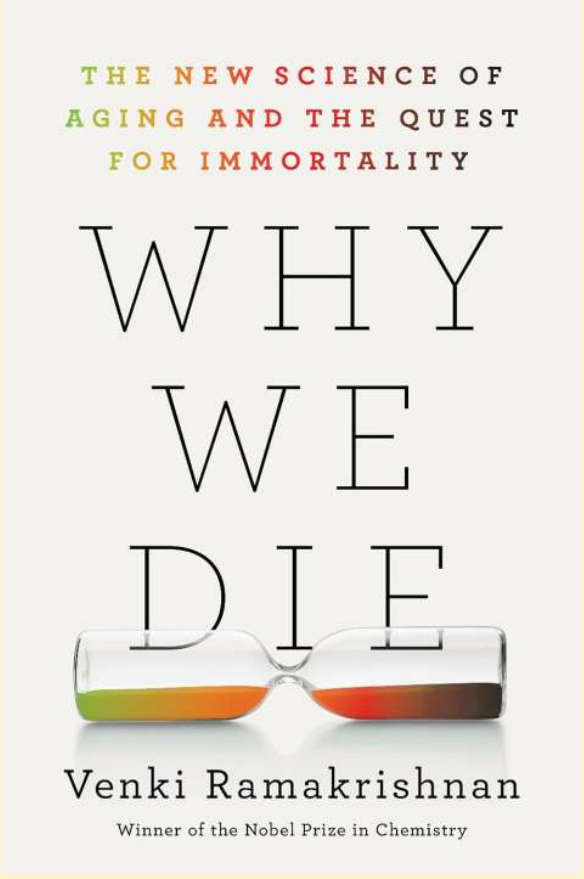
MRC and Nobel Prize-Winner in Chemistry, 2024

Four Popular Books on Aging Biology by Well-Known Authors

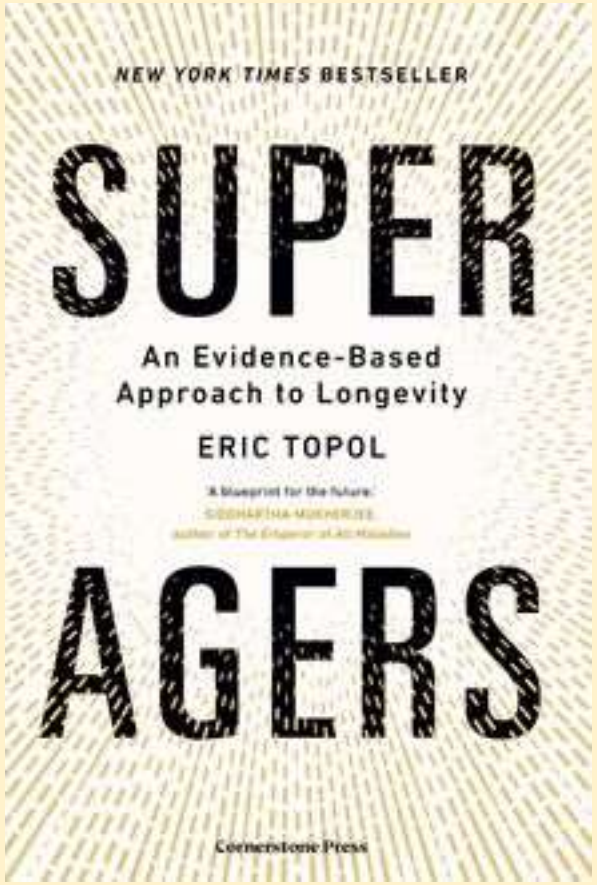


Peter Attia, 2023

Nir Barzilai, 2020



Venki Ramakrishnan, 2024



Eric Topol, 2025

Summary of the Four Books

Author / Book	Primary Lens	Core Message	Scientific Themes	Approach to Longevity	Implications for Medicine	Strengths	Limitations
 **Peter Attia** *Outlive*	Clinical / Preventive Medicine / Self-Help	Focus on **health-span**, not lifespan. "Medicine 3.0" must be proactive—using early diagnostics, exercise, nutrition, and data to prevent chronic disease.	Cardiometabolic health, insulin resistance, inflammation, exercise physiology, risk stratification.	Continuous monitoring, screening, and targeted interventions to delay "Four Horsemen" (CVD, cancer, neurodegeneration, metabolic disease).	Defines the **consumer-medical longevity market**; large opportunity in diagnostics, digital health, and lifestyle medicine platforms.	Clear framework, accessible science, bridges clinical practice and longevity.	Light on molecular biology and new therapeutics; heavily lifestyle-centric.
 **Nir Barzilai** *Age Later*	Geroscience / Genetics / Less self-help / more science	Aging is **modifiable**; centenarians reveal protective biological pathways that can be mimicked pharmacologically (e.g., metformin).	Longevity genes (CETP, APOC3), insulin/IGF-1 signaling, mitochondrial peptides, metabolic pathways.	Pursues pharmacological delay of aging via **geroprotectors** and biomarkers; focuses on *TAME* (Targeting Aging with Metformin) trial.	Identifies **translational biotech targets** (senolytics, mitochondria, metabolic modulators); aligns with early-stage longevity biotech.	Scientific grounding; credible research lineage; connects genetics to therapy.	Optimistic on timelines; focused on treatments at hand like Metformin rather than biologic possibilities
 **Venki Ramakrishnan** *Why We Die*	Review of the scientific evidence / Evolutionary biology	Explains **why aging and death exist**; argues that death is biologically necessary.	Cellular senescence, apoptosis, evolutionary trade-offs, DNA repair, proteostasis.	Advocates realism: slowing aging and reducing frailty are achievable; immortality is not.	Provides a **scientific sanity check**—separating hype from the breakthroughs. Discusses ethics of longer life.	Deep biological grounding; challenges techno-optimism; broad perspective.	Limited actionable guidance; may underplay translational opportunities.
 **Eric Topol** *Super Agers*	Integrative / Digital Medicine	Longevity arises from a convergence of **lifestyle, AI, omics, and drugs**. Focus on life extension through measurable, evidence-based tools.	Multi-omics, AI, digital biomarkers, senotherapeutics, systems medicine.	Balances lifestyle with high-tech medicine; prioritizes evidence and equity.	Highlights opportunities at the **intersection of technology and biology**—AI-guided health tracking, longevity biomarkers, precision therapeutics.	Synthesizes multiple domains; credible, balanced optimism.	Broad scope may dilute depth; regulatory and access issues underexplored.

Background Info: Various Seminars (YouTube) on Aging

1. A16Z: The Longevity Imperative: Redefining the Way We Age (Podcast). Also see a second Podcast on aging and biology
2. Peter Attia, Author of Outlive: How to Make Your Last Decade Enjoyable (TV Show)
3. Juan Carlos Belmonte of Altos Labs on Cell Reprogramming (Seminar)
4. Joe Betts-Lacroix on Retro (Seminar)
5. Elizabeth Blackburn on Aging Science and Cells that Don't Grow Old (Seminar)
6. Judith Campisi on Cell Senescence (Seminar)
7. CBS episode on dog aging (TV show)
8. Ronald de Pinho on How Could We Reverse Aging (TED Talk)
9. Economist: Can Aging Be Reversed? (Video)
10. Steve Horvath on Epigenetics and Aging (Video)
11. Michael Borsch Jensen of Gordian on Aging (Seminar)
12. Matt Kaberlein on Aging (in humans and dog) (Seminar)
13. Carina Kern of Linkgevity on the Blueprint Theory of Aging (Seminar)
14. Morgan Levine of Yale on Aging Reversal (Seminar)
15. Longevity Startups by NfX (Video)
16. Tom Rando of Stanford on Aging (Seminar)
17. Michael Ringel of Life Biosiences: Partial Epigenetic Reprogramming (Seminar)
18. Andrew Steele, Author of *Ageless: The Greatest Revolution in the History of Medicine* (Seminar)
19. Eric Topol, Author of Super-Agers: Interview on Aging (TV Interview)
20. Maria Torroella Carney of Northwell on Caring for an Aging Population (Seminar)

Our Own View of Aging Biology After Reviewing the Literature

1. There are countless *correlates* of aging. Everything breaks down with time from the brain to the immune system.
2. But correlates can disguise core *causal* factors.
3. The core causal factors are likely part of an interconnected and somewhat redundant system. A single cause story linked to something like telomere length or mTOR seems particularly implausible.
4. These causal factors reflect an organism's interaction with its environment, creating substantial cross-sectional variation in aging.
5. They are not deterministic, insofar as the organism does not follow a simple life program as was suggested by Charles Minot over a century ago. For more on this, see Kirkwood's informative paper on this and Kern's paper "Uncovering the Blueprint of Aging". Minot's work is described in our first report (pp. 122-123).
6. Further, humans have a variety of systems in place to cope with the effects of aging. Some see the breakdown of these various repair systems as the core cause of aging – the loss of resilience.
7. The right place to start is in the cell. Cell biology drives aging. We agree with Ramakrishnan.
8. The overwhelming body of evidence points to mitochondria as the core starting place for aging damage.
9. The next most credible theory is the idea that DNA damage plays an important role in aging.
10. Most other aspects of aging (e.g., immunosenescence) appear to be downstream. That is, these aspects are largely *consequences* of mitochondrial and DNA damage rather than phenomena with independent etiologies.
11. One also needs to look at multiple aspects of the cell and whether there are "programming" factors that might be able to renew cells or, alternatively, ways to remove senescent cells that contribute to the damage of aging.

Perspective

- For all the amazing research that has been carried out on aging in recent years it is surprising how little focus there has been on translational aspects of biology.
- This report reviews the various theories of aging and then, for better or for worse, takes a point of view on the science.
- We prioritize the theories of aging based on our read of the quality of supportive evidence and, specifically, try to sort out core starting causes of aging from the consequences.
- Obviously, from a translational perspective, one wants to think about how to stop a disease from taking place at the root cause level rather than having to put out the fire later.
- Once one has a point of view on causality it's easier to think through how to navigate forward. That is, you think theory X is the right one to focus on managing to impact lifespan, then it is far easier to turn to a discussion of the merits of various translational options.
- This said, so many surprising aspects of aging have been discovered in recent years – that we will spend a fair bit of time on non-root-cause strategies for combating aging including the removal of senescent cells, alterations in the cGAS pathway and cell reprogramming.
- A further critical aspect is the time frames of life associated with competing inferential frameworks. For example, we will show later in this report that certain protective mutations in AMPK and IGF1 genes are far more common in centenarians – very convincing. However, these mutations all take place within humanity's already very limited lifespan. Far more relevant biology might be that which plays out in long-lived mammals like the Bowhead Whale.
- In practice, while there are many translational attempts underway in various institutions and biotechs, our general sense is that many would benefit from taking a broad view on how one might even think about going forward with aging science.

Our Approach is Distinct from the Hallmarks of Aging Literature

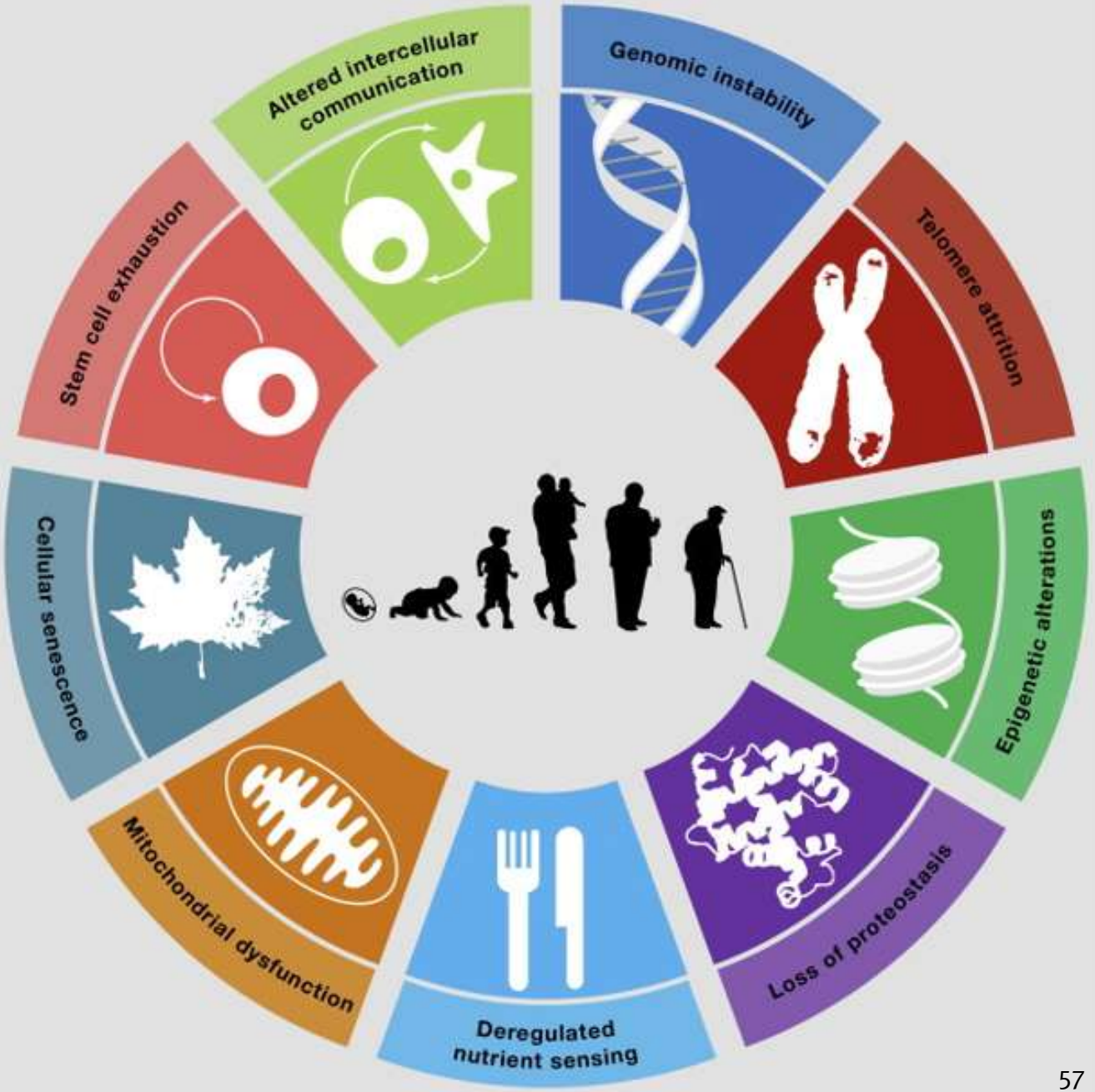
The most cited paper in the history of the aging literature is Lopez-Otin's et al.'s 2013 "Hallmarks of Aging" publication.

This paper identifies nine factors identified with aging and argues that these factors work in combination to contribute to aging. See chart at right.

This framework assumes that each factor is important and makes no effort to distinguish cause from effect or to establish the **primacy** of any one theory.

Thus, while highly influential, this framework does not appear designed to facilitate construction of interventions as, in principle, it is suggested that one need address all nine underlying factors to impact longevity.

Our view is that some of these "hallmarks" might be causal while others are likely to be effects of aging or bystanders.

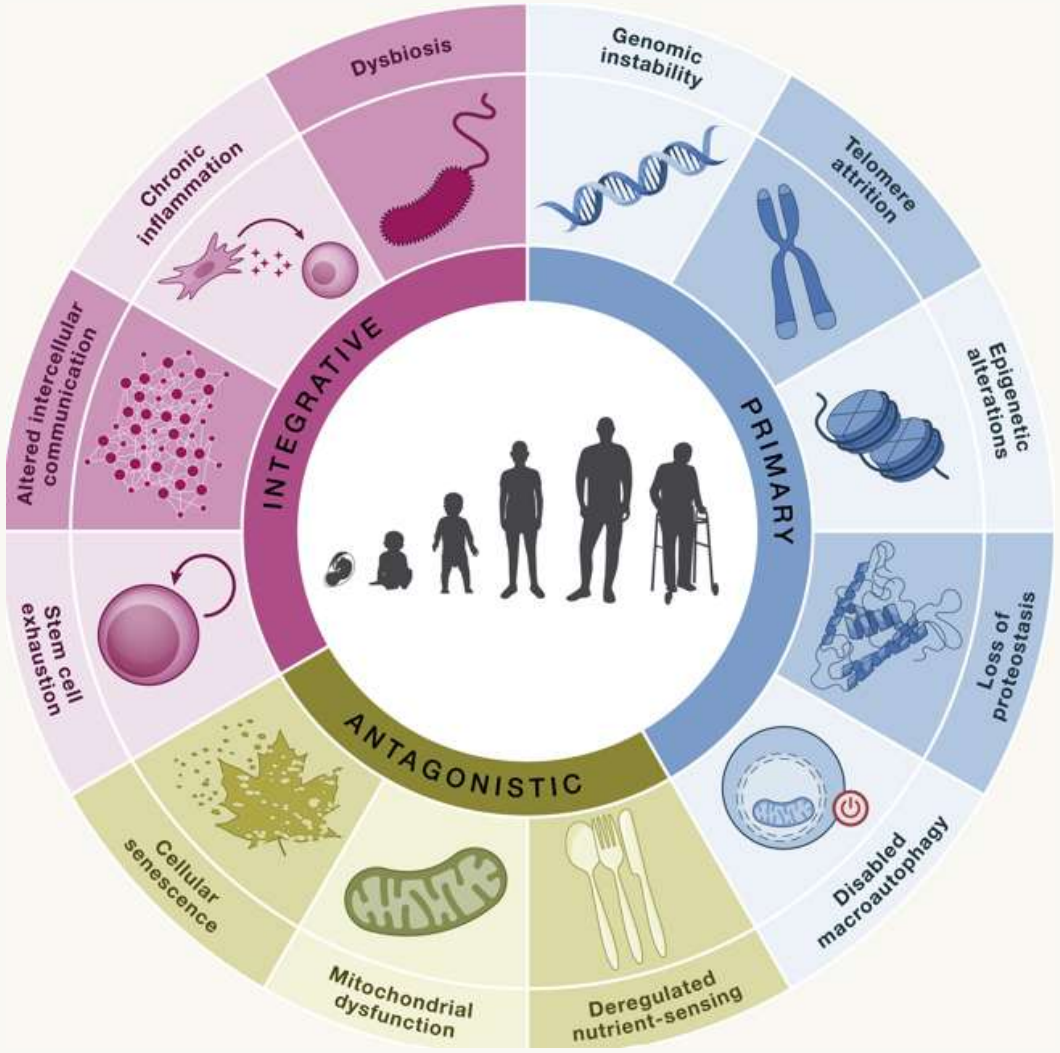


Most Recent Update of the Hallmarks of Aging Paper

In 2023 the original authors of the “Hallmarks of Aging” wrote a second paper (see chart at right) that updated the first paper to have twelve rather than nine hallmarks of aging. In 2025 the authors again updated their analysis, increasing the number of hallmarks to fourteen.

This time the authors provide an even more comprehensive review of the aging literature but again do not attempt to prioritize the principal cause of the aging process. If you will, the literature features multiple competing theories of aging and this paper attempts to give all major theories legitimacy as opposed to identify primacy. However, you will note that the paper identifies five primary hallmarks of aging and three antagonistic hallmarks of aging. This is a step in the right direction.

But the issue remains that we **lack an integrated theory of aging**. That is, these various hallmarks of aging are unlikely to all be equally important in causing our downfall. Carina Kern writes: “Understanding aging mechanisms remains a formidable challenge. While broad frameworks like the Hallmarks of Aging outline key factors—genomic instability, elevations in systemic oxidative-inflammatory-nitrosative stress, proteostasis loss, telomere shortening, senescent cell accumulation, and epigenetic changes amongst others — the difficulty lies in determining their position within a causal chain. Are they primary drivers, secondary contributors, or merely symptoms of specific age-related conditions?” (See https://www.nature.com/articles/s41388-025-03431-y, p. 1899).



Point Six:

Cell Damage, Caused by Mitochondrial Respiration, is Very Likely the Right Place to Start

There is overwhelming evidence that mitochondrial respiration has adverse effects over time that lead to cell damage, specifically DNA damage, and aging. Think of mitochondria as the internal combustion engine of the human body. As they break down, we get closer to death. In a way, aging can be considered as a universal form of mitochondrial disease.

The Central Importance of Mitochondria to Human Life

Mitochondria are the tiny power plants that power us. These organelles descended from ancient bacteria that merged with primitive cells over a billion years ago.

Mitochondria convert the chemical energy stored in food into adenosine triphosphate (ATP), the cellular currency that drives biological processes like muscle contraction, nerve signaling, DNA repair, and cell division. Without this constant process of energy conversion called “respiration”, multicellular life would simply not be possible.

Through the process of oxidative phosphorylation (OXPHOS), mitochondria couple electron flow through the respiratory chain to the production of ATP, using oxygen as the final electron acceptor.

Mitochondria do much more – regulating calcium homeostasis, control apoptosis (programmed cell death), and shaping metabolic decisions that determine whether a cell grows, differentiates, or dies.

Unfortunately, like the internal combustion engine of a car, the creation and usage of fuel in the mitochondria may also seed our decline.

As noted in our first report this idea was understood, to some degree, by Aristotle and Robert Boyle centuries ago.

The mitochondrial electron transport chain leaks small amounts of reactive oxygen species (ROS), chemically aggressive byproducts that damage DNA, lipids, and proteins over time. ROS can be quite corrosive to human life.

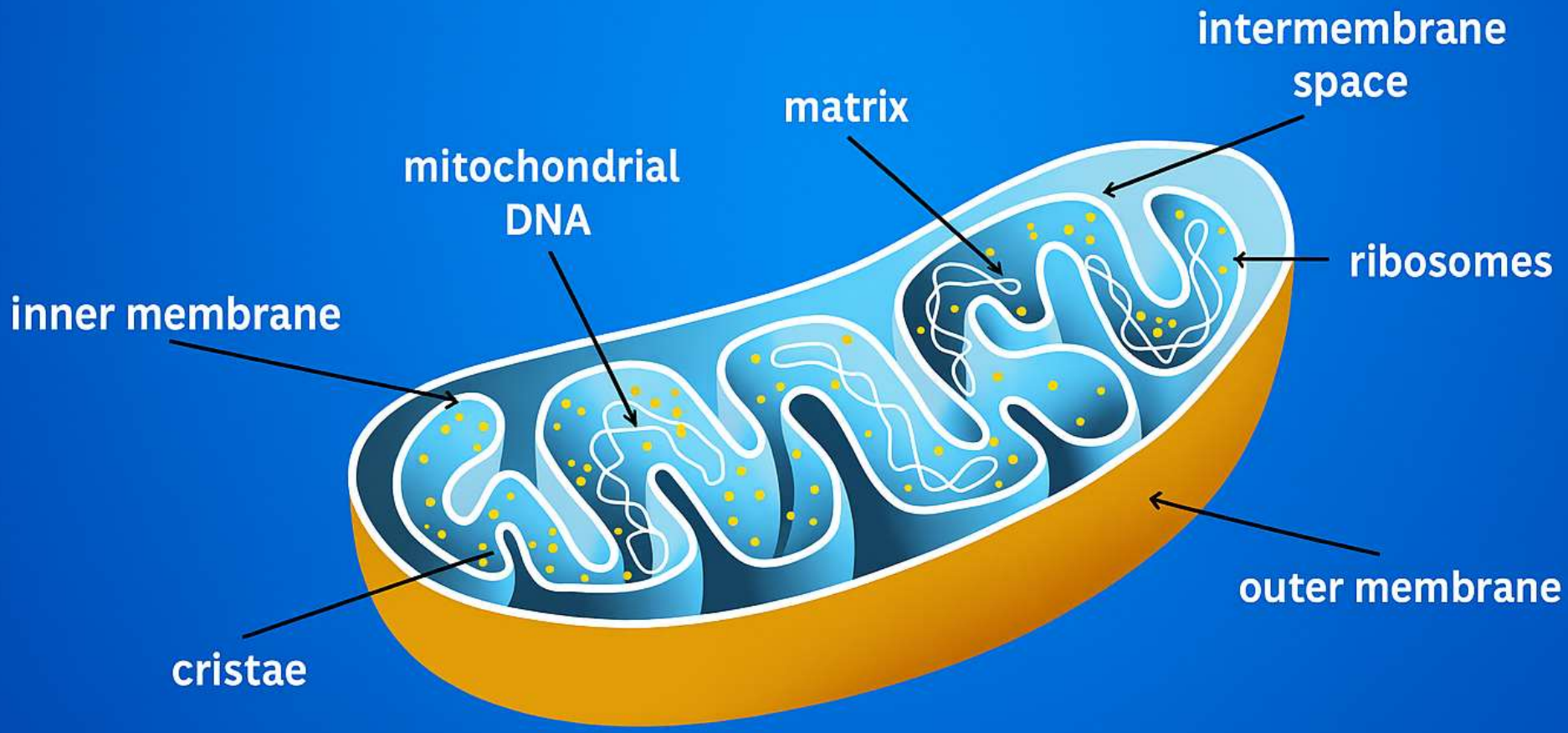
Accumulated mitochondrial mutations, impaired dynamics (fission and fusion), and diminished mitophagy compromise energy production and heighten oxidative stress, creating a vicious cycle of dysfunction.

As decades pass, this metabolic wear erodes tissue resilience, contributing to aging, inflammation, and degenerative disease. In a way, mitochondria are both the spark that keeps us alive and the slow-burning fuse that makes sure that spark doesn’t last forever. We essentially rust to death.

MITOCHONDRIA

"Powerhouse of the Cell"

Mitochondria are eukaryotic organelles that make chemical energy via aerobic cellular respiration.



How Mitochondrial Respiration Works: Starting with Glucose

Glycolysis in the Cytoplasm

GLUCOSE

Process: One glucose molecule (6 carbons) is broken down into twa molecules of pyruvate (3 carbons each).

Energy yield: Uses 2 ATP in the early steps

Produces 4 ATP later → net gain = 2 ATP
Also produces 2 NADH, which carry high-energy electrons for later use

PYRUVATE

PYRUVATE

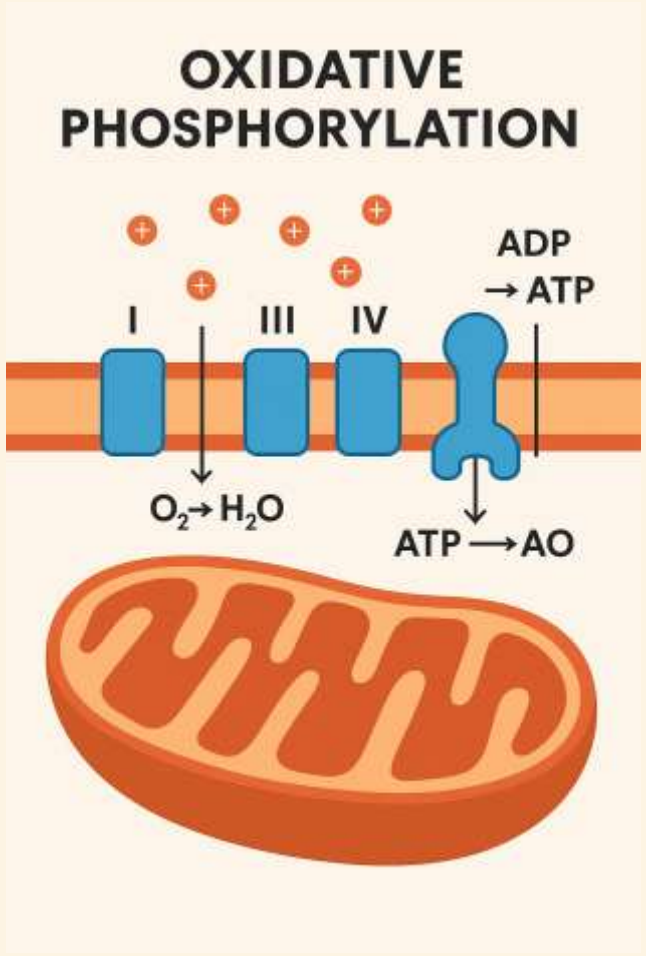
Step 2: Pyruvate oxidation (in the mitochondrial matrix)

+ CO_2

Each pyruvate → acetyl-CoA (2 carbons) + CO_2

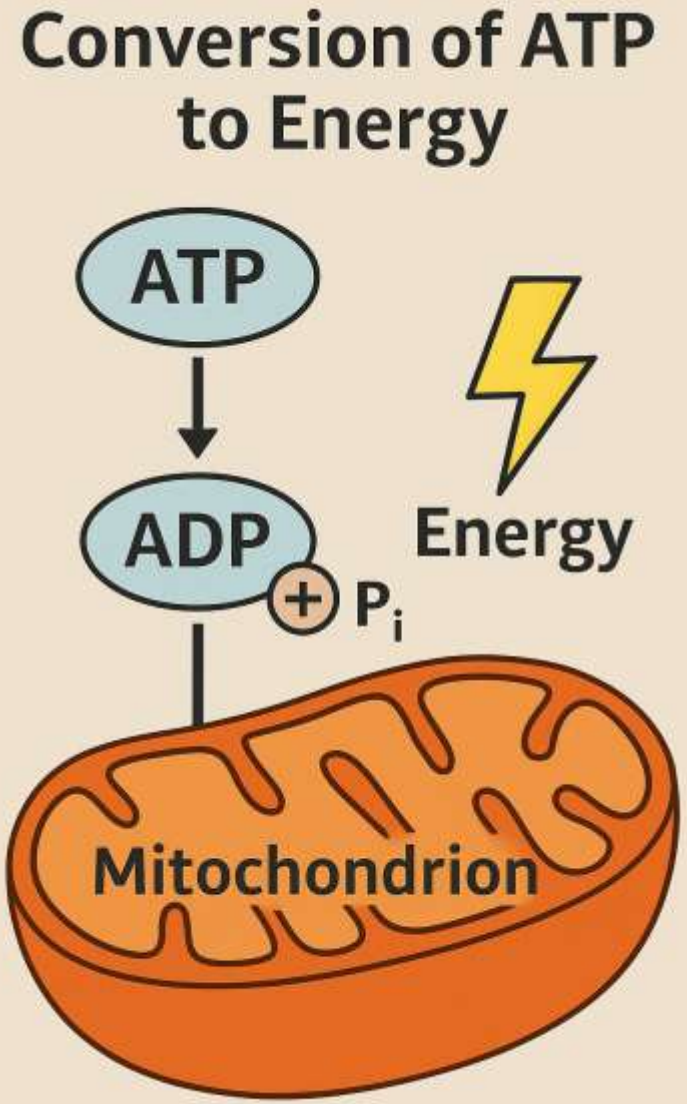
ACETYL-CoA

Generates 1 NADH per pyruvate (so 2 per glucose).



Glucose is oxidized stepwise — first in the cytoplasm, then in the mitochondria — to extract electrons whose energy is converted into ATP through a proton-driven process (ATP synthase).

How ATP is Burned in the Mitochondria to Create Energy



Inside the mitochondrion, cellular energy is generated when adenosine triphosphate (ATP) is hydrolyzed into adenosine diphosphate (ADP) and an inorganic phosphate (Pi), releasing a burst of usable chemical energy.

This energy powers countless biological processes—muscle contraction, ion transport, biosynthesis, and cell signaling.

However, not all electrons transfer cleanly—occasionally, oxygen molecules gain only a single electron, producing superoxide (O_2^-), a reactive oxygen species (ROS).

These partially reduced oxygen ions are highly reactive and can damage proteins, lipids, and DNA, but cells counteract them with antioxidant systems such as superoxide dismutase, catalase, and glutathione peroxidase to maintain redox balance and protect mitochondrial integrity.

How This Process Leads to Oxidative Stress

1. **Electron transport chain (ETC)** – Inside the mitochondrial inner membrane, electrons flow through complexes I–IV, derived from NADH and $FADH_2$ generated by glycolysis and the TCA cycle. Their passage drives proton pumping and sets up the gradient that powers ATP synthase.
2. At **complex IV** (cytochrome c oxidase), oxygen is normally reduced cleanly to water by gaining four electrons and four protons. However, a small percentage of electrons "leak" prematurely from complexes I and III before reaching oxygen.
3. **Formation of superoxide** – When an electron leaks to oxygen too soon, it forms superoxide anion ($O_2^{-}\cdot$), a type of reactive oxygen species (ROS). This is the first free radical in the chain of oxidative stress.
4. **Cascade of ROS** – Superoxide can be converted by superoxide dismutase (SOD) to hydrogen peroxide (H_2O_2), which can then react (via the Fenton reaction with Fe^{2+}) to form hydroxyl radicals (·OH)—highly reactive molecules that damage DNA, proteins, and lipids.
5. **Cumulative oxidative stress** – When antioxidant defenses (e.g., SOD, catalase, glutathione peroxidase) can't neutralize these radicals fast enough, mitochondria and surrounding cellular structures accumulate damage. Over time, this contributes to aging, neurodegeneration, and many chronic diseases.

Supportive Experimental Data Linking Mitochondrial Respiration to Oxidative Stress of the Cell

Seminal experiments (Chance & Williams, 1955; Boveris & Chance, 1973) showed that isolated mitochondria, supplied with substrates like NADH or succinate, consume oxygen and simultaneously emit small amounts of **superoxide and hydrogen peroxide**.

Oxygen electrode and spectroscopic studies quantified this leak at ~0.1–2% of total electron flow — establishing mitochondria as a physiological source of ROS. **Fluorescent probes** such as MitoSOX and DCFH-DA later visualized ROS generation within living mitochondria in real time.

Studies using ETC inhibitors (e.g., rotenone for Complex I, antimycin A for Complex III) have shown increased superoxide formation, pinpointing these complexes as the main culprits.

Mitochondria with specific ETC mutations (in ND1, ND5, or cytochrome b genes) exhibit higher ROS output, confirming a mechanistic connection between electron leakage and oxidative damage.

mtDNA, being near the ETC and lacking protective histones, accumulates oxidized nucleotides (8-oxo-dG) and deletions over time. Comparative studies (e.g., Harman's mitochondrial theory of aging, 1972; Linnane et al., 1989) show that ROS-related mtDNA mutations rise with age and correlate with declines in respiratory efficiency.

MnSOD (**SOD2**) knockout mice die shortly after birth due to severe oxidative injury in mitochondria. Overexpression of SOD2 or catalase targeted to mitochondria reduces oxidative stress, improves insulin sensitivity, and extends lifespan in mice.These cause–effect results directly link ROS from respiration to physiological stress and pathology.

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Chance, B., and G. R. Williams. 1955. "A Method for the Measurement of the Respiratory Chain and Oxidative Phosphorylation in Mitochondria." *Nature* 176: 250–254.

Loschen, G., L. Flohé, and B. Chance. 1971. "Respiratory Chain Linked H_2O_2 Production in Pigeon Heart Mitochondria." *FEBS Letters* 18(2): 261–264.

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Turrens, J. F. 2003. "Mitochondrial Formation of Reactive Oxygen Species." *Journal of Physiology* 552(2): 335–344.

II. Identification of ROS Leak Sites in the Electron Transport Chain

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Chen, Q., E. J. Vazquez, S. Moghaddas, C. L. Hoppel, and E. J. Lesnefsky. 2003. "Production of Reactive Oxygen Species by Mitochondria: Central Role of Complex III." *Journal of Biological Chemistry* 278(38): 36027–36031.

Brand, M. D. 2016. "The Sites and Topology of Mitochondrial Superoxide Production." *Free Radical Biology and Medicine* 100: 14–31.

Murphy, M. P. 2009. "How Mitochondria Produce Reactive Oxygen Species." *Biochemical Journal* 417(1): 1–13.

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IV. Genetic Manipulation of Antioxidant Enzymes

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Schriner, S. E., N. J. Linford, G. M. Martin, M. Treuting, P. Ogburn, and P. S. Rabinovitch. 2005. "Extension of Murine Life Span by Overexpression of Catalase Targeted to Mitochondria." *Science* 308(5730): 1909–1911.

Van Remmen, H., and A. Richardson. 2001. "Oxidative Damage to Mitochondria and Aging." *Experimental Gerontology* 36(7): 957–968.

Treuting, P. M., and S. E. Schriner. 2015. "Mitochondrial Catalase Expression Prevents Oxidative Damage and Extends Lifespan in Mice." *Annals of the New York Academy of Sciences* 1365: 68–78.

Mitochondrial Free Radical Theory of Aging (MFRTA)

The MFRTA argues that aging results from the accumulation of damage caused by reactive oxygen species (ROS) that are byproducts of mitochondrial respiration.

Over time, these ROS damage cellular components such as DNA, proteins, and lipids, leading to dysfunction and contributing to the aging process. Key elements of the theory:

Mitochondria generate ROS as a byproduct of energy production. The electron transport chain in mitochondria leaks electrons during oxidative phosphorylation, and these electrons can react with oxygen to form ROS.

Over time, the accumulation of ROS-induced damage to mitochondrial DNA (mtDNA) and proteins impairs mitochondrial function, resulting in more ROS production, forming a feedback loop that accelerates aging.

Just as importantly, ROS impacts other aspects of cellular integrity, triggering a host of additional processes that contribute to aging.

Evidence That Supports the Free Radical Theory of Aging

1. **Increased oxidative damage in aging cells and tissues:** Numerous studies have shown that aged tissues have higher levels of oxidized proteins, lipids, and DNA, suggesting that oxidative damage accumulates with age.
2. **Lifespan and antioxidant enzyme levels:** A number of studies have demonstrated a correlation between lifespan and the expression of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, which neutralize ROS. For example, certain animal models with overexpression of SOD show extended lifespans.
3. **Genetic modifications:** In animal models like C. elegans, mice, and fruit flies, manipulating antioxidant enzymes or genes involved in mitochondrial function alters lifespan. For example, mutations that enhance antioxidant defenses often extend lifespan, while mutations that impair them shorten lifespan.
4. **Pharmacological interventions:** Some compounds, such as mitochondrial-targeted antioxidants (e.g., MitoQ and SkQ1), have shown promise in reducing oxidative damage in experimental models and delaying some aging-related changes.
5. **Caloric restriction:** Caloric restriction (CR) is one of the most robust interventions known to extend lifespan in a variety of organisms, from yeast to mammals. CR reduces mitochondrial ROS production by shifting metabolism, suggesting that reduced oxidative stress is one of the mechanisms through which CR delays aging.
6. **Mitochondrial Uncoupling:** Mild mitochondrial uncoupling reduces ROS production by decreasing the efficiency of oxidative phosphorylation. Studies in mice have shown that mitochondrial uncouplers can decrease ROS levels and extend lifespan.
7. **Evidence from Human Studies:** Human studies show a correlation between markers of oxidative damage (e.g., oxidized DNA or lipid peroxides) and age-related diseases like cardiovascular disease, neurodegeneration, and cancer.
8. **Relationship between biomarkers and aging:** Biomarkers that are closely related to mitochondrial dysfunction, are strikingly strong predictors of human lifespan.

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Mitochondrial DNA Damage:

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Kujoth, G. C., et al. (2005). Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. *Science*, 309(5733), 481-484. (link)

Caloric Restriction and Mitochondrial Function:

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Guarente, L., & Picard, F. (2005). Calorie restriction—the SIR2 connection. *Cell*, 120(4), 473-482. (link)

Antioxidant Enzymes and Lifespan:

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Perez, V. I., et al. (2009). The overexpression of major antioxidant enzymes does not extend the lifespan of mice. *Aging Cell*, 8(1), 73-75. (link)

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Lapointe, J., & Hekimi, S. (2010). When a theory of aging ages badly. *Cellular and Molecular Life Sciences*, 67(1), 1-8. (link)

Point / Counterpoint

The Skeptic's View

Mitochondrial dysfunction and longevity in animals: Untangling the knot

Ying Wang and Siegfried Hekimi*

Science, Dec 4, 2015

Mitochondria generate adenosine 5′-triphosphate (ATP) and are a source of potentially toxic reactive oxygen species (ROS). It has been suggested that the gradual mitochondrial dysfunction that is observed to accompany aging could in fact be causal to the aging process. Here we review findings that suggest that age-dependent mitochondrial dysfunction is not sufficient to limit life span. Furthermore, mitochondrial ROS are not always deleterious and can even stimulate pro-longevity pathways. Thus, mitochondrial dysfunction plays a complex role in regulating longevity.

The Counterargument

While Wang and Hekimi agree that mitochondrial respiration results in release of ROS, they argue that this is not enough to explain aging and mortality. They use mouse data to make their point. The counterarguments are this:

1. There is overwhelming evidence that mitochondrial damage in humans' results in shorter lifespans. This is true of normal "wear and tear" mitochondrial damage and monogenic mitochondrial disease. (link)(link) Monogenic patients have lifespans of five years or less (link).
2. Cross-sectional differences in animal lifespans are consistent with the mitochondrial free radical theory of aging.
3. There is potential survival bias in the paper's work. Mouse models with total loss of ETC function die embryonically, so only mild partial knockouts survive to be studied. The paper therefore overrepresents adaptive partial dysfunction, not the full continuum of mitochondrial decline in normal aging.
4. Biomarkers of mitochondrial damage (see next section) are highly predictive of cross-sectional differentials in human mortality.
5. Animal studies show that measures to reduce mitochondrial damage in mice (e.g., mitochondrial uncouplers) can substantially reduce mortality. (link) (link)
6. The proposed pro-longevity roles of mtROS via intrinsic apoptosis and UPR^mt are largely inferred from *C. elegans* RNAi data in their paper. Later work (post-2017) has shown inconsistent conservation in mammals.

Mitochondrial Dysfunction is a Central Cause of Disruption of Age-Related Muscle Homeostasis

Marzetti E, Calvani R, Coelho-Junior HJ, Landi F, Picca A. Defective mitochondrial quality control in the aging of skeletal muscle. *Mech Ageing Dev.*, Sep 8. 2025; 228:112112.

Age-related skeletal muscle decline is a major contributor to frailty, functional impairment, and loss of independence in advanced age. This process is characterized by selective atrophy of type II fibers, impaired excitation–contraction coupling, and reduced regenerative capacity. **Emerging evidence implicates mitochondrial dysfunction as a central mechanism in the disruption of muscle homeostasis with age. Beyond ATP production, mitochondria orchestrate redox signaling, calcium handling, and apoptotic pathways, which are increasingly compromised in aged muscle due to chronic oxidative stress and defective quality control.** High-resolution respirometry has revealed intrinsic, lifestyle-independent declines in mitochondrial respiratory capacity, while large-scale phenotyping and transcriptomic profiling have established robust associations between mitochondrial integrity, physical performance, and mobility. These findings have prompted a paradigm shift from static descriptions of mitochondrial decline toward dynamic analyses of mitochondrial signaling networks and stress adaptability. Several quality control mechanisms, including mitochondrial biogenesis, dynamics, mitophagy, and vesicle trafficking, emerge as critical regulators of myocyte integrity. Understanding how these systems deteriorate with age will be pivotal for developing therapeutic targets to preserve muscle function, mitigate sarcopenia, and extend health span.

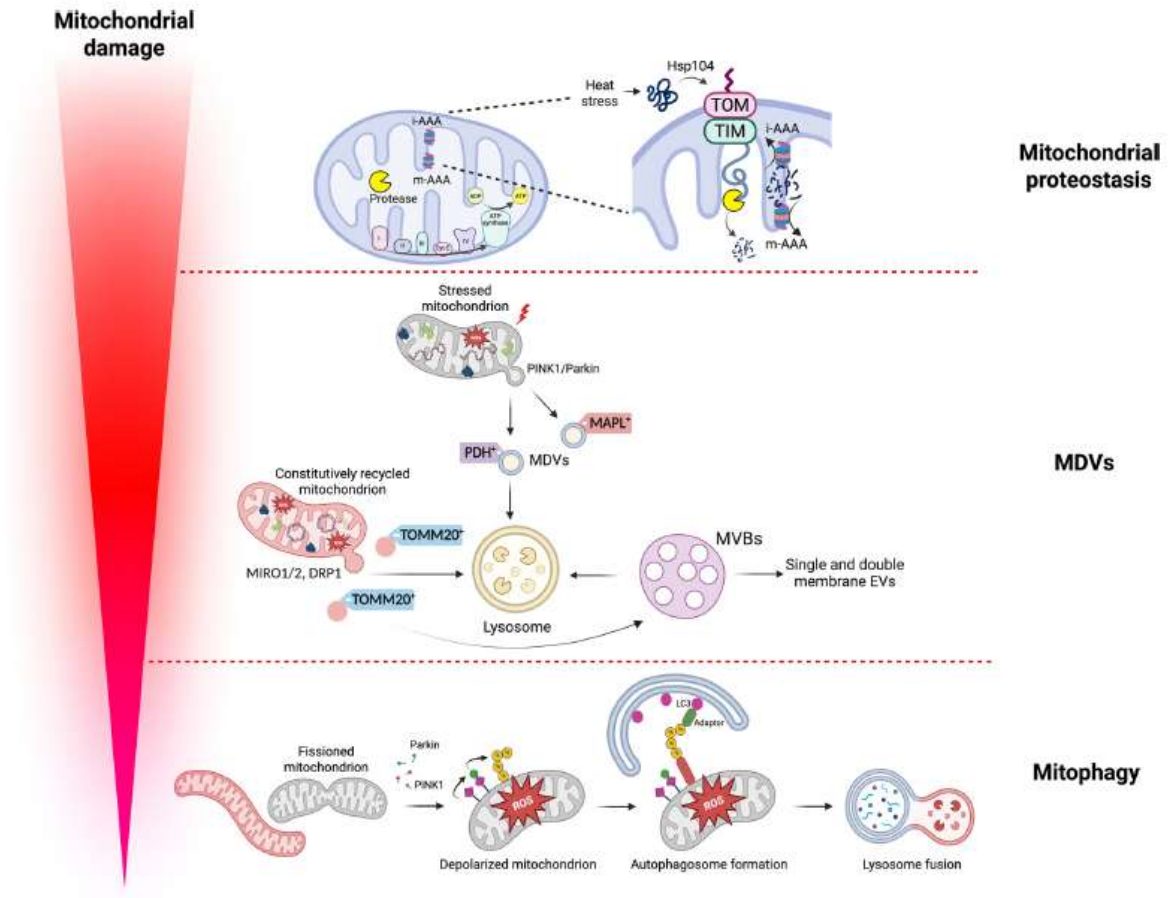


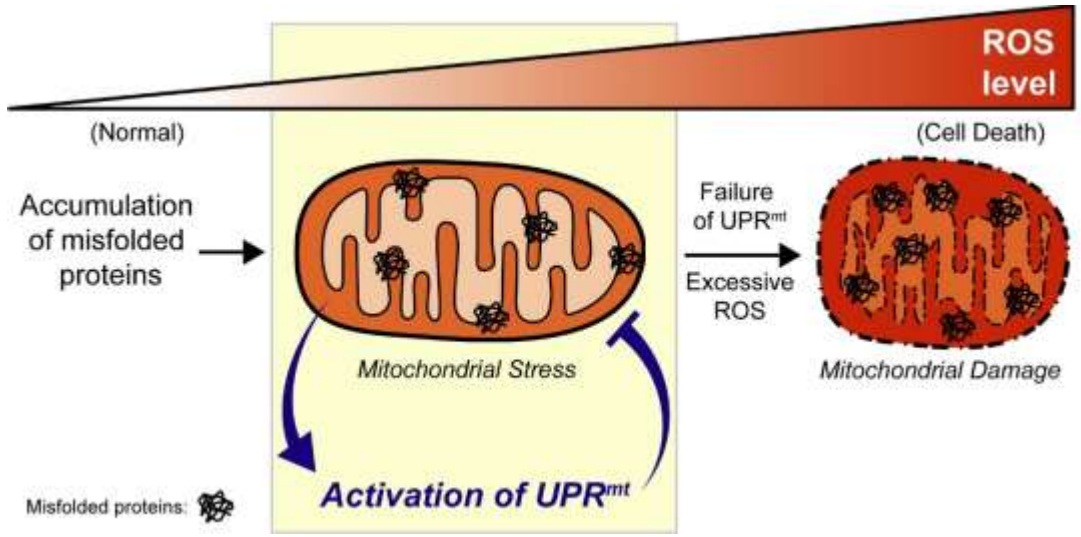
Fig. 1. Schematic representation of the mitochondrial quality control pathways recruited according to varying degree of mitochondrial damage. Abbreviations: DRP1, dynamin related protein 1; EVs, extracellular vesicles; Hsp, heat shock protein; i-AAA, intermembrane space-AAA metalloproteases; LC3, microtubule-associated protein 1 light chain 3; m-AAA, matrix-AAA metalloproteases; MAPL, Mitochondria-Associated Protein Ligase; MDVs, mitochondria-derived vesicles; MIRO1/2, Mitochondrial Rho GTPase 1 and 2; MVBs, multivesicular bodies; PDH, pyruvate dehydrogenase; PINK, phosphatase and tensin homologue-induced putative kinase 1; ROS, reactive oxygen species; TIM, translocase of inner membrane; TOM, translocase of outer membrane.

Source: https://www.sciencedirect.com/science/article/pii/S0047637425000880?via%3Dihub

The Unfolded Protein Response (UPR) Pathway Defends Against Oxidative Stress from Mitochondrial Respiration

The Unfolded Protein Response (UPR) is a crucial cellular defense mechanism that safeguards cells from the oxidative stress generated during mitochondrial respiration. As mitochondria produce ATP through oxidative phosphorylation, they inevitably release reactive oxygen species (ROS), which can damage proteins, lipids, and DNA. When ROS accumulation leads to misfolded or damaged proteins in the endoplasmic reticulum (ER), the UPR is activated to restore proteostasis. It does so by halting protein translation, upregulating molecular chaperones, and enhancing protein degradation systems such as ER-associated degradation (ERAD). The UPR also communicates with mitochondrial stress pathways through signaling molecules like ATF4, CHOP, and PERK, promoting antioxidant gene expression and metabolic reprogramming to limit further ROS production. In this way, the UPR forms a dynamic protective interface between mitochondrial metabolism and cellular homeostasis—mitigating oxidative injury, preserving energy balance, and extending cellular longevity.

The UPR has limits: If stress is too intense, chronic, or prolonged, the UPR can be overwhelmed and cannot fully compensate. The UPR deals with proteostasis (folding/degradation) but not all aspects of oxidative or metabolic stress. For example, ROS damage lipids, DNA, and organelle membranes — beyond just misfolded proteins. The UPR does not directly reverse all of that.



See: https://labs.icahn.mssm.edu/germainlab/mitochondrial-unfolded-protein-response/

Note: The UPR was discussed extensively in our previous aging report. See pages 209, 214, 215, 217, 221, 225, 227.

Point Seven:

Proteomic Analysis of the Determinants of Mortality Point Us in the Right Direction

While it is hard to know without clinical trials what biologic factor has to specifically change to extend lifespan, proteomic analysis provides important clues as to where to look.

DeCODE Study (2021) Identifies Five Proteins that are Predictive of Mortality Differentials for a Group of 21,000 people of Diverse Ages Using Almost 5,000 Somalogic Proteins

communications biology

ARTICLE

https://doi.org/10.1038/s42003-021-02289-6 OPEN

Predicting the probability of death using proteomics

Thjodbjorg Eiriksdottir[1], Steinthor Ardal[1], Benedikt A. Jonsson[1], Sigrun H. Lund[1], Erna V. Ivarsdottir[1], Kristjan Norland[1], Egil Ferkingstad[1], Hreinn Stefansson[1], Ingileif Jonsdottir[1,2,3], Hilma Holm[1], Thorunn Rafnar[1], Jona Saemundsdottir[1], Gudmundur L. Norddahl[1], Gudmundur Thorgeirsson[1,2,3], Daniel F. Gudbjartsson[1,2], Patrick Sulem[1], Unnur Thorsteinsdottir[1,2], Kari Stefansson[1,2✉] & Magnus O. Ulfarsson[1,2✉]

GDF-15 and WFDC2 are *very* strong predictors of 5-year mortality risk in this study of Icelandic people. Quite a few other proteins also score high.

Death within 5 years	Protein	HR	p-value
Growth/differentiation factor 15	GDF15	1.20	1.91E-167
WAP four-disulfide core domain protein 2	WFDC2	0.82	2.05E-111
Thrombospondin-2	THBS2	0.62	9.07E-100
Anthrax toxin receptor 2	ANTXR2	-0.56	4.62E-88
Retinoblastoma-like protein 2	RBL2	0.65	9.23E-88
Alpha-1-antichymotrypsin complex	SERPINA3	0.61	1.51E-86
Tumor necrosis factor receptor superfamily member 1A	TNFRSF1A	0.64	9.82E-85
Angiopoietin-2	ANGPT2	0.64	1.11E-82
Macrophage metalloelastase	MMP12	0.66	3.94E-81
Spondin-2	SPON2	0.67	1.40E-80

Source: https://www.nature.com/articles/s42003-021-02289-6

Evidence on GDF-15 and Mitochondrial Function

GDF-15 Expression is one of the Main Factors Used to Identify Mitochondrial Disease

GDF-15 is significantly upregulated in response to mitochondrial dysfunction. This upregulation occurs because of mitochondrial stress or damage, such as defects in the respiratory chain or mutations in mitochondrial DNA.*

Study Evidence: Multiple models of mitochondrial disease (including both patient-derived cells and animal models) demonstrate that GDF-15 levels are elevated in tissues with impaired mitochondrial function.*

Study Evidence: A study measuring GDF-15 levels in various mitochondrial diseases, such as mitochondrial myopathies and disorders of oxidative phosphorylation, showed that GDF-15 levels were significantly elevated compared to healthy controls.**

In patients with primary mitochondrial diseases, GDF-15 was found to be significantly higher in those with more severe phenotypes, correlating with clinical assessments such as muscle weakness and exercise intolerance.**

We have identified over 20 epidemiologic studies across vastly different populations that find that GDF-15 is an important longitudinal predictor of human mortality.

Because of the known association of this protein with genetic mitochondrial disease we view this association as a key clue that mitochondrial dysfunction is a principal driver of human mortality.

* Burtscher J, Soltany A, Visavadiya NP, Burtscher M, Millet GP, Khoramipour K, Khamoui AV, "Mitochondrial stress and mitokines in aging," *Aging Cell*, Feb 2023; 22(2):e13770. (link)
** Yatsuga, S., et al. (2015), "Growth differentiation factor 15 as a useful biomarker for mitochondrial disorders," *Annals of Neurology*, 78(5), 814-823. (link)

GDF-15 Upregulation in Mitochondrial Damage is Linked to Stress Response Pathways (UPR)

Chung HK, et al., "Growth differentiation factor 15 is a myomitokine governing systemic energy homeostasis," *Journal of Cell Biology*, Jan 2, 2017; 216(1):149-165.

Reduced mitochondrial electron transport chain activity promotes longevity and improves energy homeostasis via cell-autonomous and -non-autonomous factors in multiple model systems. This mitohormetic effect is thought to involve the mitochondrial unfolded protein response (UPRmt), an adaptive stress-response pathway activated by mitochondrial proteotoxic stress. Using mice with skeletal muscle-specific deficiency of Crif1 (muscle-specific knockout [MKO]), an integral protein of the large mitoribosomal subunit (39S), **we identified growth differentiation factor 15 (GDF-15) as a UPRmt-associated cell-non-autonomous myomitokine that regulates systemic energy homeostasis.** MKO mice were protected against obesity and sensitized to insulin, an effect associated with elevated GDF-15 secretion after UPRmt activation. In ob/ob mice, administration of recombinant GDF-15 decreased body weight and improved insulin sensitivity, which was attributed to elevated oxidative metabolism and lipid mobilization in the liver, muscle, and adipose tissue. Thus, GDF-15 is a potent mitohormetic signal that safeguards against the onset of obesity and insulin resistance.

Source: https://rupress.org/jcb/article/216/1/149/46165/Growth-differentiation-factor-15-is-a-myomitokine

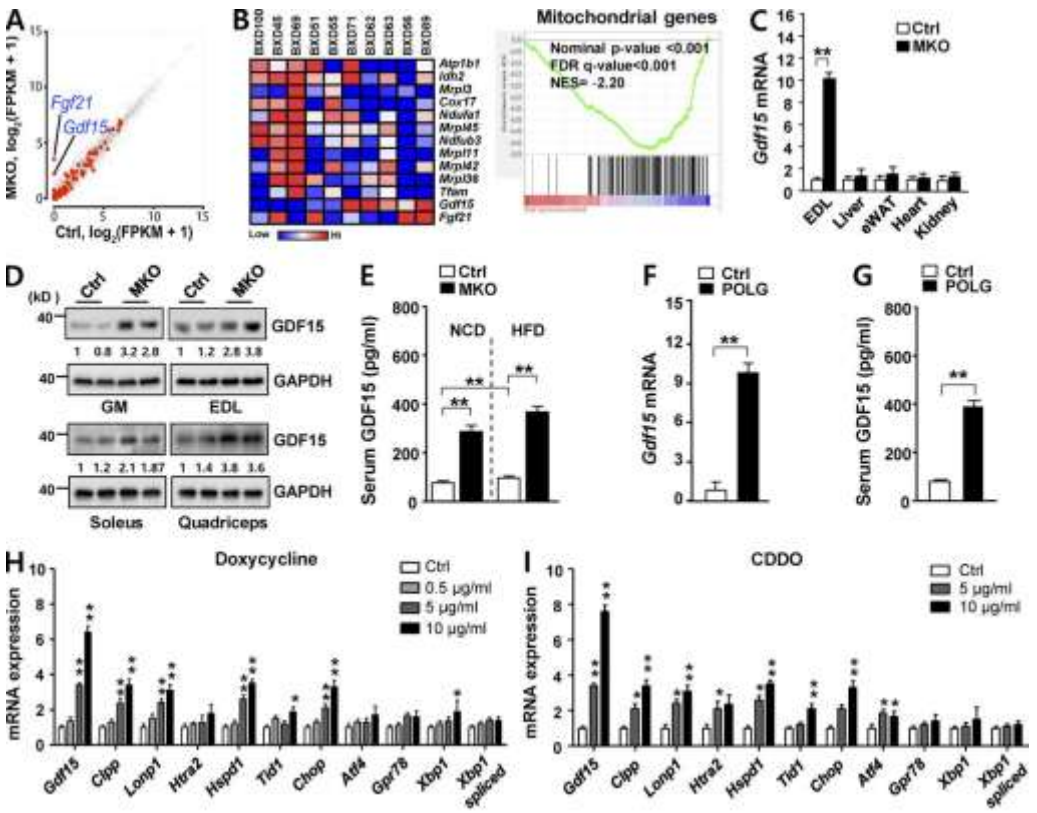
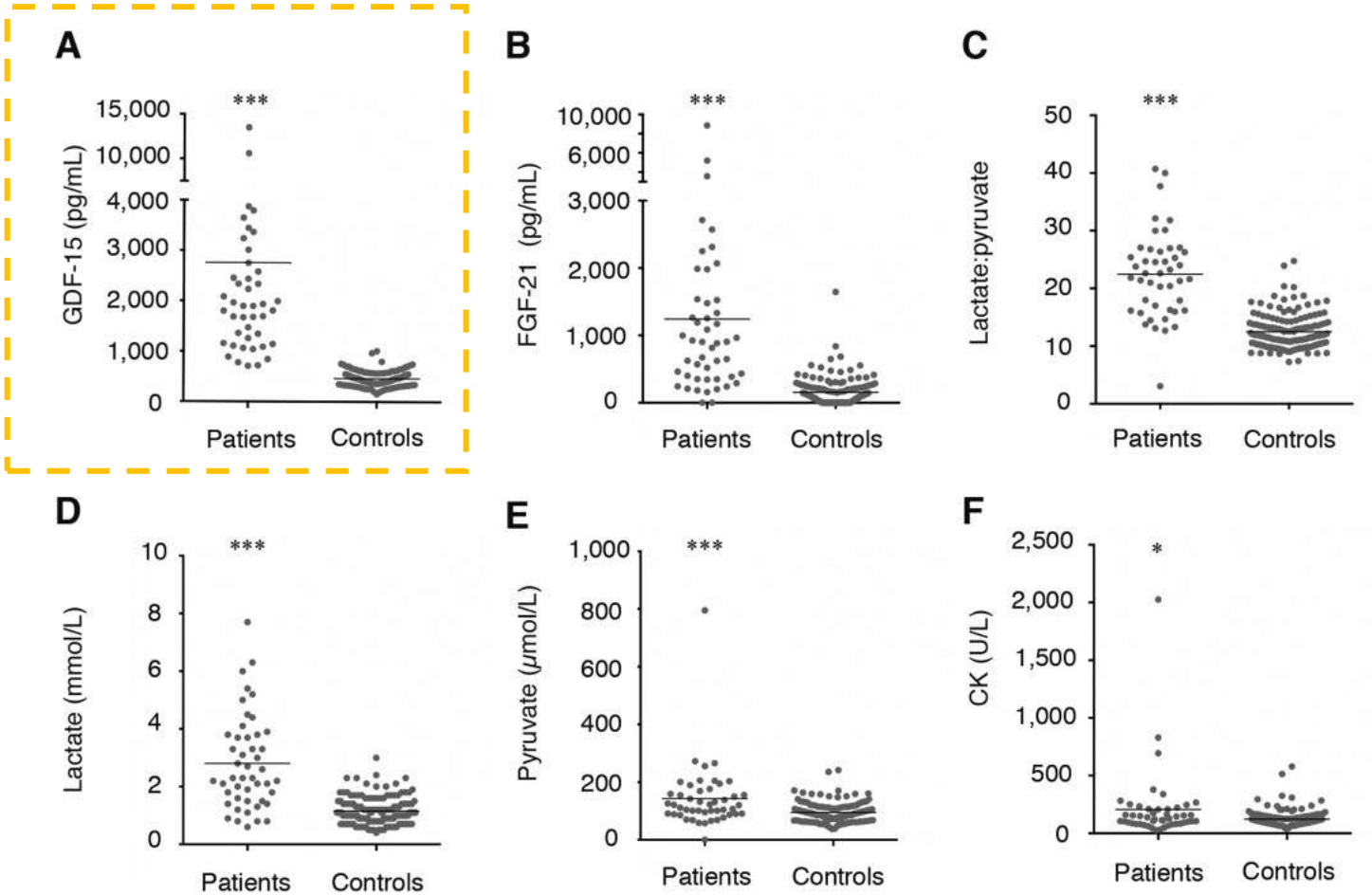


Figure 3. GDF-15 induction is associated with activation of the UPR^{mt} in MKO and POLG mice. (A) Scatterplot of RNA-seq data, displaying transcript levels in EDL muscle of 8-wk-old male Ctrl (x axis) and MKO (y axis) mice. Gene sets encoding secretory proteins are represented in red. (B) Gene Set Enrichment Analysis was performed on skeletal muscle transcriptome data from BXD genetic reference population mice (*GDF-15* expression in skeletal muscle transcriptomes of BXD mice on HFD; GeneNetwork accession numbers GN379 and GN380). The gene set encompassing mitochondria genes has an enrichment score of –0.477, a normalized enrichment score (NES) of –2.202, nominal P ‹ 0.001, false discovery rate (FDR) *q* ‹ 0.001, and family-wise error rate P ‹ 0.001. (C) *GDF-15* mRNA expression levels in EDL, liver, eWAT, heart, and kidney of 8-wk-old MKO mice. (D) GDF-15 expression in GM, EDL, soleus, and quadriceps muscles in 8-wk-old male Ctrl and MKO mice fed a chow diet (*n* = 5 per group). (E) Serum GDF-15 concentration in chow-fed 8-wk-old male Ctrl and MKO mice in the fasting state (*n* = 6 per group). (F and G) *GDF-15* mRNA expression in GM (F) and serum GDF-15 concentration (G) of 8-wk-old male POLG and control mice fed a chow diet (*n* = 5 per group). (H and I) Expression of *GDF-15* and UPR^{mt} genes after treatment of C2C12 myotubes with doxycycline (H) or CDDO (I) for 24 hAll data represent mean ± SEM. *, P ‹ 0.05; **, P ‹ 0.01.

GDF-15 Almost Perfectly Separates Children with Mitochondrial Disease From Healthy Controls

Yatsuga S, et al., "Growth differentiation factor 15 as a useful biomarker for mitochondrial disorders," *Annals of Neurology*, Nov 2015, 78(5):814-23.



"The diagnosis of mitochondrial disorders (MDs) is occasionally difficult because patients often present with solitary, or a combination of, symptoms caused by each organ insufficiency, which may be the result of respiratory chain enzyme deficiency. We measured the serum levels of GDF-15 and fibroblast growth factor 21 (FGF-21), as well as other biomarkers, in 48 MD patients and in 146 healthy controls in Japan. GDF-15 and FGF-21 concentrations were measured by enzyme-linked immunosorbant assay and compared with lactate, pyruvate, creatine kinase, and the lactate-to-pyruvate ratio. Mean GDF-15 concentration was 6-fold higher in MD patients compared to healthy controls (2,711 ± 2,459 pg/ml vs 462.5 ± 141.0 pg/mL; $p < 0.001$). Using a receiver operating characteristic curve, the area under the curve was significantly higher for GDF-15 than FGF-21 and other conventional biomarkers. Our data suggest that GDF-15 is the most useful biomarker for MDs of the biomarkers examined, and it is associated with MD severity."

Source: https://pubmed.ncbi.nlm.nih.gov/26463265/

It's Logical to Consider GDF-15 as an Index of the Severity of Mitochondrial Dysfunction in Aging

Fujita Y, Taniguchi Y, Shinkai S, Tanaka M, Ito M., "Secreted growth differentiation factor 15 as a potential biomarker for mitochondrial dysfunctions in aging and age-related disorders," *Geriatr Gerontol Int.* 2016 Mar;16 Suppl 1:17-29.

We and others have recently shown that growth differentiation factor 15 (GDF-15) is a useful diagnostic marker for mitochondrial diseases, which are inherited disorders caused by mitochondrial or nuclear genomic mutations that lead to impaired energy production. As the primary cause of mitochondrial diseases is mitochondrial dysfunction, the blood level of GDF-15 might reflect mitochondrial function in patients, and thus could be a marker for mitochondrial dysfunction. GDF-15 has been implicated in aging and various age-related disorders, such as cardiovascular diseases and diabetes, the blood level of which is reportedly elevated in older adults as well as in patients. Although GDF-15 might be induced as a result of various cellular stresses and dysfunctions, it would also be possible that the blood GDF-15 level reflects at least in part mitochondrial dysfunction in aging and age-related disorders. In the present review, we summarized the current literature regarding GDF-15 in aging and age-related disorders from the perspective of biomarkers, with a particular focus on mitochondrial dysfunction.

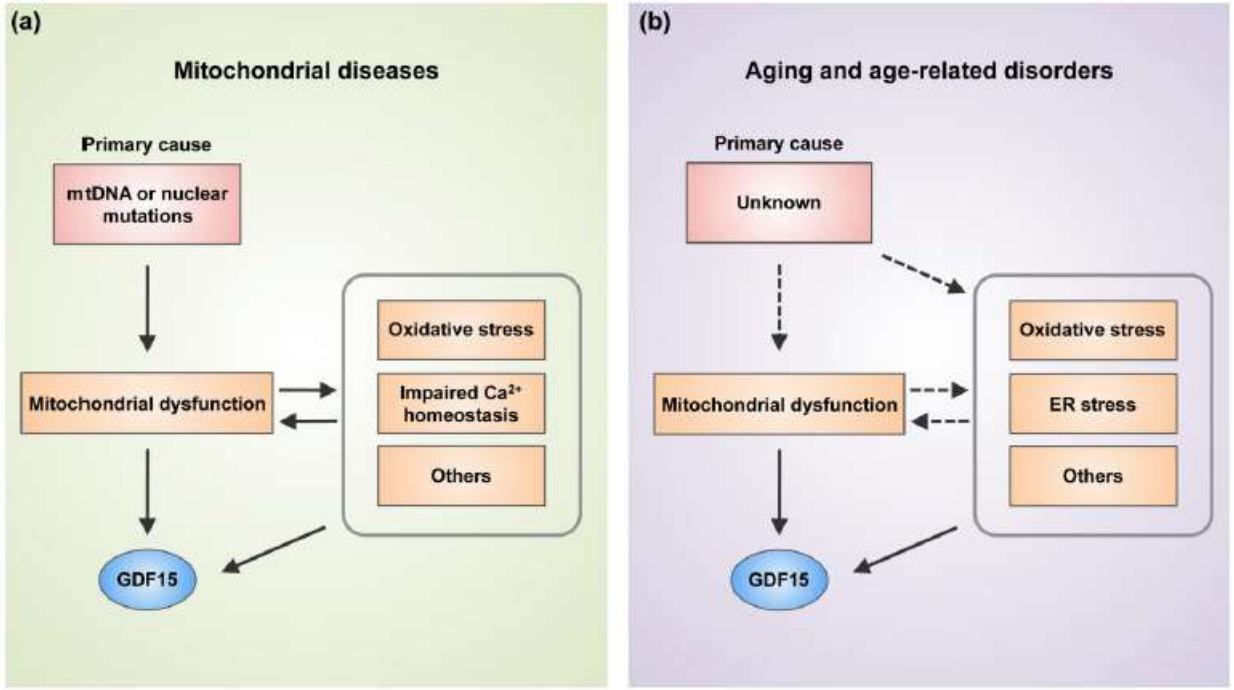
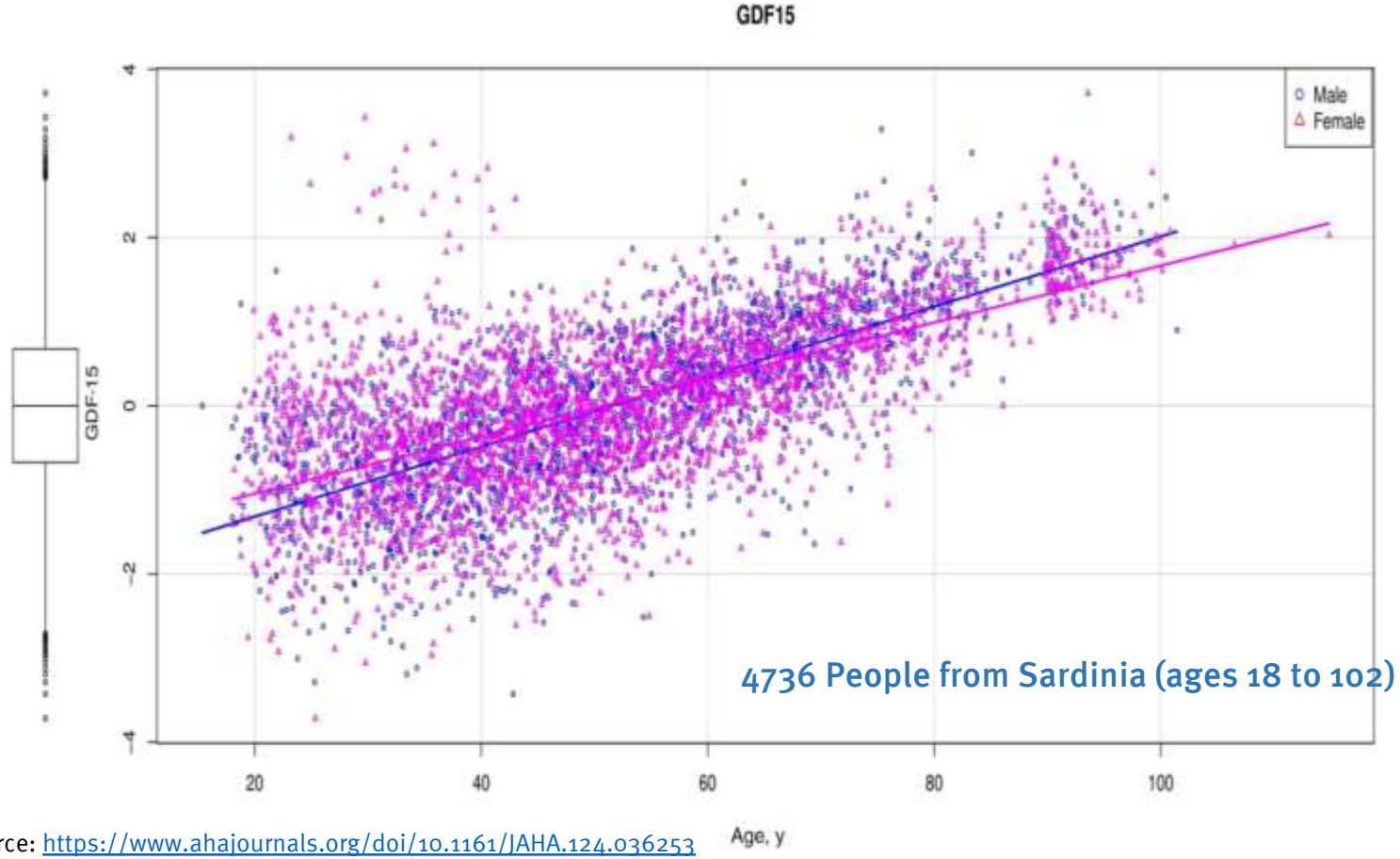


Figure 1 The mechanisms of growth differentiation factor 15 (GDF15) induction by mitochondrial dysfunction (a) in mitochondrial diseases and (b) in aging and age-related disorders. Mitochondrial diseases are primarily caused by pathogenic mtDNA or nuclear mutations, which lead to mitochondrial dysfunction. The mitochondrial dysfunction and other concomitant cellular responses, such as increased reactive oxygen species generation and impaired Ca^{2+} homeostasis, might induce intracellular GDF15 expression, resulting in increased blood GDF15 levels in patients with mitochondrial diseases. Although the primary causes of aging and age-related disorders remain to be established, mitochondrial dysfunction has been shown to be involved in their pathogenesis. The elevation of the blood GDF15 levels in older adults and patients with age-related disorders could be at least in part ascribed to mitochondrial dysfunction. ER, endoplasmic reticulum

Source: https://onlinelibrary.wiley.com/doi/10.1111/ggi.12724

GDF-15 Levels Rise Steadily With Age

Given GDF-15's association with mitochondrial disease and lack of association with DNA damage, it looks to us like there is a good argument that aging can be thought of as a sort of mitochondrial disease. GDF-15 levels rise monotonically with age. It's very clear from this chart that there is substantial variation in the levels of GDF-15 at a given age. There are some young people with very high GDF-15's. They could be quite ill, be obese, have mitochondrial disease or, alternatively, be pregnant (which temporarily elevates GDF-15 – notice the early outliers are almost all female). There is also an association between metformin use and GDF-15 – this is because metformin disturbs mitochondrial function. However, its effect is relatively modest.



"Serum GDF-15 levels were measured cross-sectionally (at visit 3) in 4736 participants from the SardiNIA study population. Average serum GDF-15 levels were 252.0±172.1 pg/mL and 251.0±195.0 pg/mL in women and men, respectively. Figure 1 (at left) illustrates serum GDF-15 levels in these participants as a continuous function of age. GDF-15 levels were strongly and positively associated with age ($r=0.430$, $P<0.0001$)…"

Source: https://www.ahajournals.org/doi/10.1161/JAHA.124.036253

Factors Besides Mitochondrial Dysfunction Can Also Lead to Upregulation of GDF-15

Fujita Y, Taniguchi Y, Shinkai S, Tanaka M, Ito M., "Secreted growth differentiation factor 15 as a potential biomarker for mitochondrial dysfunctions in aging and age-related disorders," *Geriatr Gerontol Int.* 2016 Mar;16 Suppl 1:17-29.

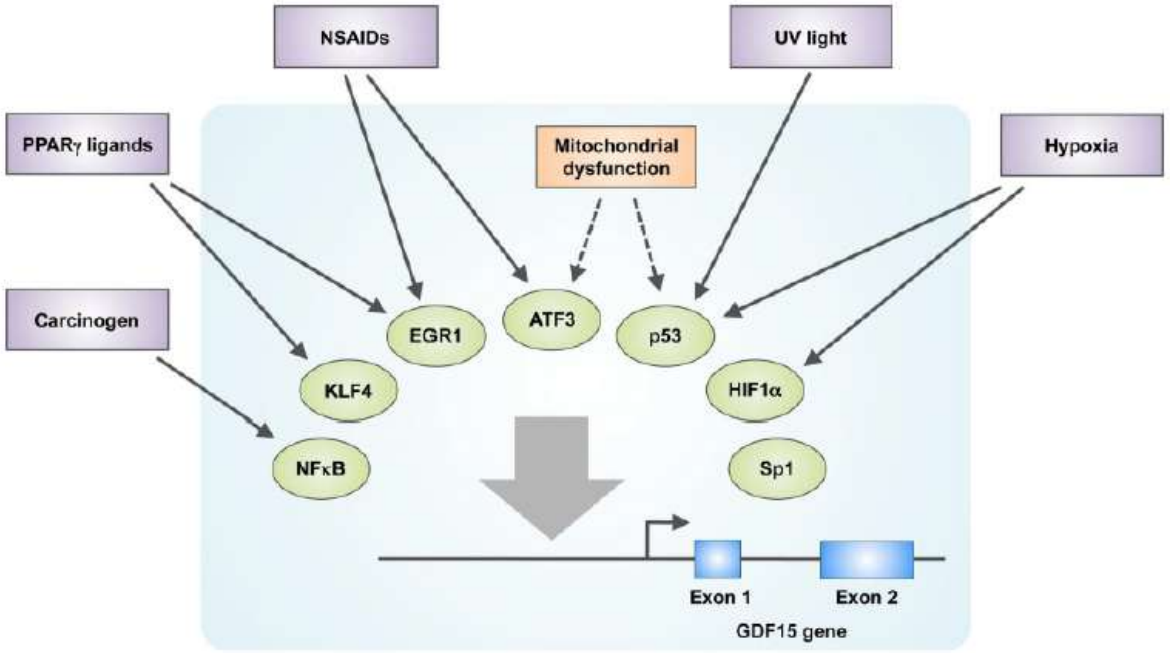


Figure 2 Transcriptional regulation of the growth differentiation factor 15 (GDF15) gene. Transcription of the GDF15 gene is upregulated by various stimuli, such as carcinogens, ultraviolet (UV) light and hypoxia, as well as by non-steroidal anti-inflammatory drugs (NSAID) and peroxisome proliferator activated receptor-γ (PPAR-γ) ligands through activation of transcription factors including nuclear factor-κB (NFκB), kruppel-like factor-4 (KLF4), early growth response protein 1 (EGR1), p53 and hypoxia-inducible factor-1α (HIF1α). We and others have suggested that p53 and activating transcription factor 4 (ATF4), an upstream effector of ATF3, might be involved in increased transcription of the GDF15 gene in patients with mitochondrial diseases.[7,9]

We do not wish to suggest that GDF-15 is a *perfect* proxy for mitochondrial stress in aging. Other environmental factors can cause it to be upregulated as well.

Source: https://onlinelibrary.wiley.com/doi/10.1111/ggi.12724

Two Proteins Beyond GDF-15 Score High in Predicting Mortality in the UK Biobank (Biogen Study)

Letter

https://doi.org/10.1038/s43587-024-00655-7

Blood protein assessment of leading incident diseases and mortality in the UK Biobank

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Check for updates

Danni A. Gadd[1,2], Robert F. Hillary[1,2], Zhana Kuncheva[1,3], Tasos Mangelis[1,3], Yipeng Cheng[2], Manju Dissanayake[1,3], Romi Admanit[4], Jake Gagnon[4], Tinchi Lin[4], Kyle L. Ferber[4], Heiko Runz[5], Biogen Biobank Team*, Christopher N. Foley[1,3,7] ✉, Riccardo E. Marioni[1,2,7] ✉ & Benjamin B. Sun[5,6,7] ✉

The circulating proteome offers insights into the biological pathways that underlie disease. Here, we test relationships between 1,468 Olink protein levels and the incidence of 23 age-related diseases and mortality in the UK Biobank (n = 47,600). We report 3,209 associations between 963 protein levels and 21 incident outcomes. Next, protein-based scores (ProteinScores) are developed using penalized Cox regression. When applied to test sets, six ProteinScores improve the area under the curve estimates for the 10-year onset of incident outcomes beyond age, sex and a comprehensive set of 24 lifestyle factors, clinically relevant biomarkers and physical measures. Furthermore, the ProteinScore for type 2 diabetes outperforms a polygenic risk score and HbA1c—a clinical marker used to monitor and diagnose type 2 diabetes. The performance of scores using metabolomic and proteomic features is also compared. These data characterize early proteomic contributions to major age-related diseases, demonstrating the value of the plasma proteome for risk stratification.

Table 1 | The 24 incident outcomes profiled over a maximum of 15 years of follow-up in the UK Biobank (n = 47,600)

Incident diagnosis	Incident cases (n)	Controls (n)	Mean years to incident case diagnosis (s.d.)
Schizophrenia	54	47,449	6.5 (3.4)
Brain/CNS cancer	82	47,507	5.5 (2.8)
Multiple sclerosis	96	47,165	5.6 (3.2)
Major depression	111	47,229	4.2 (3.1)
Systemic lupus erythematosus	134	47,096	5.1 (2.6)
Endometriosis[a]	157	24,768	4.8 (3.3)
Vascular dementia[b]	195	33,907	8.1 (3)
Gynecological cancer[a]	256	25,185	5 (3)
Amyotrophic lateral sclerosis	264	47,269	5.4 (2.7)
Inflammatory bowel disease	275	46,727	5.9 (3.3)
Lung cancer	403	47,158	5.9 (3.2)
Liver disease	432	47,104	7 (3.3)
Alzheimer's dementia[b]	446	33,642	7.8 (2.8)
Colorectal cancer	508	46,890	5.8 (3.1)
Cystitis[a]	531	24,160	4.1 (3)
Rheumatoid arthritis	593	46,310	6.8 (3.2)
Parkinson's disease	659	46,802	5.4 (3.2)
Ischemic stroke	765	46,657	6.8 (3.4)
Breast cancer[a]	772	24,086	5.2 (3.1)
Prostate cancer[a]	1,001	20,628	5.7 (3.1)
COPD	1,998	44,948	6.3 (3.4)
Type 2 diabetes	2,822	43,370	6 (3.3)
Ischemic heart disease	3,338	41,341	6.3 (3.4)
Death	4,445	43,155	7.9 (3.5)

Counts for incident cases and controls are provided, with mean years to diagnosis for incident cases. These data were used in individual Cox PH models to identify protein levels that were associated with incident outcomes. CNS, central nervous system. [a]Sex-stratified traits. [b]Alzheimer's and vascular dementias were restricted to individuals aged 65 years or older at the time of diagnosis for cases or at the time of censoring for controls.

Source: https://www.nature.com/articles/s43587-024-00655-7

The Other Two Factors are PLAUR/uPar and WFDC2/HE4

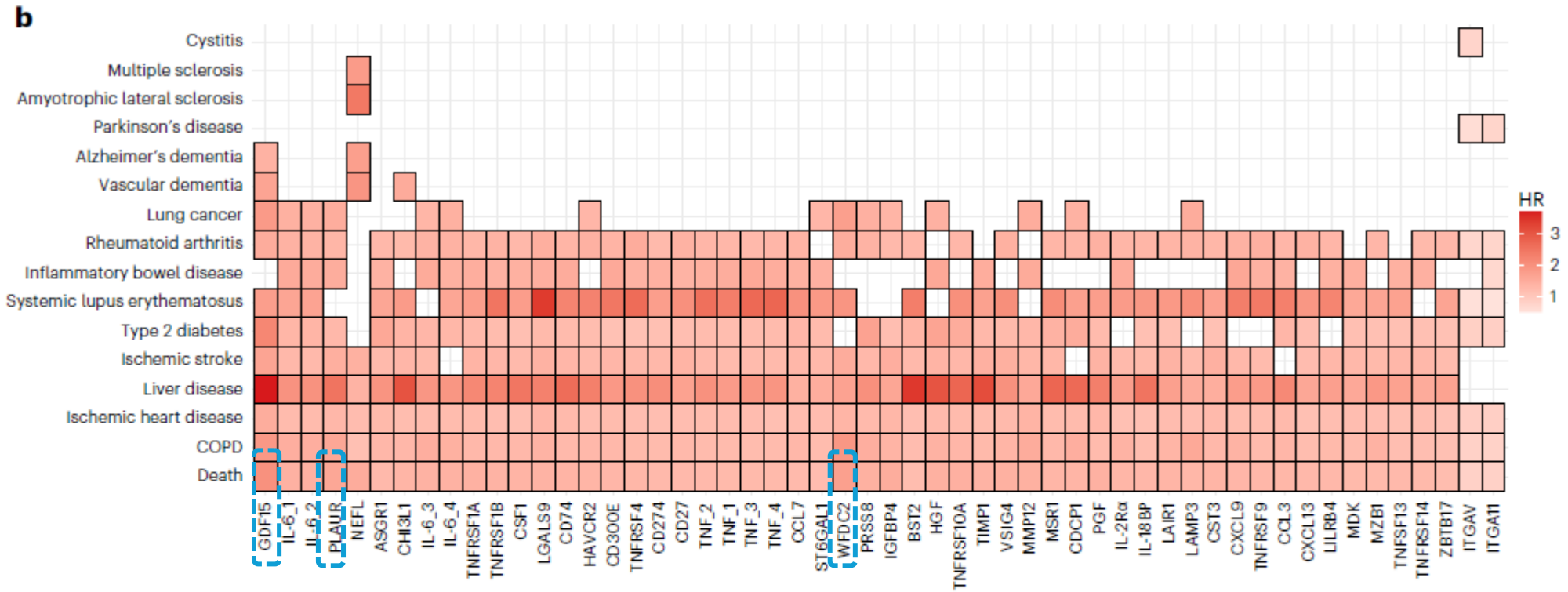


Fig. 1 | Individual protein associations with incident outcomes in the UK Biobank (n = 47,600). a, Number of associations between protein analytes and time to onset for 21 outcomes that had $P < 3.1 \times 10^{-6}$ (Bonferroni-adjusted threshold) in both basic and fully adjusted Cox PH models. There were 3,209 associations in total involving 963 protein analytes. Two-sided tests were used in all cases. **b**, HR per 1 s.d. higher level of the transformed protein analytes (compared within individuals at baseline). Fifty-four protein analytes that were associated with eight or more outcomes in the individual Cox PH models are shown. Each association is represented by a rectangle. Cox PH models were adjusted for age, sex and six lifestyle factors (BMI, alcohol consumption, social deprivation, educational attainment, smoking status and physical activity). Every association identified for these proteins had HR > 1 (red), and associations are shaded based on the HR effect size (darkest coloration indicating a larger magnitude of effect). The largest HR shown is for the association between GDF15 levels and liver disease (HR = 3.7).

Plaur is also typically called uPar or suPAR

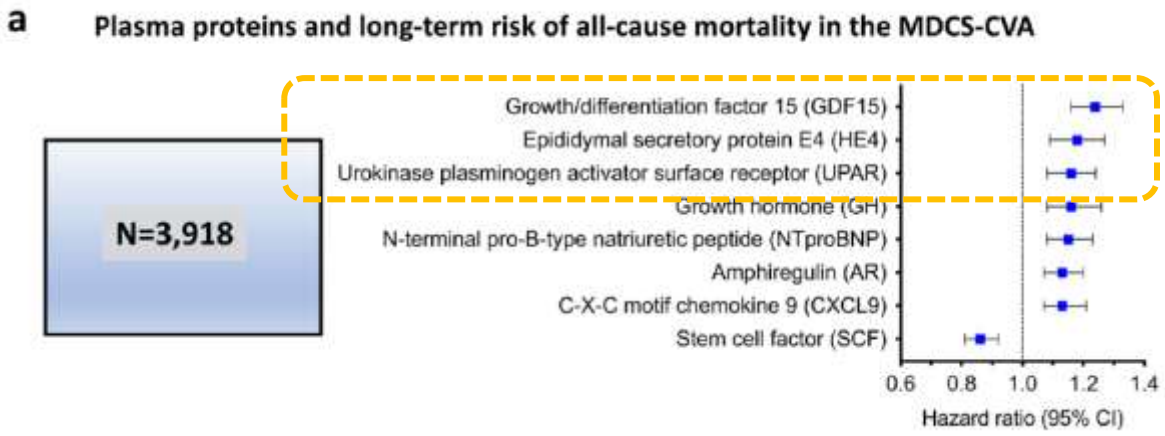
WFDC2 is also typically called HE4

A separate study was recently published by Calico Life Sciences that had very similar findings. They identified six proteins that were highly predictive of mortality in the UK Biobank dataset using Olink protein data.

Source: https://www.nature.com/articles/s43587-024-00655-7

Separate Study Predicting Mortality: Malmo Heart

The same three proteins are the top predictors of mortality in Malmo Heart



Source: https://www.nature.com/articles/s41598-021-85991-z

Methodological considerations for identifying multiple plasma proteins associated with all-cause mortality in a population-based prospective cohort

Isabel Drake[1✉], George Hindy[1,2], Peter Almgren[1,3], Gunnar Engström[4], Jan Nilsson[5], Olle Melander[3] & Marju Orho-Melander[1]

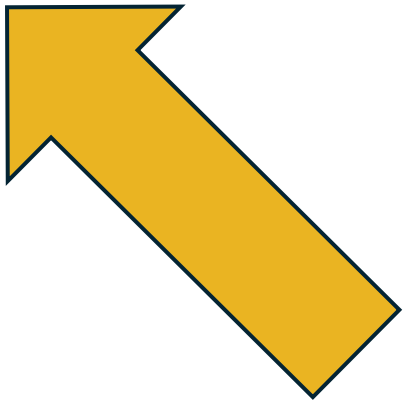
Novel methods to characterize the plasma proteome has made it possible to examine a wide range of proteins in large longitudinal cohort studies, but the complexity of the human proteome makes it difficult to identify robust protein-disease associations. Nevertheless, identification of individuals at high risk of early mortality is a central issue in clinical decision making and novel biomarkers may be useful to improve risk stratification. With adjustment for established risk factors, we examined the associations between 138 plasma proteins measured using two proximity extension assays and long-term risk of all-cause mortality in 3,918 participants of the population-based Malmö Diet and Cancer Study. To examine the reproducibility of protein-mortality associations we used a two-step random-split approach to simulate a discovery and replication cohort and conducted analyses using four different methods: Cox regression, stepwise Cox regression, Lasso-Cox regression, and random survival forest (RSF). In the total study population, we identified eight proteins that associated with all-cause mortality after adjustment for established risk factors and with Bonferroni correction for multiple testing. In the two-step analyses, the number of proteins selected for model inclusion in both random samples ranged from 6 to 21 depending on the method used. However, only three proteins were consistently included in both samples across all four methods (growth/differentiation factor-15 (GDF-15), N-terminal pro-B-type natriuretic peptide, and epididymal secretory protein E4). Using the total study population, the C-statistic for a model including established risk factors was 0.7222 and increased to 0.7284 with inclusion of the most predictive protein (GDF-15; $P < 0.0001$). All multiple protein models showed additional improvement in the C-statistic compared to the single protein model (all $P < 0.0001$). We identified several plasma proteins associated with increased risk of all-cause mortality independently of established risk factors. Further investigation into the putatively causal role of these proteins for longevity is needed. In addition, the examined methods for identifying multiple proteins showed tendencies for overfitting by including several putatively false positive findings. Thus, the reproducibility of findings using such approaches may be limited.

The Same Variables Predict Healthspan Although Not in the Same Order

Kuo et al. study, *PNAS*, "A Proteomic Signature of Healthspan," June 6, 2025

Table S7 Proteins associated with healthspan (test sample, n=12,935)

Assay Target	Gene symbol	UniProt	Gene CHR	Gene start	Gene end	HR	Lower	Upper	Padj
AREG	AREG	P15514	4	74445136	74455005	0.66	0.64	0.69	<1E-323
GDF15	GDF15	Q99988	19	18374731	18389176	0.56	0.53	0.58	<1E-323
PLAUR	PLAUR	Q03405	19	43646095	43670547	0.53	0.51	0.56	<1E-323
WFDC2	WFDC2	Q14508	20	45469753	45481532	0.51	0.49	0.53	<1E-323



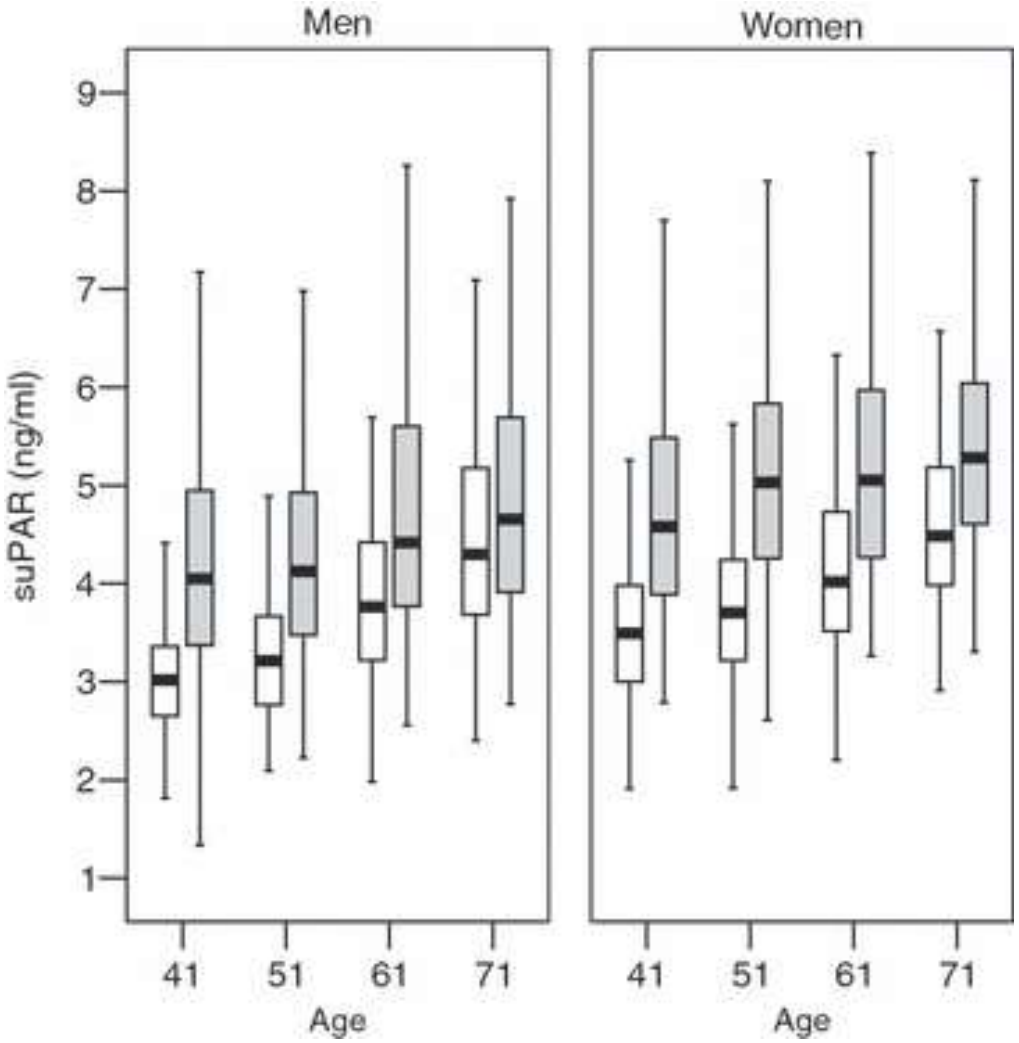
Kuo et al. defined healthspan as the time until a first hospitalization for a major medical condition. The top four predictors of healthspan (out of 3000 proteins) were among the top six predictors identified in the recent Calico Labs model of mortality. The one difference is that the ranking is a bit different. GDF-15 dominates for mortality prediction whereas amphiregulin (AREG) is the top predictor of time to first hospitalization whereas it is ranked #6 in predicting mortality in the UK Biobank Cohort.

Source: https://www.pnas.org/doi/10.1073/pnas.2414086122?

uPAR Levels Rise With Age

Eugen-Olsen J, et al., "Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population," *J Intern Med.* 2010 Sep;268(3):296-308.

Box-plot of suPAR levels amongst nonsmokers (white boxes) and current smokers (grey boxes) according to age and gender. Boxes represent 25–75% percentiles and whiskers are 5–95% percentiles.



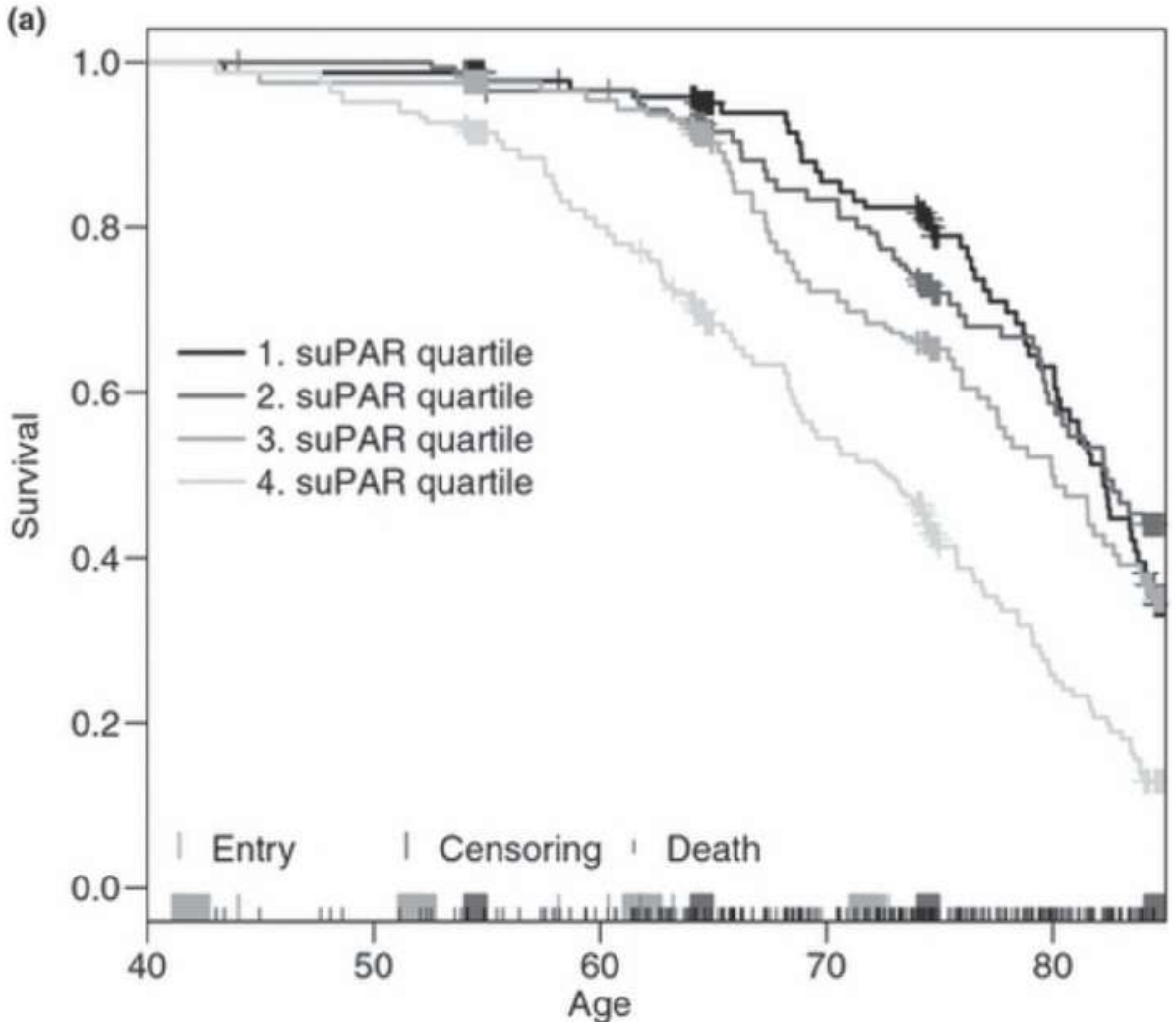
Source: https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2010.02252.x

Survival Curves in Danish Males as a Function of uPAR Levels

Eugen-Olsen J, et al., "Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population," *J Intern Med.* 2010 Sep;268(3):296-308.

Kaplan–Meier plot showing age-specific suPAR quartiles and survival for men. For each age group (41, 51, 61 and 71 years), suPAR was divided into quartiles.

The darkest grey line (1. suPAR quartile) refers to individuals with suPAR in the lowest quartile (0–25%). Similarly, the lightest grey line (4. suPAR quartile) refers to individuals with the highest suPAR level (75–100%).



Source: https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2010.02252.x

Plaur/uPAR/suPAR and Mortality Risk

1. **General population**: Elevated suPAR levels are a strong independent predictor of all-cause mortality, even among healthy individuals. (1) (2) (9) (11)
2. **Long-term follow-up**: Higher suPAR predicts mortality over 5–15 years, with effects persisting after adjustment for inflammation, smoking, or chronic disease. (2)
3. **Cardiovascular disease**: suPAR correlates with higher risk of myocardial infarction, heart failure events, and cardiovascular death. (4) (6) (7)
4. **Kidney disease**: Elevated suPAR predicts all-cause and cardiovascular mortality in chronic kidney disease and dialysis cohorts. (4)
5. **Critical illness and emergency settings**: High suPAR levels predict short-term (30–90 day) mortality, ICU admission, post-ICU and prolonged hospital stay. (3) (5) (8)
6. **Pulmonary disease**: In COPD and other respiratory conditions, high suPAR indicates higher near-term mortality. (10)

References

1. Haupt et al., Healthy lifestyles reduce suPAR and mortality in a Danish general population study, Immune Ageing, Jan 2019. (link)
2. Tavenier, J., Rasmussen, L.J.H., Tolstrup, J. et al. Self-rated health and chronic inflammation are related and independently associated with hospitalization and long-term mortality in the general population. Sci Rep 12, 19761 (2022). (Link)
3. Rasmussen L. et al., "Soluble urokinase plasminogen activator receptor (suPAR) in acute care: a strong marker of disease presence and severity, readmission and mortality. A retrospective cohort study," Emergency Medicine Journal (2016) (Link)
4. Torino C,et al., "Soluble Urokinase Plasminogen Activator Receptor (suPAR) and All-Cause and Cardiovascular Mortality in Diverse Hemodialysis Patients," *Kidney Int Rep.* 2018 May 22;3(5):1100-1109. (Link)
5. Koch A, et al. "Circulating soluble urokinase plasminogen activator receptor is stably elevated during the first week of treatment in the intensive care unit and predicts mortality in critically ill patients," Crit Care. 2011;15(1):R63. (Link)
6. Al. Badri et al., suPAR and Troponin predict outcomes in CAD, *JAHA,* 2020. (Link)
7. Chew-Harris et al., suPAR in acute dyspnea and heart failure prediction, Int Journal of Cardiology, 2024 (Link).
8. Rehan et al., Meta-analysis of suPAR in emergency department outcomes, *Medicine* 2024 (Link)
9. Rasmussen et al., suPAR and Accelerated Biological Aging, J Gerontol A Biol Sci Med Sci. 2021 (Link)
10. Huang. et al., suPAR and COPD (Therap Adv Resp Diseases, 2020). (Link)
11. Rasmussen et al., suPAR in the general population, J. Int Medicine, 2010 (Link)

uPar is Broadly Considered a Marker of Cell Senescence

uPAR, encoded by *PLAUR*, has emerged as a consistent **cell-surface hallmark of senescence** across tissues. During cellular aging triggered by DNA damage, oxidative stress, or oncogene activation, senescent cells upregulate uPAR through inflammatory and fibrogenic pathways—especially **NF-κB and TGF-β signaling**.

This upregulation accompanies the senescence-associated secretory phenotype (SASP), in which cytokines such as IL-6, IL-1β, and TNF-α reinforce PLAUR transcription. uPAR enables senescent cells to remodel their extracellular environment by binding urokinase (uPA) and integrins, promoting matrix degradation, fibroblast recruitment, and local immune activation.

These functions position uPAR not only as a **marker of senescent identity** but also as an **active participant** in the maintenance of chronic, low-grade inflammation and fibrosis characteristic of aging tissues.

The soluble form of uPAR (suPAR), released into the circulation, mirrors this process at the organismal level.

Elevated plasma suPAR correlates strongly with biological age, frailty, cardiovascular risk, and multimorbidity—traits all linked to systemic senescent-cell burden and “inflammaging.”

Experimental clearance of uPAR-positive senescent cells in mice restores tissue function and extends healthspan, demonstrating a causal link between uPAR expression and senescence-driven pathology.

Together, these findings define uPAR as both a biological fingerprint and functional amplifier of cellular senescence, bridging molecular aging processes to measurable human health decline.

Papers Linking Plaur/uPAR/suPAR With Cell Senescence

Amor, C., et al. "Senolytic CAR T cells reverse senescence-associated pathologies. Nature. 2020 Jul;583(7814):127-132.

Identified uPAR as a universal senescent-cell surface antigen; CAR-T clearance rejuvenated aged mice. (link)

Amor C., et al. "Prophylactic and long-lasting efficacy of senolytic CAR T cells against age-related metabolic dysfunction," *Nature Aging,* 2024 Mar;4(3):336-349.

Confirmed uPAR upregulation in senescent cells; immune removal improved tissue function. (link)

Saul D, Kosinsky RL, Atkinson EJ, Doolittle ML, Zhang X, LeBrasseur NK, Pignolo RJ, Robbins PD, Niedernhofer LJ, Ikeno Y, Jurk D, Passos JF, Hickson LJ, Xue A, Monroe DG, Tchkonia T, Kirkland JL, Farr JN, Khosla S. A new gene set identifies senescent cells and predicts senescence-associated pathways across tissues. Nat Commun. 2022 Aug 16;13(1):4827.

The SenMayo panel is likely the most rigorous panel of senescence genes. This panel includes PLAUR as a key gene. Notably, this panel does not include GDF-15 and does not include HE4 as pure senescence markers. (Link)

Liu Y, Chen J., "Senescence-related genes and proteins in the development of Alzheimer's disease: evidence from transcriptomic and Mendelian randomization analysis," *Frontiers Aging Neuroscience,* Aug 2, 2024;16:1423725.

Shows uPAR is a key senescence associated gene and protein upregulated in Alzheimer's Disease. (link)

Jiang B, Zhang W, Zhang X, Sun Y., "Targeting senescent cells to reshape the tumor microenvironment and improve anticancer efficacy," *Seminars Cancer Biology*, June 2024;101:58-73.

Classically speaking, cell senescence can be thought of as protection against cancer from dysregulated cells, there is strong evidence that suggests that senescent cells can make cancer worse and that uPar is part of this cancerous mileu. (Link)

HE4 is an Important Marker of Cell Stress, Fibrosis and Cancer Risk

HE4 (human epididymis protein 4) has become one of the most powerful predictors of mortality because it reflects the cumulative biological stress of aging across multiple organ systems. Produced mainly by epithelial tissues in the kidney, lung, and reproductive tract, HE4 rises in response to chronic tissue injury, fibrosis, and inflammatory signaling. Rather than signaling a single disease, it functions as a systemic indicator of cellular wear and tear — capturing the same biological processes that drive frailty, renal decline, and cardiovascular failure. This makes it a cross-organ biomarker of the aging process itself, not merely a tumor marker as once thought.

Mechanistically, HE4 is part of the WFDC family of protease inhibitors, which modulate extracellular matrix remodeling and inflammatory cascades. Elevated HE4 suggests that tissues are engaged in constant repair and fibrosis — key features of “inflammaging.” Its concentration correlates closely with reduced kidney function, vascular stiffening, and fibrotic remodeling in heart and lung tissue, all of which are among the strongest determinants of mortality in aging populations. Because these pathologies often precede overt disease, HE4 can detect risk long before clinical symptoms appear.

HE4 shows up again and again as either the #2 or #3 predictor of mortality across datasets and proteomic measurement approaches.

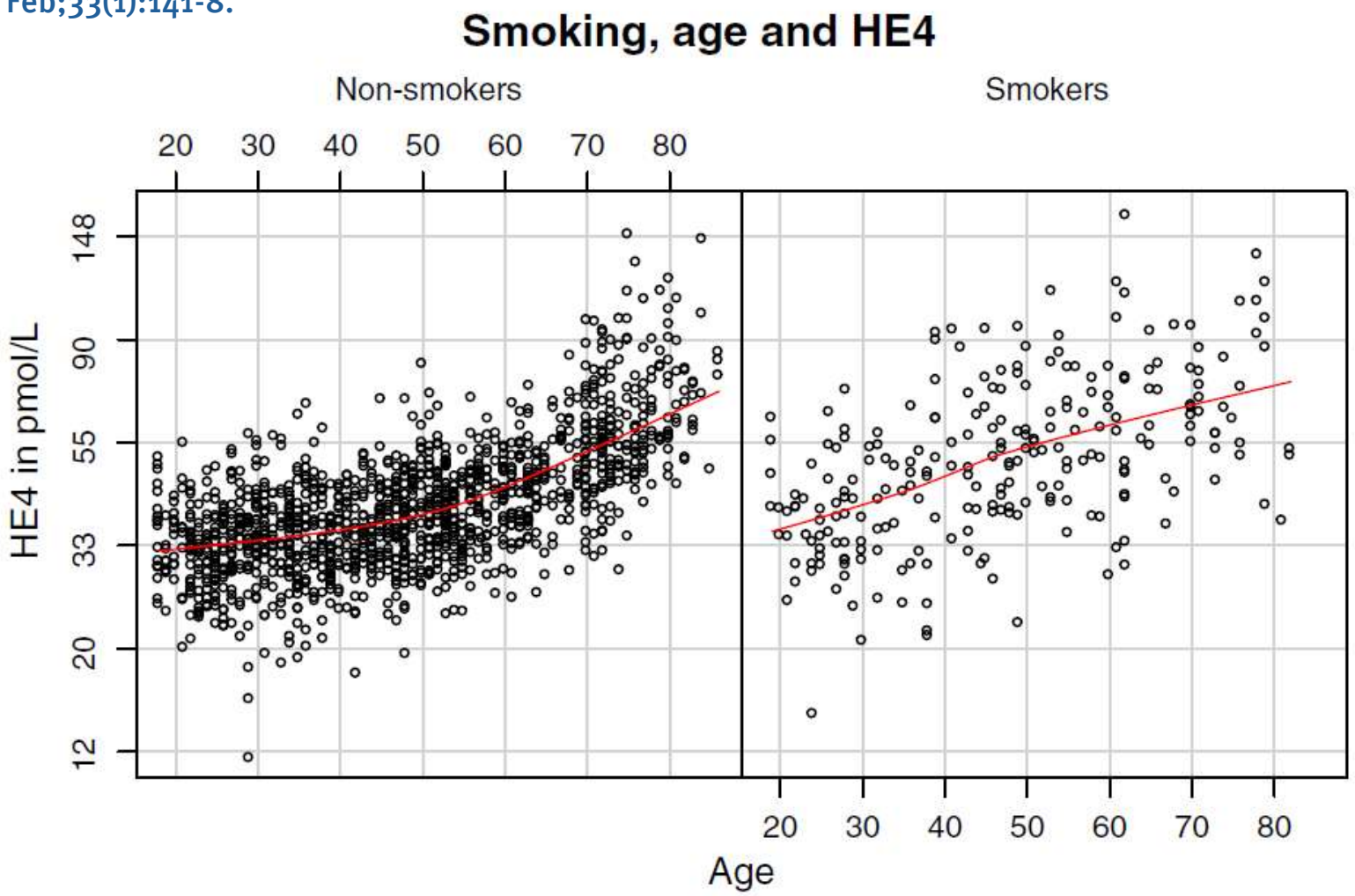
Cell stress is a key part of aging biology.

High HE4 points to a person with substantial Inflammation and fibrosis as part of their aging.

HE4 is not a canonical biomarker of cell senescence.

HE4 Rises at an Increasing Rate with Age

Bolstad N, Øijordsbakken M, Nustad K, Bjerner J. Human epididymis protein 4 reference limits and natural variation in a Nordic reference population. *Tumour Biol.* 2012 Feb;33(1):141-8.



Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC3235278/. Also see https://pmc.ncbi.nlm.nih.gov/articles/PMC3987114/

Key Papers Linking HE4/WFDC2 with Aging, Cancer Risk and Fibrosis

Zhang, L., et al. "Hypoxia-Induced HE4 in Tubular Epithelial Cells Promotes Renal Fibrosis via HIF-1α/HE4/NF-κB Signaling." Kidney International 97 (2020): 1068–1084.

Mechanism + tissue correlation with renal fibrosis. (link)

Nagy, B. Jr., et al. "Elevated Human Epididymis Protein 4 Concentrations in Chronic Kidney Disease." Clinical Chemistry and Laboratory Medicine 50 (2012): 1729–1736.

CKD elevates HE4 independent of cancer. (link)

Key paper

Yamamoto, M., et al. "HE4 Predicts Progressive Fibrosis and Cardiovascular Events in Patients with Dilated Cardiomyopathy." Journal of the American Heart Association 10, no. 15 (2021): e021069.

Cardiac fibrosis progression + CV events/mortality. (link)

James, N. E., et al. "The Biomarker HE4 (WFDC2) Promotes a Pro-Angiogenic and Immunomodulatory Tumor Microenvironment." Scientific Reports 10 (2020): 17609.

Pro-tumorigenic and a cancer biomarker (link)

Tian, M., et al. "Elevated Serum Human Epididymis Protein 4 Is Associated with Disease Severity and Worse Survival in Idiopathic Pulmonary Fibrosis." Frontiers in Medicine 9 (2022): 1019508.

IPF severity and survival linked to HE4. (link)

Proteomics of DNA Damage

Diego Quinta-Torres et.al, "The secretome atlas of two mouse models of progeria," *Aging Cell*, Oct 2023.

Hutchinson-Gilford progeria syndrome (HGPS) is a rare genetic disease caused by nuclear envelope alterations that lead to accelerated aging and premature death. Several studies have linked health and longevity to cell-extrinsic mechanisms, highlighting the relevance of circulating factors in the aging process as well as in age-related diseases. We performed a global plasma proteomic analysis in two preclinical progeroid models ($Lmna^{G609G/G609G}$ and $Zmpste24^{-/-}$ mice) using aptamer-based proteomic technology. Pathways related to the extracellular matrix, growth factor response and calcium ion binding were among the most enriched in the proteomic signature of progeroid samples compared to controls.

Both of these models of genetic premature aging involve heavy DNA damage and no known damage to mitochondria. Interestingly, the upregulated proteins seen in these models are quite different than those highlighted in this section. GDF-15 is upregulated in control mice but not in progeria, for example.

This suggests that GDF-15 is largely reflected of mitochondrial damage and not reflective of DNA damage.

Summary of this Section

We find it quite interesting that the same three proteins emerge as being very good predictors of the date of death of humans in longitudinal studies built from three datasets and two different protein measurement approaches. GDF-15 and HE4 are particularly robust biomarkers. uPAR emerges as a very strong predictor of mortality in the UK Biobank and Malmo Heart Study. There are, of course, many other markers as well that one could look at. We argue that GDF-15 can be thought of as a proxy for mitochondrial damage and that the evidence supporting this is strong. There is a separate literature that identifies GDF-15 as a secreted protein from senescent cells (SASP protein). We will dive into this area shortly, but mitochondrial damage appears to be required for SASP protein release, so GDF-15 appears to be an isomorphic proxy for both mitochondrial damage and SASP. In contrast, uPAR is a cell surface marker that is widely expressed on senescent cells. That is, uPAR is not a SASP protein *per se,* but rather provides an index of how extensive the distribution of senescent cells might be in an organism. HE4 is a frequent and powerful predictor of mortality risk across studies and can be thought of as a general indicator of cell stress. In practice, levels of HE4 and GDF-15 are reasonably well correlated. HE4 is not a SASP protein (at least in the extant literature) and is not generally considered a biomarker of cell senescence – but is associated with inflammatory and fibrotic states.

The key takeaway in this section is that the incredibly strong predictive power of GDF-15 points us to the mitochondrial damage theory of aging as being of primary importance. In addition, the uPAR story points us to the senescent cell story as also being important.

We also have some reasonably good animal data that shows that GDF-15 is not a major player in progeria. Because most progerias are largely diseases of DNA damage but not of mitochondrial damage this suggests that GDF-15 elevation is specific to mitochondrial status.

There is much we don’t know. It would be interesting to have more data on levels of these proteins as persons become much older and there should be experiments that would better isolate their role.

We know that GDF-15 starts to increase at an increasing rate as persons go past the age of 75 but we don’t have data of this type, for example, for uPAR. The reason that this is interesting is that SASP release from senescent cells is thought to create a snowball effect of cell shutdown and seems to be a good way of explaining why marginal death probabilities increase rather rapidly as persons get into their 80s. While we haven’t seen it spelled out in the literature it seems logical that the “metastatic” effects of SASP are a good explanation of why no one makes it past 125 years of age. As SASP triggers ever more cells to shut down, a negative feedback loop triggers organismal mortality. No human can survive a massive and progressive shutdown of their cells through such a process.

Interpreting the Proteomic Data

Our focus on biomarkers in this report is mainly to use them as way of sorting through theories of aging.

If you believed, for example, that aging was mainly driven by autophagy genes you should see associated proteins be highly predictive of mortality in datasets of community-dwelling adults. We will soon show that this is not the case.

We should note that the next section of this report makes a case that DNA damage is the principal cause of aging – not mitochondrial respiration. Further, DNA damage can happen without oxidative stress from mitochondrial respiration.

So, to pause for a moment, this evidence on GDF-15 and mortality is quite important to us in deciding how to sort out aging theories.

We know that DNA damage is not associated with GDF-15 elevation *per se*.

This said, as we shall soon see, the case for DNA damage as a principal driver of aging is also quite strong.

We find the animal data, the fact that mutations in DNA damage repair machinery led to accelerated aging in humans and the mole rat biology story all to be quite persuasive.

These two critical aspects of aging biology are not one and the same but are, very likely, closely linked.

Interestingly, the literature does not disentangle how linked these two biological phenomena are in practice.

Thus, we see mitochondrial respiration and DNA damage as quite important drivers of aging. Cell senescence, loss of proteostasis and loss of autophagy all appear to be important as well. But from our vantage point, these three factors result from oxidative stress, mitochondrial damage and DNA damage.

There are other pathways, of course, that matter quite a bit such as nutrient sensing pathways, IGF1, mTOR etc. However, our general view based on biomarker data, is that these are not central factors in explaining the timing of human mortality. This said, genetic mutational data show that IGF1 is important.

Broader Implications of Findings in this Section

It may be rather obvious to the thoughtful reader that the proteomic predictors of mortality and disease should be of primary importance to the practice of medicine.

Of course, today's doctor is unlikely to know what uPAR, GDF-15 or HE4 are. A Danish company, Virogates, has been pushing hard to for uPAR adoption in medicine and has not made that much progress (their market cap is around $15 million).

These proteins are not to be found on any typical medical panels from mainstream diagnostic laboratories and call for novel assay development. Today, Mayo's diagnostic labs offer GDF-15 and Virogates will analyze uPAR. Labcorp and Mayo can do HE4. Roche offers GDF-15 on its analyzer platform – but not in the United States.

But, if the entirety of our lives basically depend on cellular health, mitochondrial health and senescence cell status, it is logical that a physician should want to know what these variables are. Indeed, our sense would be that these should be primary, and the usual lipid and metabolite panels may be less important in understanding a patient's true health. Importantly, there are things one can do about mitochondrial health, senescence etc. That is, in a way, the main point of this report.

Interestingly, several groups offer extensive panels for the DYI life "hacker" to understand their health. Function Health offers "100+ lab tests" in a membership model, suggesting that you "own your health" by baseline testing and tracking. All of the tests offered by Function are standard and can be run off of existing analyzers with current FDA approved assays.

Iollo Health goes further and gives you a report on 500 biomarkers. Interestingly, their giant marker set is a core dump from a metabolite analyzer such as that Metabolome would use. No proteins like HE4 or GDF-15 are measured by either Function or Iollo. Even today's top aging clinics and specialists do not dig into these things. We have spoken to Nathan LeBrasseur, who leads Mayo's aging group, about this at length.

He understands the obvious medical implications of these markers very well and has developed a 28-protein panel for analyzing aging and is thinking this should get incorporated into Mayo's Executive Health program. Great idea!

Another obvious idea that we will expand on later is the idea that if you think you are doing something to expand lifespan you should see it in biomarkers. If you cure a kid of mitochondrial disease his GDF-15 is going to drop. Likewise, if you restore my mitochondria, then my GDF-15 should drop. There is ample supportive evidence that this is the case.

Point Eight:

Overwhelming Evidence Supports the Idea that Aging Results from DNA Damage

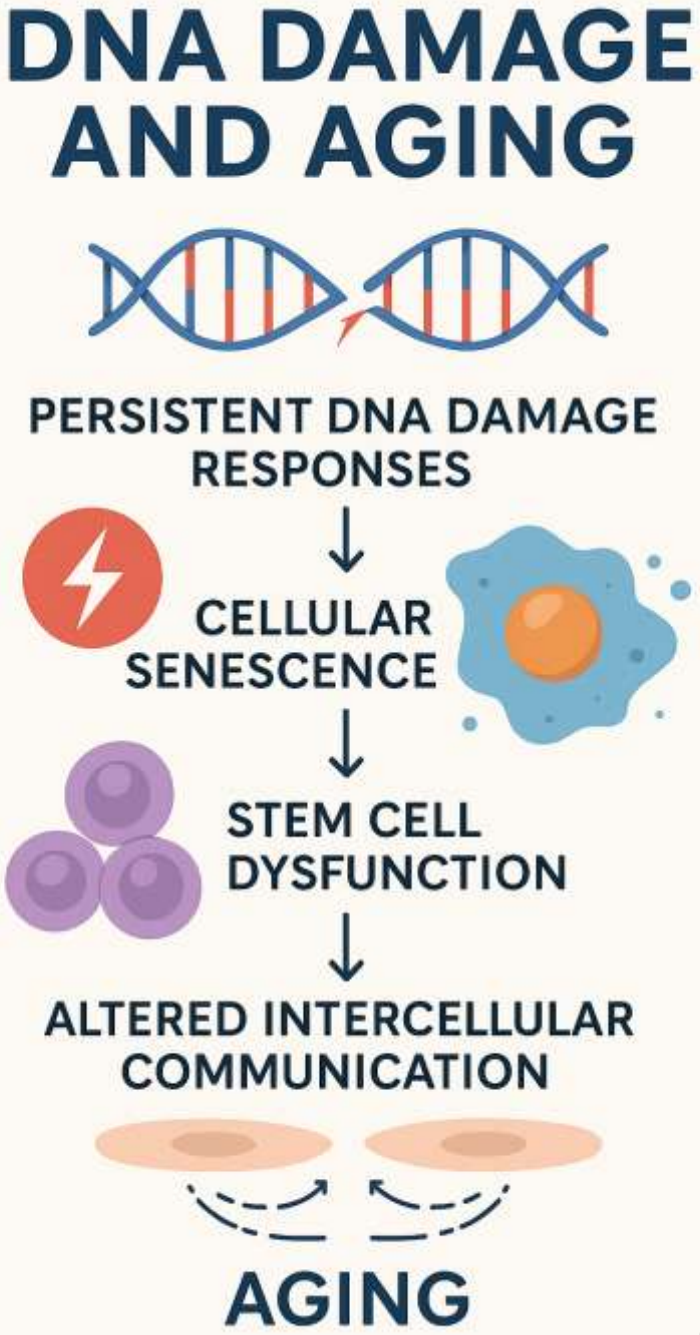
Arguably DNA damage drives aging independent of mitochondrial damage.

DNA Damage Is An Important Cause of Aging

DNA damage is a central, independent driver of aging, even in the absence of elevated reactive oxygen species (ROS). Every cell accumulates DNA lesions every day from endogenous, non-oxidative processes such as spontaneous hydrolysis, cytosine deamination, replication fork collapse, and crosslinking by aldehydes or lipid peroxidation products.

Though most of these lesions are rapidly repaired, a small proportion persist, especially in long-lived, post-mitotic cells. Persistent DNA damage activates the DNA damage response (DDR) and signaling through ATM, ATR, and p53, which induce cell-cycle arrest, senescence, or apoptosis. Over time, these outcomes contribute to stem-cell exhaustion, altered intercellular communication, and loss of tissue homeostasis—hallmarks of aging observed across species.

Evidence from progeroid DNA-repair-deficiency models **strongly supports causality**: defects in nucleotide excision repair (e.g., XPA, ERCC1), double-strand break repair (e.g., Ku80, Lig4), and crosslink repair (FANCD2, XPF) cause accelerated aging with tissue atrophy, neurodegeneration, and shortened lifespan, despite normal or low ROS levels.



DNA Damage Is An Important Cause & Consequence of Aging

Similarly, mitochondrial DNA mutator mice, in which polymerase proofreading is impaired, accumulate somatic mtDNA mutations that trigger metabolic decline and premature aging phenotypes.

These models demonstrate that the ongoing burden of DNA lesions—and the chronic activation of DDR signaling they provoke—can recapitulate many aspects of natural aging.

In humans, accumulation of unrepaired nuclear and mitochondrial DNA damage correlates with frailty, hematopoietic stem-cell senescence, and systemic inflammation, suggesting that genomic instability is not just a correlate but a fundamental causal part of the aging process.

Prematurely Aged Mouse with DNA Damage

Quick Summary of the Literature Linking DNA Damage to Aging

López-Gil L, Pascual-Ahuir A, Proft M, "Genomic Instability and Epigenetic Changes during Aging," *Int J Mol Sci.* Sep 19, 2023;24(18):14279.

1. **Genome instability as a hallmark of aging:** DNA is inherently unstable and prone to mutations (base changes, deletions, chromosomal abnormalities), which accumulate over time and impair cellular function, driving both aging and cancer.
2. **Sources of DNA damage:** Damage arises from replication and repair errors, endogenous toxins (e.g., ROS, aldehydes), and external insults (e.g., radiation, chemicals), leading to lesions, strand breaks, crosslinks, and aberrant DNA structures.
3. **Repair failure accelerates aging:** DNA cannot be replaced like other biomolecules; thus, weakened repair mechanisms or chronic exposure to damaging agents hasten aging, as seen in genetic syndromes and after chemotherapy.
4. **Link to cellular senescence:** Persistent or unrepaired DNA damage activates apoptosis or senescence programs to prevent propagation of damaged genomes—yet accumulation of senescent cells is itself a key driver of organismal aging.
5. **Oxidative stress as a central driver:** Reactive oxygen species (ROS) from mitochondrial respiration oxidize DNA bases (notably guanine to 8-OHdG), causing mutations and epigenetic disruption, particularly in CpG-rich promoter regions.
6. **rDNA instability and nucleolar stress:** The ribosomal DNA locus is especially damage-prone due to its repetitive structure; instability here leads to nucleolar stress and senescence—mechanisms conserved from yeast to mammals.
7. **Mitochondrial DNA vulnerability:** mtDNA suffers high oxidative damage due to lack of histone protection and limited repair, contributing to age-related mitochondrial dysfunction, though its quantitative impact remains debated.
8. **Epigenetic consequences of DNA repair:** Repeated DNA damage and repair introduce stable epigenetic "scars," altering methylation and chromatin states, leading to transcriptional drift and loss of gene expression control with age.
9. **Secondary cellular stresses:** Accumulated DNA damage triggers downstream effects such as proteostatic stress and protein aggregation, linking genome instability to neurodegenerative diseases like Alzheimer's and Parkinson's.
10. **Unified concept:** Aging arises from the cumulative failure of genomic maintenance—where persistent DNA lesions, impaired repair, and their epigenetic and proteostatic aftermath collectively erode cellular integrity over time.

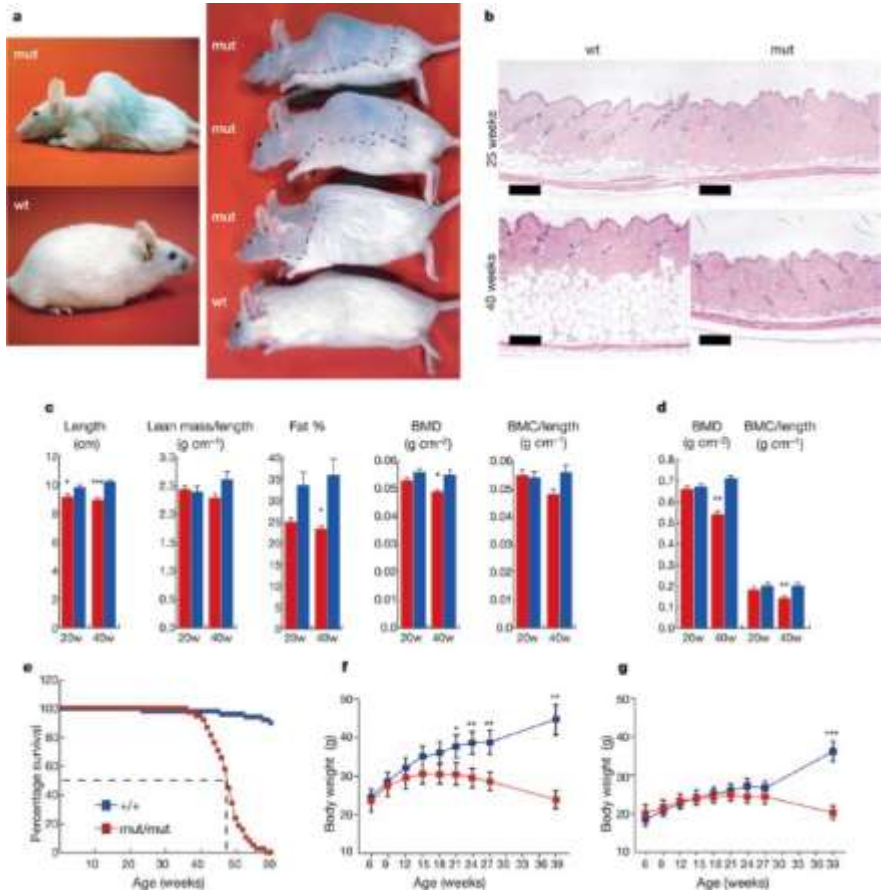
Source: https://www.mdpi.com/1422-0067/24/18/14279

DNA Damage Can Accelerate Aging

Human Mutations Involving DNA Damage Repair Genes Can Lead to Premature Aging (Progeria)

Progeria syndromes lead to rapid aging. Some are caused by breakdown in DNA damage repair genes (like Cockayne and Werner Syndromes). Others, like HGPS, involve DNA damage only indirectly. Sam, shown here, died at age 17 when his biological age was well advanced relative to his parents.

Induced Mutations in DNA Damage Genes Lead to a Similar Progeria Phenotype of Premature Aging

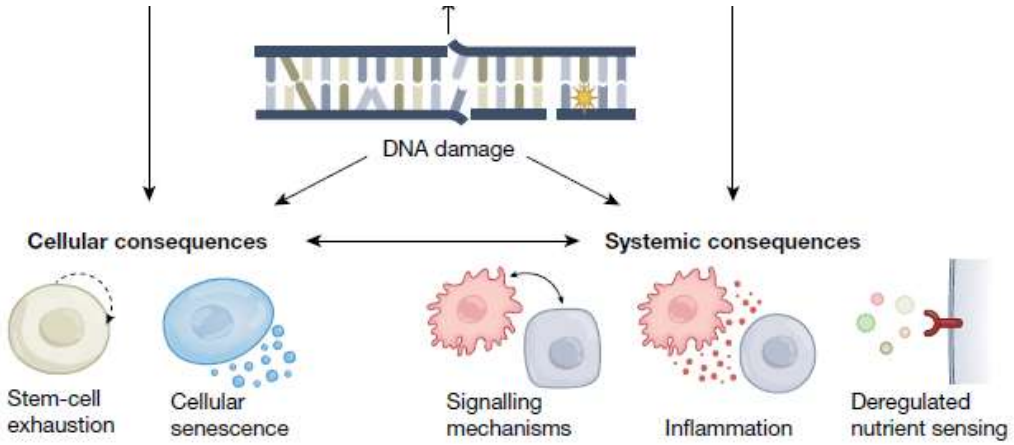


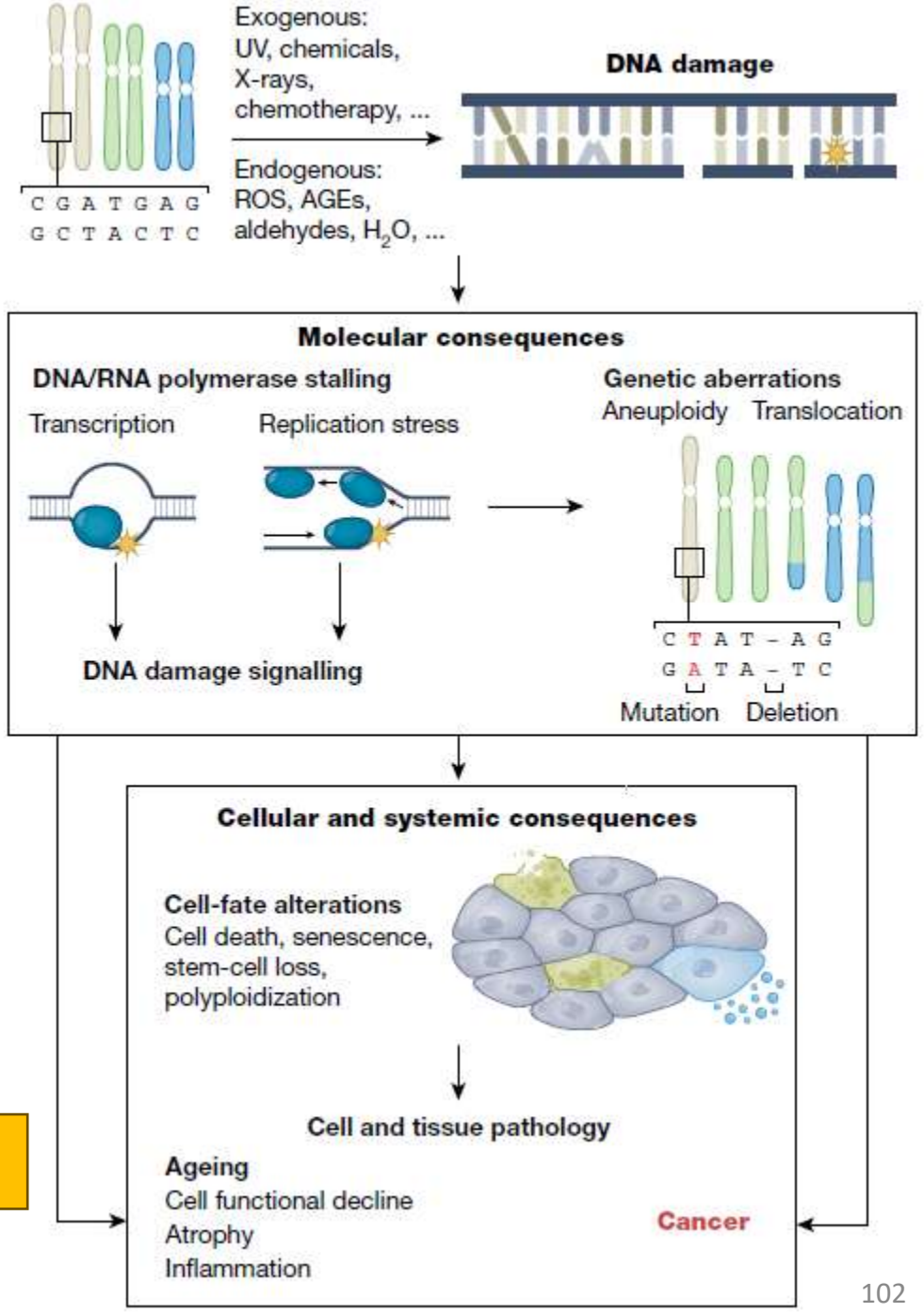
Source: https://www.nature.com/articles/nature02517

Multiple Authors See DNA Damage As the Central Driver of Aging

Schumacher B, Pothof J, Vijg J, Hoeijmakers JHJ. "The central role of DNA damage in the ageing process," *Nature*, April 2021; 592(7856):695-703.

DNA damage is the driver of ageing. The nuclear and mitochondrial genomes are continuously damaged by exogenous agents (such as UV, X-rays, chemical compounds in food, water and air), endogenous sources such as reactive oxygen species (ROS), aldehydes and advanced glycation end products (AGEs) and spontaneous reactions (hydrolysis). Molecular consequences of time-dependent accumulating DNA damage are: (1) genetic aberrations, such as mutations and chromosomal instability, and (2) stalling of RNA and DNA polymerases by DNA lesions, which provokes DNA damage signalling and interferes with primary DNA functions. Cellular and tissue consequences of DNA damage include cell fate decisions such as cell death and senescence, leading to functional loss of cells and organs, cancer, atrophy and inflammation.

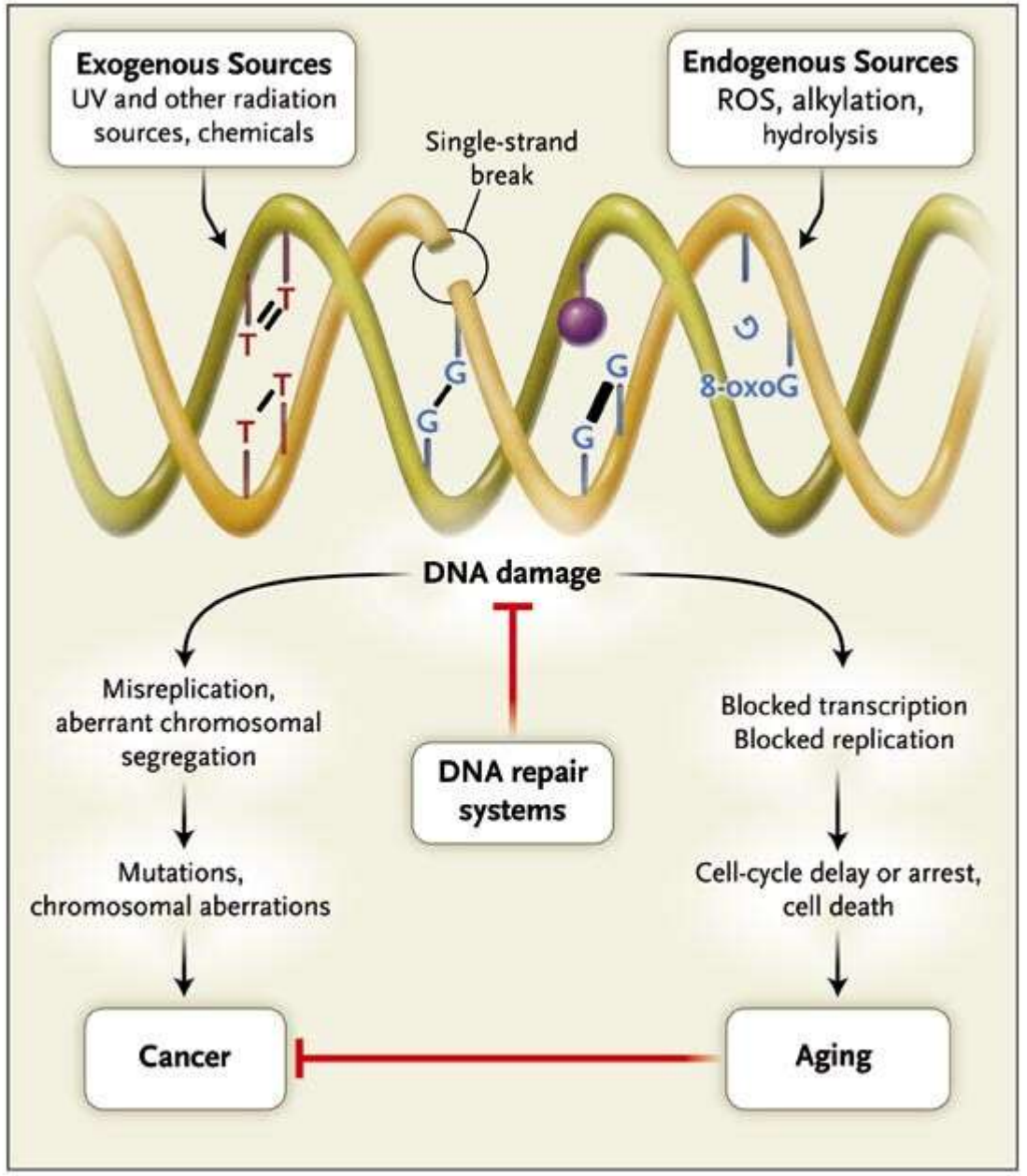




Source: https://www.nature.com/articles/s41586-021-03307-7

DNA Damage Can Lead Both to Cancer and Aging

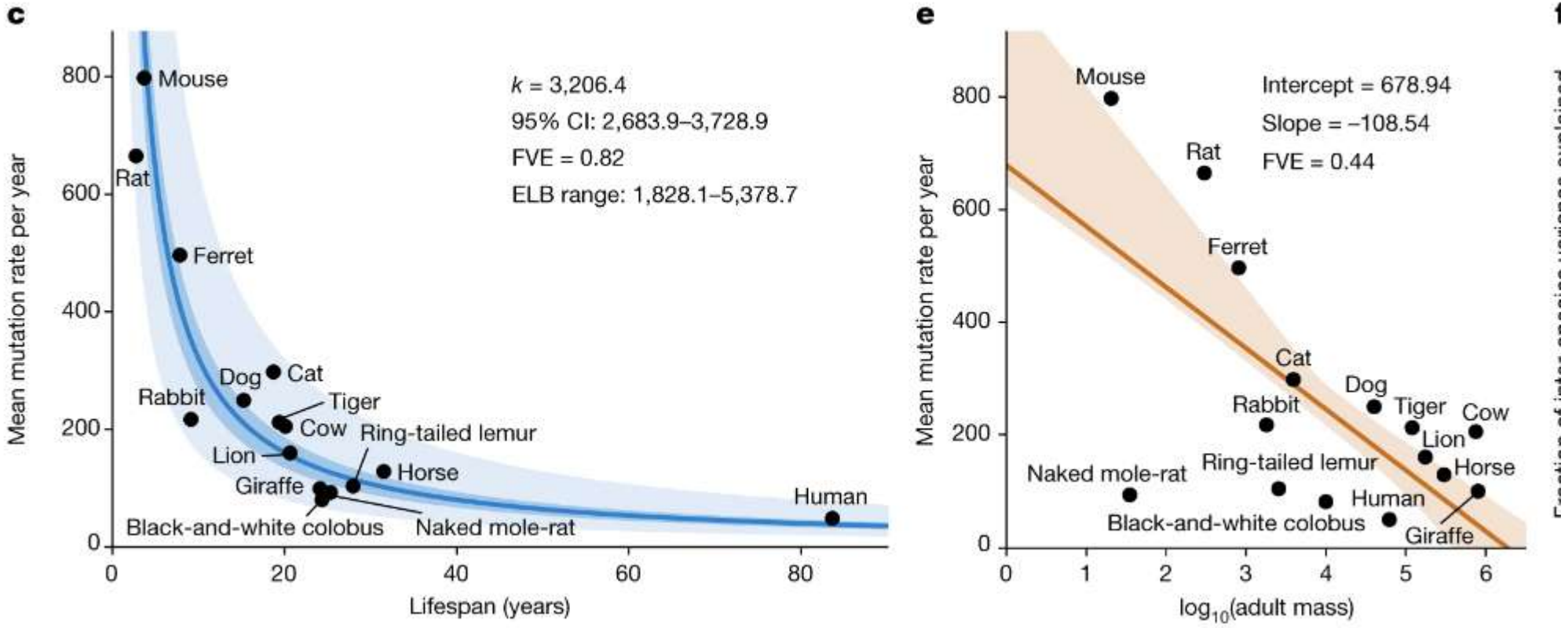
DNA damage can be induced by exogenous physical agents, by endogenous chemical genotoxic agents that are the products of metabolism, such as reactive oxygen species (ROS), or by spontaneous chemical reactions, such as hydrolysis. Examples of DNA damage are ultraviolet (UV)-induced photoproducts (left), interstrand and intrastrand crosslinks, bulky chemical adducts (purple sphere), abasic sites, and oxidative damage such as 8-oxoguanine (8-oxoG). The consequences of DNA damage are essentially twofold. After misrepair or replication of the damaged template, surviving cells may be subject to permanent changes in the genetic code in the form of mutations or chromosomal aberrations, both of which increase the risk of cancer. Alternatively, damage may interfere with the vital process of transcription or induce replication arrest, which may trigger cell death or cellular senescence, contributing to aging. Damage-induced cell death protects the body from cancer. G denotes guanine, and T thymidine.



Source: https://www.nejm.org/doi/full/10.1056/NEJMra0804615

DNA Mutation Rates Lower in Longer Lived Species

(Also, smaller species tend to have higher mutation rates – except for the naked mole rat).



Source: https://www.nature.com/articles/s41586-022-04618-z

The Naked Mole Rat is a Very Special Case

OK, we will be the first to admit, this guy isn't world's most handsome animal.

However, there is something glorious here. The naked mole-rat lives *far longer* than any other rodent—often three to four decades—without showing the usual signs of aging. Unlike most mammals, its risk of death doesn't steadily rise with age. Scientists now think that this longevity is tied to unusually effective DNA maintenance. The naked mole-rat seems able to repair double-strand breaks and other genetic damage with remarkable efficiency, preventing the gradual erosion of cellular function that drives aging in other species.

Despite living in low-oxygen, high-stress underground environments that should accelerate wear and tear, it maintains stable proteins, resilient membranes, and a balanced metabolism that protects its genome from cumulative damage.

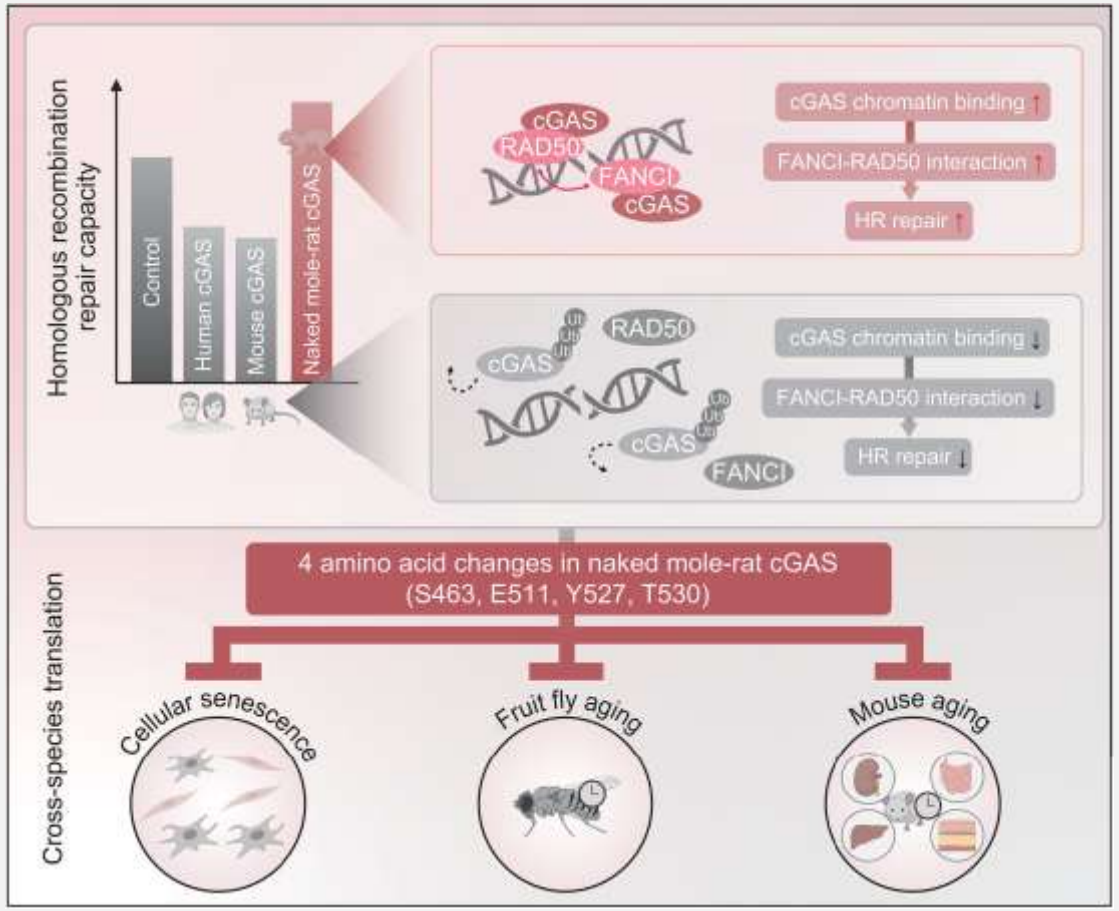
This biology could potentially be introduced into humans using gene editing.

The Mole Rat Reengineers cGAS to be a DNA Repair Enhancer

A particularly intriguing discovery is that the naked mole-rat has re-engineered the role of a key immune sensor called cGAS, part of the cGAS–STING pathway that normally detects damaged DNA and triggers inflammation. In most mammals, this pathway contributes to cellular aging when it reacts to leaked nuclear fragments. This was spelled out in an Oct 9, 2025 article by Chen et al. in *Science*.

But in the naked mole-rat, small mutations make cGAS act as a DNA repair enhancer instead of an inflammation trigger (see chart).

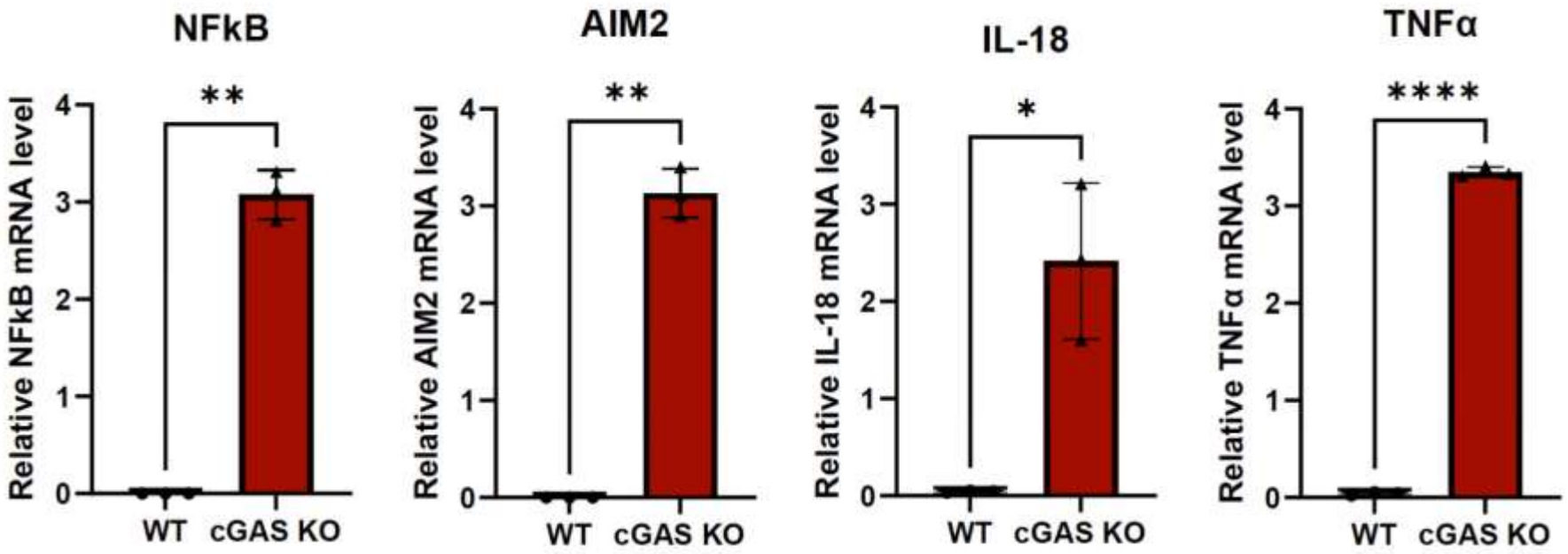
This shift means the animal not only fixes its genome more efficiently but also avoids the chronic inflammatory cascade that drives senescence in others. In effect, the species has turned a danger sensor into a repair system—one of the most elegant natural adaptations for long life discovered so far.



The cGAS-mediated suppression of homologous recombination repair is reversed in the longest-lived rodent, the naked mole-rat. Four amino acid changes maintain its cGAS at a low level of ubiquitination after DNA damage, conferring prolonged chromatin binding (E, Glu; S, Ser; T, Thr; Y, Tyr). This facilitates FANCI and RAD50 interaction, enhancing HR repair. These molecular changes contribute to reduced cellular senescence, delayed organ aging, and life-span extension.

cGAS Knockout Mice Have Shortened Lives

Eric Topol Blog Post (Oct 2025): the *Science* paper was a comprehensive assessment of the impact of naked mole rat's cGAS in multiple species, with or without the 4 key mutations. Independent of the new report, a recent preprint by Martinez and colleagues looked at mice with knockout of cGAS (cGAS KO) and demonstrated shortened lifespan and increased inflammation in multiple organs, stemming from genomic instability (loss of chromatin organization and de-repression of transposable elements known as "jumping genes").



That independent corroboration of the new report strengthens the assertion that the cGAS is a fundamental pathway underpinning healthspan and lifespan in mammals, and that the 4 amino acid changes in the naked mole rat are the most likely explanation for their unique outlier status.

Source: https://erictopol.substack.com/p/a-long-awaited-longevity-mystery

Strong Evidence Links cGAS/STING Pathway to Aging

cGAS–STING drives ageing-related inflammation and neurodegeneration

Muhammet F. Gulen[1,9], Natasha Samson[1,9], Alexander Keller[1], Marius Schwabenland[2], Chong Liu[1], Selene Glück[1], Vivek V. Thacker[1], Lucie Favre[3], Bastien Mangeat[4], Lona J. Kroese[5], Paul Krimpenfort[5], Marco Prinz[2,6,7] & Andrea Ablasser[1,8]✉

Nature, Aug 10, 2023

Low-grade inflammation is a hallmark of old age and a central driver of ageing-associated impairment and disease[1]. Multiple factors can contribute to ageing-associated inflammation[2]; however, the molecular pathways that transduce aberrant inflammatory signalling and their impact in natural ageing remain unclear. Here we show that the cGAS–STING signalling pathway, which mediates immune sensing of DNA[3], is a critical driver of chronic inflammation and functional decline during ageing. Blockade of STING suppresses the inflammatory phenotypes of senescent human cells and tissues, attenuates ageing-related inflammation in multiple peripheral organs and the brain in mice, and leads to an improvement in tissue function. Focusing on the ageing brain, we reveal that activation of STING triggers reactive microglial transcriptional states, neurodegeneration and cognitive decline. Cytosolic DNA released from perturbed mitochondria elicits cGAS activity in old microglia, defining a mechanism by which cGAS–STING signalling is engaged in the ageing brain. Single-nucleus RNA-sequencing analysis of microglia and hippocampi of a cGAS gain-of-function mouse model demonstrates that engagement of cGAS in microglia is sufficient to direct ageing-associated transcriptional microglial states leading to bystander cell inflammation, neurotoxicity and impaired memory capacity. Our findings establish the cGAS–STING pathway as a driver of ageing-related inflammation in peripheral organs and the brain, and reveal blockade of cGAS–STING signalling as a potential strategy to halt neurodegenerative processes during old age.

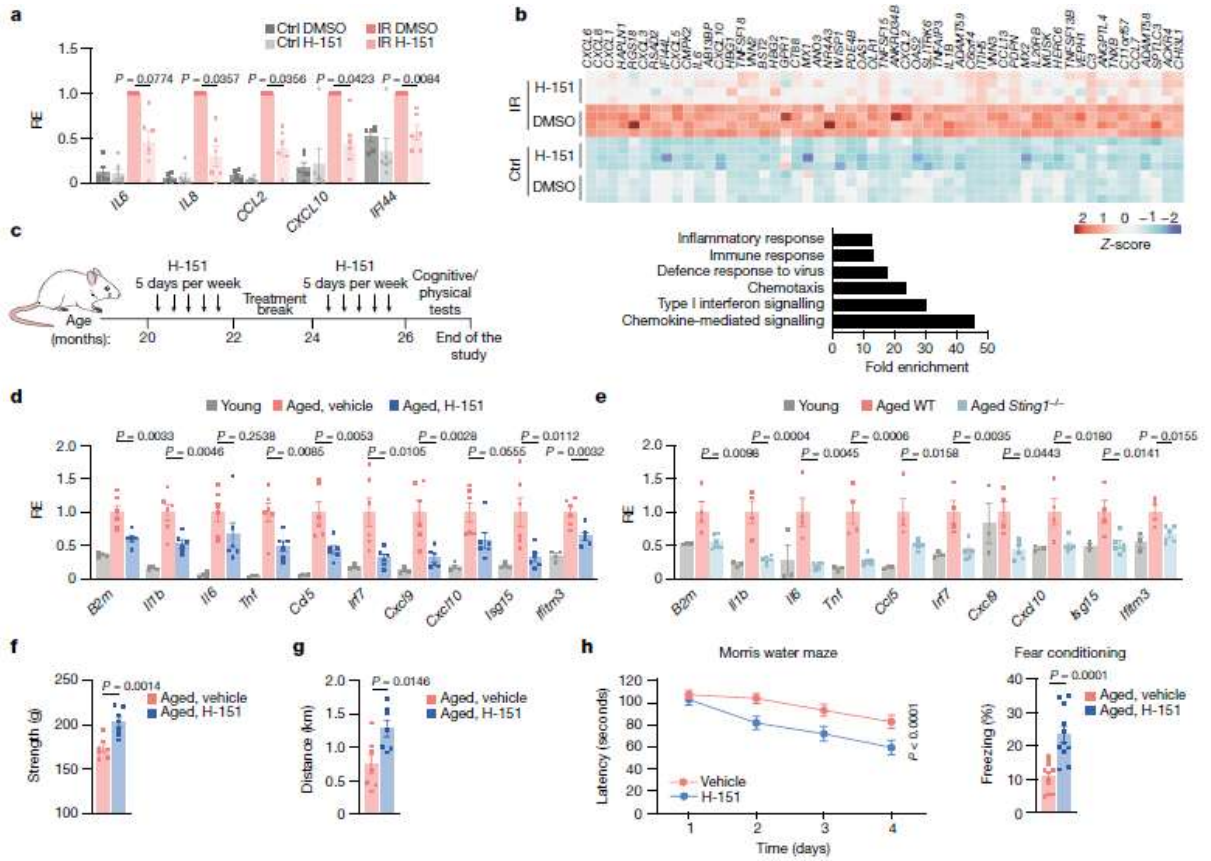
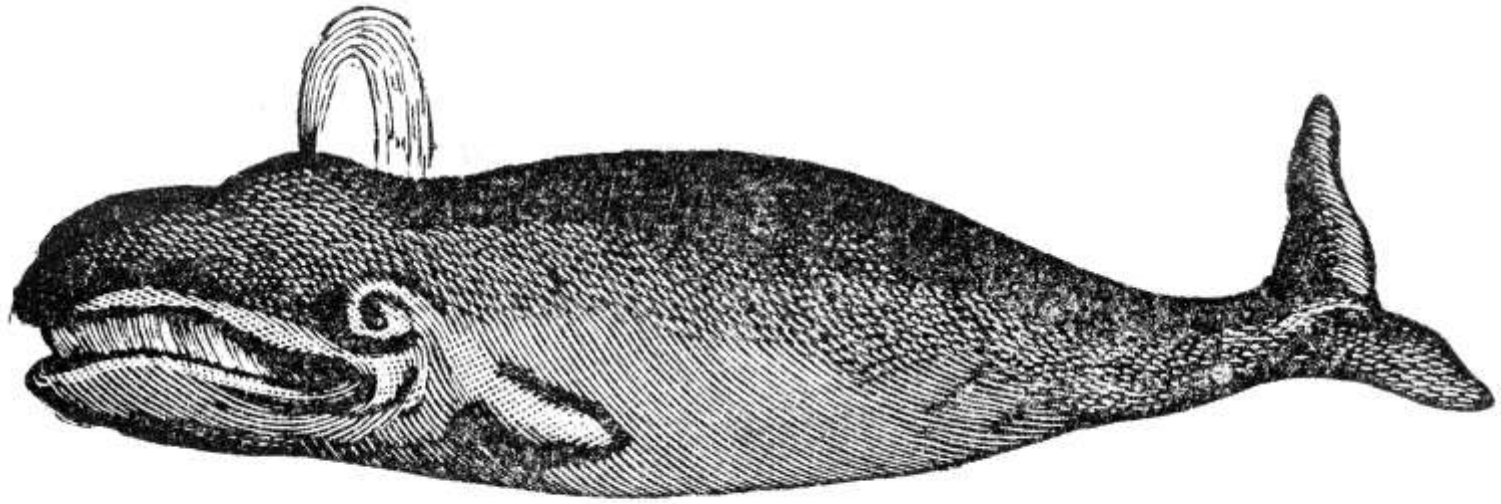


Fig. 1 | STING promotes low-grade inflammation and functional decline in aged mice. a,b, mRNA expression levels of proinflammatory genes and ISGs (**a**) and RNA-seq analysis (**b**) of human WI-38 fibroblasts irradiated (12 Gy, IR) or maintained at 5% O_2 (Ctrl), and treated with H-151 (daily, 0.5 μM) or DMSO for 10 days when senescent (day 10 to 20). The relative expression (RE) was measured for each experiment ($n = 6$) relative to the induction level in the irradiated DMSO condition (**a**). **b**, The top 50 genes most upregulated after irradiation and suppressed after H-151 treatment ($n = 4$ experiments) (top), and a gene set enrichment analysis showing the fold enrichment based on the above list of genes (bottom). **c**, Schematic of the treatment of wild-type (WT) aged mice with H-151 related to data shown in **d** and **f**–**h**. **d**,**e**, Kidney mRNA expression levels of proinflammatory genes and ISGs in young ($n = 4$) and aged mice treated with or without H-151 ($n = 6$) (**d**) and of young ($n = 3$), aged WT ($n = 4$) and *Sting1*$^{-/-}$ mice ($n = 6$) (**e**). Expression was measured relative to the average of aged vehicle-treated (**d**) or aged WT (**e**) mice. **f**,**g**, The physical condition of aged mice treated with or without H-151 ($n = 7$), evaluated by grip strength (**f**) and treadmill running distance (**g**). **h**, Cognitive function tests ($n = 11$ mice) were evaluated using the Morris water maze test (left, latency to reach the platform over multiple days) and fear conditioning (right, percentage of time spent freezing. $P = 3 \times 10^{-5}$. Data are mean ± s.e.m. *P* values were obtained using two-sided paired ratio Student's *t*-tests (**a**), two-sided unpaired Student's *t*-tests (**f**–**h** (right)), one-way analysis of variance (ANOVA) followed by Tukey's multiple-comparison test (**d** and **e**) and ordinary two-way ANOVA (**h**, left).

Source: https://www.nature.com/articles/s41586-023-06373-1

The Incredible Bowhead Whale

Bowhead whales are the longest-living mammals on Earth, with an estimated lifespan of over 200 years. Scientists have determined their extreme longevity by analyzing stone harpoon tips found in their blubber and through modern genetic and eye tissue analysis. Australian scientists at CSIRO estimate that the maximum lifespan of the whale is 268 years based on genetic analysis.



The Bowhead Whale (*baleana mysticetus*) has an average length of 15 to 18 m (49 to 59 ft) but have been reported up to 20 m (65 ft) and can weigh up to 100 tonnes (220,462 lb).

The bow-shaped skull can be over 16.5 feet long—about a third of a bowhead's body length. The bowhead whale also has a 17- to 19-inch-thick blubber layer

The Mystery of Bowhead Whale Longevity Solved

In a just published paper in *Nature*, Firsanov and colleagues show that the bowhead whale's exceptional lifespan is explained by five interlocking biological mechanisms shown at right.

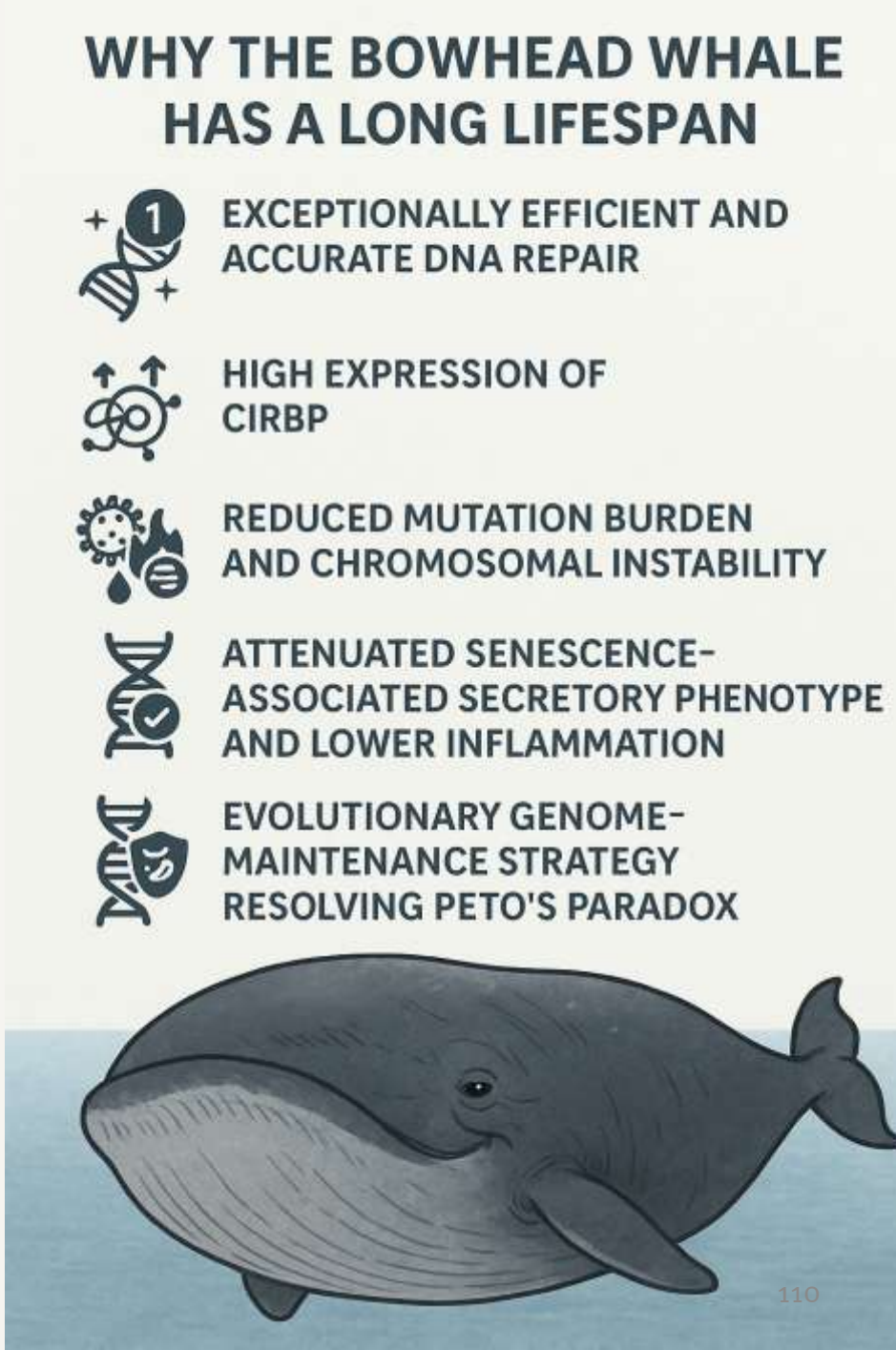
Long life and large body mass predispose the bowhead whale to accumulating large numbers of DNA mutations throughout life.

However, an increased number of cells and cell divisions in larger organisms does not lead to increased cancer incidence and shorter lifespans.

The apparent contradiction between expected and observed cancer rates in relation to species body mass has been noted for decades and is known as Peto's paradox. To remain alive for so long the bowhead whale must possess uniquely potent genetic mechanisms to prevent cancer and other age-related diseases.

Firsanov and colleagues found that the whale has really good DNA damage repair genetics. A similar story holds for the Greenland Shark – which can live for 400 years or more.

Source: https://www.nature.com/articles/s41586-025-09694-5



Reduced Mutational Rate and Highly Efficient, Accurate DNA Repair Explains the Whale's Long Life

1. **Exceptionally Efficient and Accurate DNA Repair.** Bowhead whale cells show enhanced double-strand break (DSB) repair capacity and fidelity, using both non-homologous end joining (NHEJ) and homologous recombination (HR) at levels far above other mammals. These pathways correct DNA damage without introducing errors, maintaining genomic integrity for centuries.

2. **High Expression of the Cold-Inducible RNA-Binding Protein (CIRBP).** A key adaptation is massive upregulation of CIRBP, a protein that binds both RNA and PARP polymers and directly promotes DNA end protection and joining. CIRBP overexpression in human cells increased repair accuracy and reduced mutation rates, while its depletion in whale cells impaired these functions. In Drosophila, CIRBP overexpression even extended lifespan and conferred radiation resistance, implying a direct role in longevity.

3. **Reduced Mutation Burden and Chromosomal Instability**. Whole-genome and mutation assays show significantly lower spontaneous and induced mutation rates in bowhead fibroblasts compared with human or mouse cells. Structural variants (deletions, duplications, inversions › 500 kb) are markedly reduced, indicating that bowhead DNA is not only repaired more often but also repaired more cleanly, minimizing cumulative mutational load with age

4. **Attenuated Senescence-Associated Secretory Phenotype (SASP) and Lower Inflammation**. When whale cells become senescent, they secrete far fewer inflammatory cytokines than human cells. This muted SASP response reduces tissue-level chronic inflammation ("inflammaging") and prevents secondary DNA damage in neighboring cells. Bowhead fibroblasts also display low basal p53 activity and resist apoptosis, favoring repair over cell elimination—an energy-efficient longevity strategy.

5. **Evolutionary Genome-Maintenance Strategy Resolving Peto's Paradox.** Despite enormous body size (~80 tons) and cell number, bowheads exhibit low cancer incidence. Unlike elephants (which expanded TP53 copies), bowheads achieve cancer resistance through qualitative improvements in genome maintenance—efficient, faithful DNA repair rather than extra tumor-suppressor redundancy. This "repair-not-destroy" strategy preserves functional cells for decades and prevents both cancer and degenerative aging

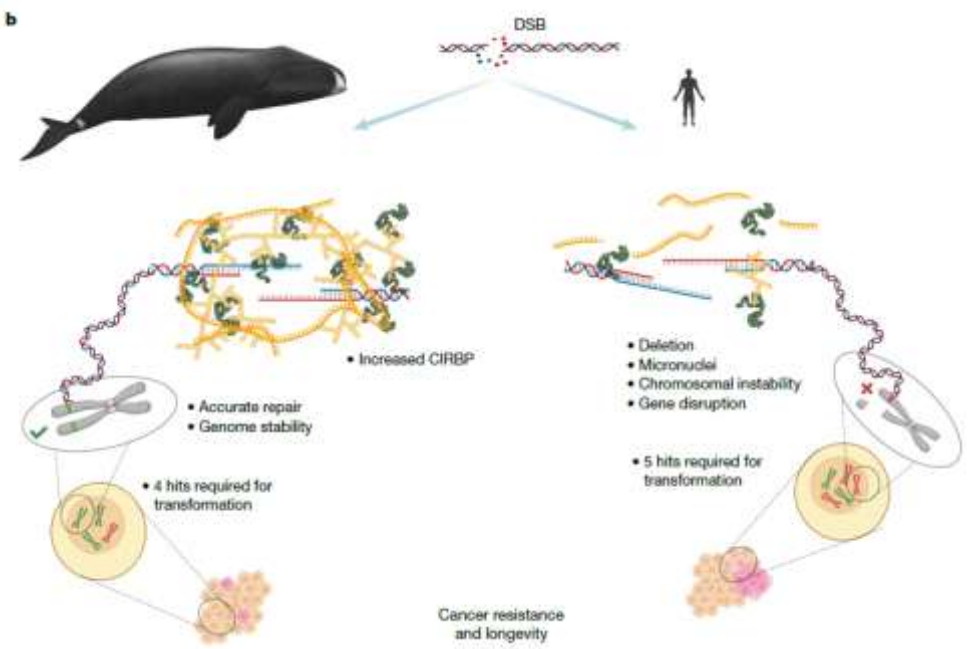
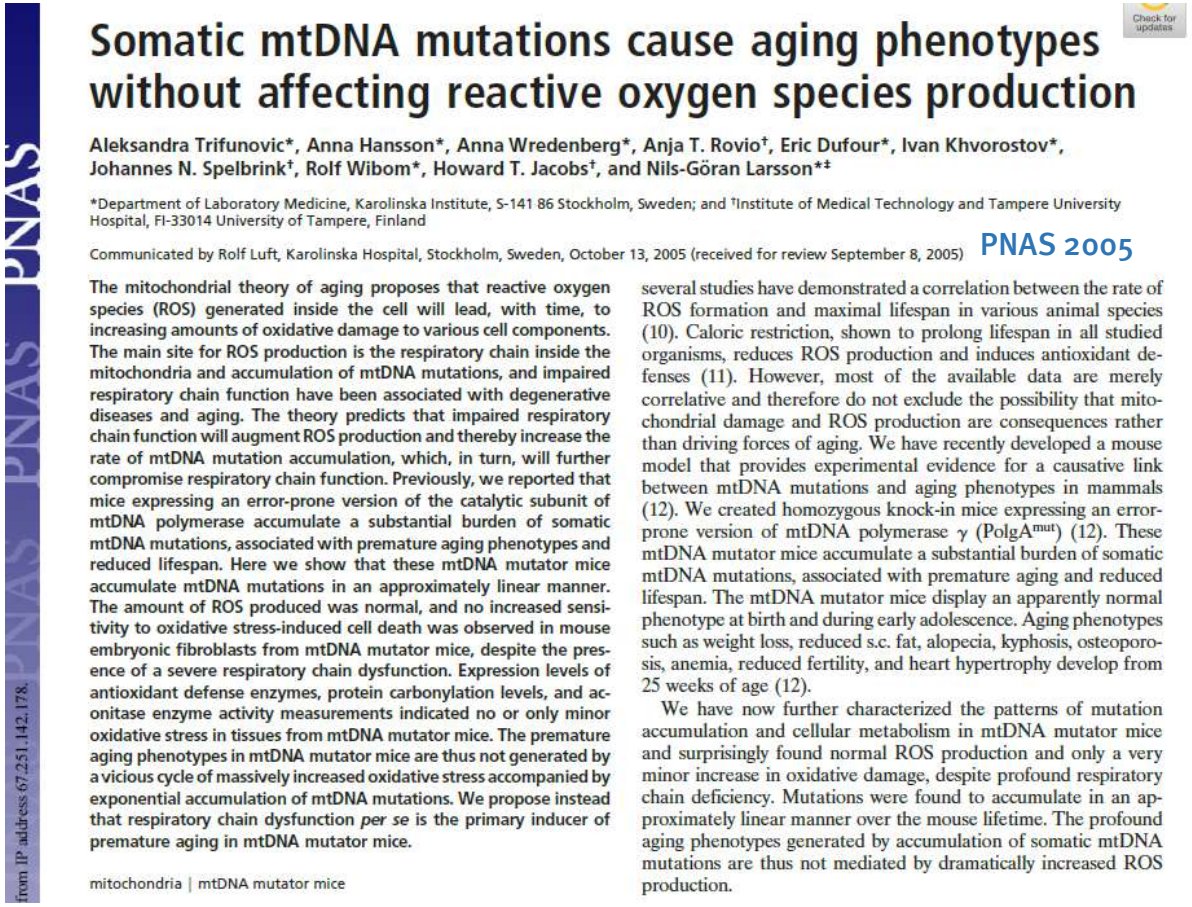


Fig 5b. Genome maintenance strategies in bowhead whale and human. The bowhead whale has evolved efficient and accurate DSB repair, mediated in part by high CIRBP expression. This enhanced repair capacity may contribute to cancer resistance, despite bowhead whale cells requiring fewer mutational hits for oncogenic transformation than human cells. Instead of relying primarily on elimination of damaged cells through apoptosis or senescence, improved DNA repair may underlie the bowhead whale's exceptional longevity and resistance to cancer.

Source: https://www.nature.com/articles/s41586-025-09694-5

Damage to Mitochondria DNA and its Effect on Aging Can Occur Even in the Absence of Oxidative Stress



Somatic mtDNA mutations cause aging phenotypes without affecting reactive oxygen species production

Aleksandra Trifunovic*, Anna Hansson*, Anna Wredenberg*, Anja T. Rovio†, Eric Dufour*, Ivan Khvorostov*, Johannes N. Spelbrink†, Rolf Wibom*, Howard T. Jacobs†, and Nils-Göran Larsson*‡

*Department of Laboratory Medicine, Karolinska Institute, S-141 86 Stockholm, Sweden; and †Institute of Medical Technology and Tampere University Hospital, FI-33014 University of Tampere, Finland

Communicated by Rolf Luft, Karolinska Hospital, Stockholm, Sweden, October 13, 2005 (received for review September 8, 2005)

PNAS 2005

The mitochondrial theory of aging proposes that reactive oxygen species (ROS) generated inside the cell will lead, with time, to increasing amounts of oxidative damage to various cell components. The main site for ROS production is the respiratory chain inside the mitochondria and accumulation of mtDNA mutations, and impaired respiratory chain function have been associated with degenerative diseases and aging. The theory predicts that impaired respiratory chain function will augment ROS production and thereby increase the rate of mtDNA mutation accumulation, which, in turn, will further compromise respiratory chain function. Previously, we reported that mice expressing an error-prone version of the catalytic subunit of mtDNA polymerase accumulate a substantial burden of somatic mtDNA mutations, associated with premature aging phenotypes and reduced lifespan. Here we show that these mtDNA mutator mice accumulate mtDNA mutations in an approximately linear manner. The amount of ROS produced was normal, and no increased sensitivity to oxidative stress-induced cell death was observed in mouse embryonic fibroblasts from mtDNA mutator mice, despite the presence of a severe respiratory chain dysfunction. Expression levels of antioxidant defense enzymes, protein carbonylation levels, and aconitase enzyme activity measurements indicated no or only minor oxidative stress in tissues from mtDNA mutator mice. The premature aging phenotypes in mtDNA mutator mice are thus not generated by a vicious cycle of massively increased oxidative stress accompanied by exponential accumulation of mtDNA mutations. We propose instead that respiratory chain dysfunction *per se* is the primary inducer of premature aging in mtDNA mutator mice.

mitochondria | mtDNA mutator mice

several studies have demonstrated a correlation between the rate of ROS formation and maximal lifespan in various animal species (10). Caloric restriction, shown to prolong lifespan in all studied organisms, reduces ROS production and induces antioxidant defenses (11). However, most of the available data are merely correlative and therefore do not exclude the possibility that mitochondrial damage and ROS production are consequences rather than driving forces of aging. We have recently developed a mouse model that provides experimental evidence for a causative link between mtDNA mutations and aging phenotypes in mammals (12). We created homozygous knock-in mice expressing an error-prone version of mtDNA polymerase γ (PolgA^{mut}) (12). These mtDNA mutator mice accumulate a substantial burden of somatic mtDNA mutations, associated with premature aging and reduced lifespan. The mtDNA mutator mice display an apparently normal phenotype at birth and during early adolescence. Aging phenotypes such as weight loss, reduced s.c. fat, alopecia, kyphosis, osteoporosis, anemia, reduced fertility, and heart hypertrophy develop from 25 weeks of age (12).

We have now further characterized the patterns of mutation accumulation and cellular metabolism in mtDNA mutator mice and surprisingly found normal ROS production and only a very minor increase in oxidative damage, despite profound respiratory chain deficiency. Mutations were found to accumulate in an approximately linear manner over the mouse lifetime. The profound aging phenotypes generated by accumulation of somatic mtDNA mutations are thus not mediated by dramatically increased ROS production.

> "We demonstrate that increased ROS formation and oxidative damage are unlikely to be major pathophysiological events in the premature aging process induced by elevated levels of mtDNA mutations. These results are in agreement with findings from a similar mtDNA mutator mouse model that was described recently. We have previously studied mitochondrial transcription factor A (Tfam) conditional knockout mice and demonstrated that loss of this protein causes severe mtDNA depletion and a profound respiratory chain deficiency in affected tissues. Loss of Tfam leads to considerable cell death by apoptotic and or necrotic pathways in embryos and differentiated tissues such as heart, neurons, and insulin-secreting–cells."

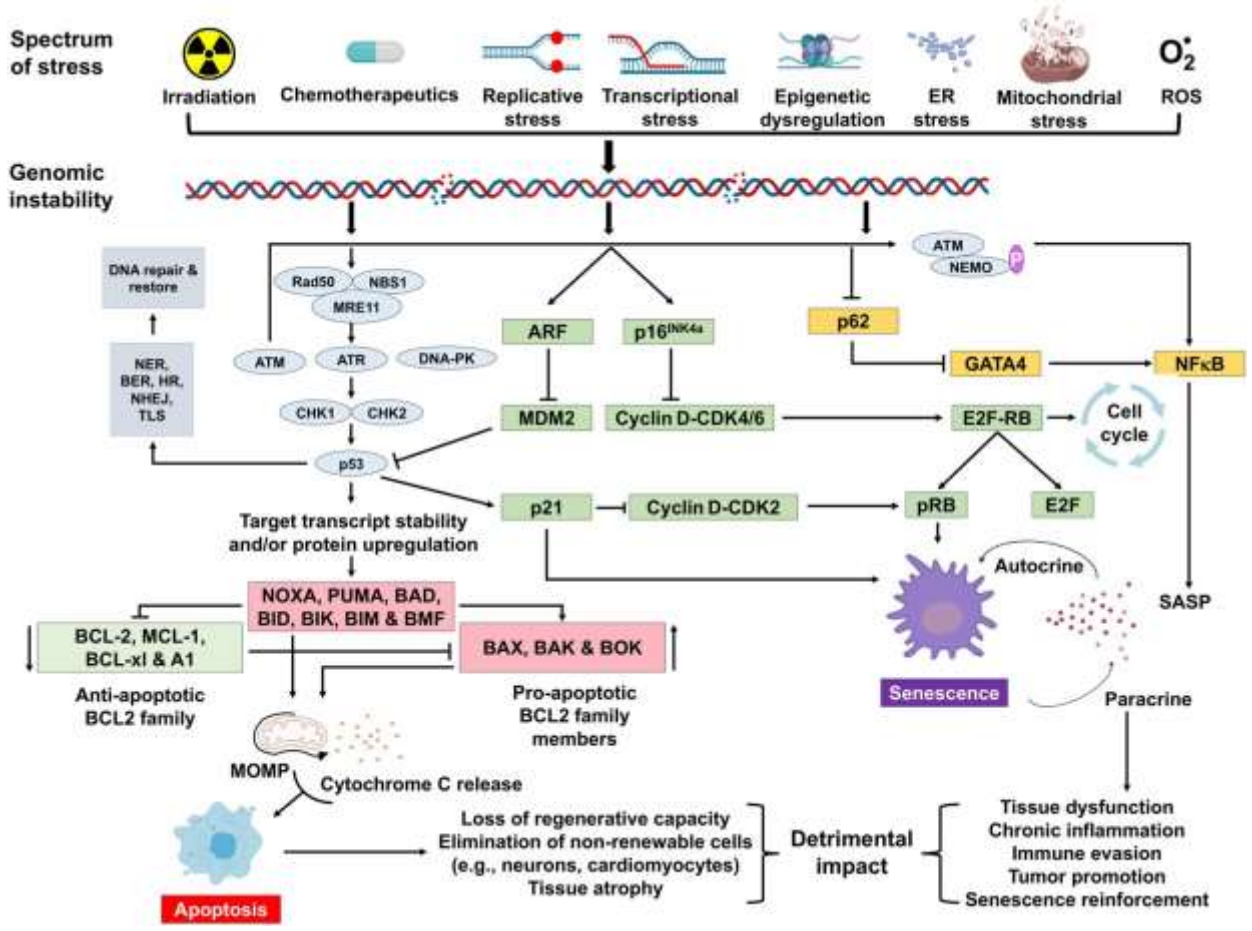
Source: https://www.pnas.org/doi/full/10.1073/pnas.0508886102

Despite the Possibility of DNA Damage Independent of Oxidative Stress, DNA Damage is Heavily Linked to Such Stress

Yousefzadeh M, Henpita C, Vyas R, Soto-Palma C, Robbins P, Niedernhofer L., "DNA damage-how and why we age?," *Elife*. 2021 Jan 29;10:e62852.

If DNA damage drives aging, mechanistically how does it do so? Through activating signaling responses (d'Adda di Fagagna et al., 2003), blocking transcription (Vermeij et al., 2016) and other DNA metabolism, altering the epigenome (Oberdoerffer et al., 2008), mutagenesis (Vijg, 2014), triggering cells senescence or apoptosis? **DNA damage occurs stochastically but the amount and types of DNA damage one experiences is influenced by the expression of genes encoding antioxidant enzymes, genes linked to energetics and mitochondrial function, and a myriad of other factors** such as histones, methylases, sirtuins, transcription, and replication factors.

Every aspect of how DNA damage might drive aging is also genetically determined via the cellular response to DNA damage. The somewhat surprising finding is that DNA damage has far-reaching effects on many aspects of cellular metabolism tied to aging, the so-called pillars of aging (Kennedy et al., 2014). This suggests that aging might be driven by many types of cellular damage yet does not occur until one reaches a state where multiple aspects of cell biology are perturbed, for example, genome integrity, proteostasis, and mitochondrial function.

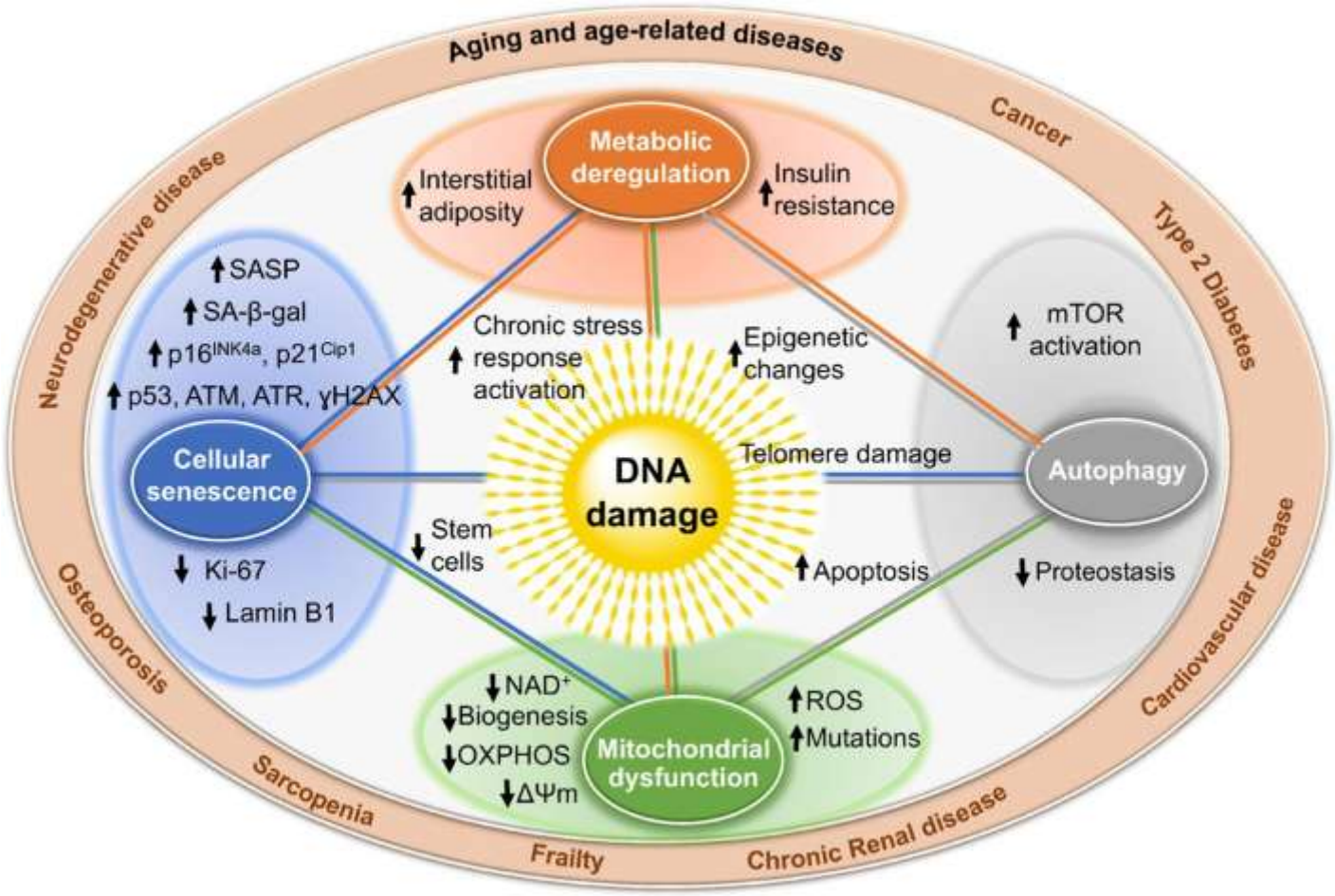


Source: https://elifesciences.org/articles/62852

DNA Damage Impacts Every Major Cause of Aging Including Cell Senescence, Mitochondria Dysfunction, Autophagy and Metabolic Dysfunction

Yousefzadeh M, Henpita C, Vyas R, Soto-Palma C, Robbins P, Niedernhofer L., "DNA damage-how and why we age?," *Elife,* Jan 29 2021; 10:e62852.

DNA damage impacts every aspect of cell biology. Genotoxic stress is a potent driver of cellular senescence and senescent cells play a causal role in driving aging and age-related disease. What is truly remarkable is looking within cells harboring genotoxic stress and finding how profoundly cellular homeostasis is perturbed (chart at left). For example, in tissues of DNA repair-deficient mice (caused by reduced expression of XPF-ERCC1 due to genetic depletion of Ercc1), spontaneous oxidative DNA damage accumulates rapidly, albeit not to a greater extent than what occurs with aging in repair-proficient mice (Wang et al., 2012). As a consequence of this genotoxic stress, mitochondrial and metabolic dysfunction, and increased reactive oxygen species arise, identical to changes seen with normal aging (Robinson et al., 2018).



Source: https://elifesciences.org/articles/62852

DNA Damage Biomarkers: Modern Biological Tools Have Enormous Power to Diagnose the Status of Human Cells

Today, we have the benefit of spatial biology powered by single cell analysis methods that allow one to examine thousands of cells at the genomic, transcriptomic and the proteomic level.

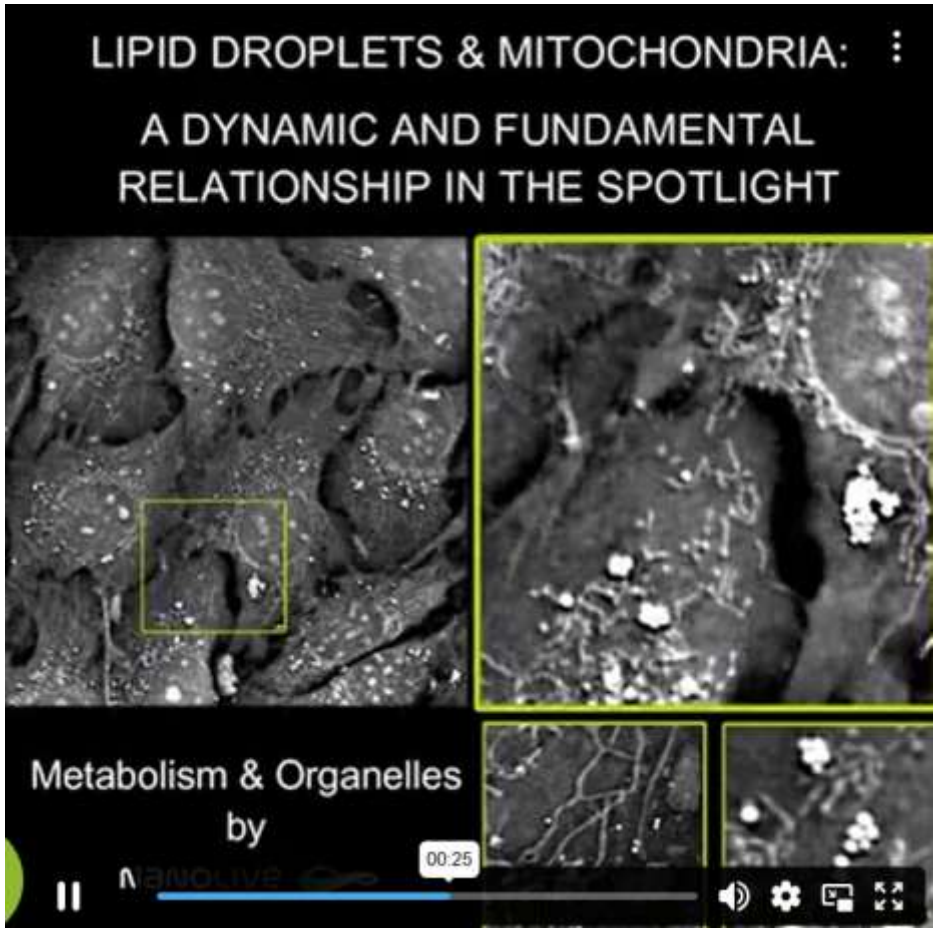
Further, one can use *live cell microscopy* to correlate single cell data with morphological data to understand cell biology but also to learn what is going at the level of organelles. It's possible to create movies of cells at an incredibly high magnification.

Such methods have been rapidly consolidated into multimodal cell analysis where AI is used to figure out relevant information about a cell. More than a few groups are getting really good at this presently. One of our favorites is the Israeli AI company Nucleai that uses AI to combine seven levels of cellular data to figure what is happening in a cancer cell.

To our knowledge these types of methods have not been routinized for the analysis of aging cells but if we can figure out the cancer cell it should be child's play to understand the status of the aging cell and to quantify the extent of mitochondrial damage, DNA damage and overall cell damage. The screen capture of a Nanolive video of mitochondria in a live cell at right gives a sense of the possibilities.

These tools obviously give us the ability to analyze cells obtained from living humans to figure out mutational status and the organization and status of organelles – in the same way that pathology has gotten incredibly good at analyzing cancer cells.

Nanolive Technology Permits Deep Analysis of Mitochondrial Health and Interactions



Source: https://www.nanolive.com/mitochondria/

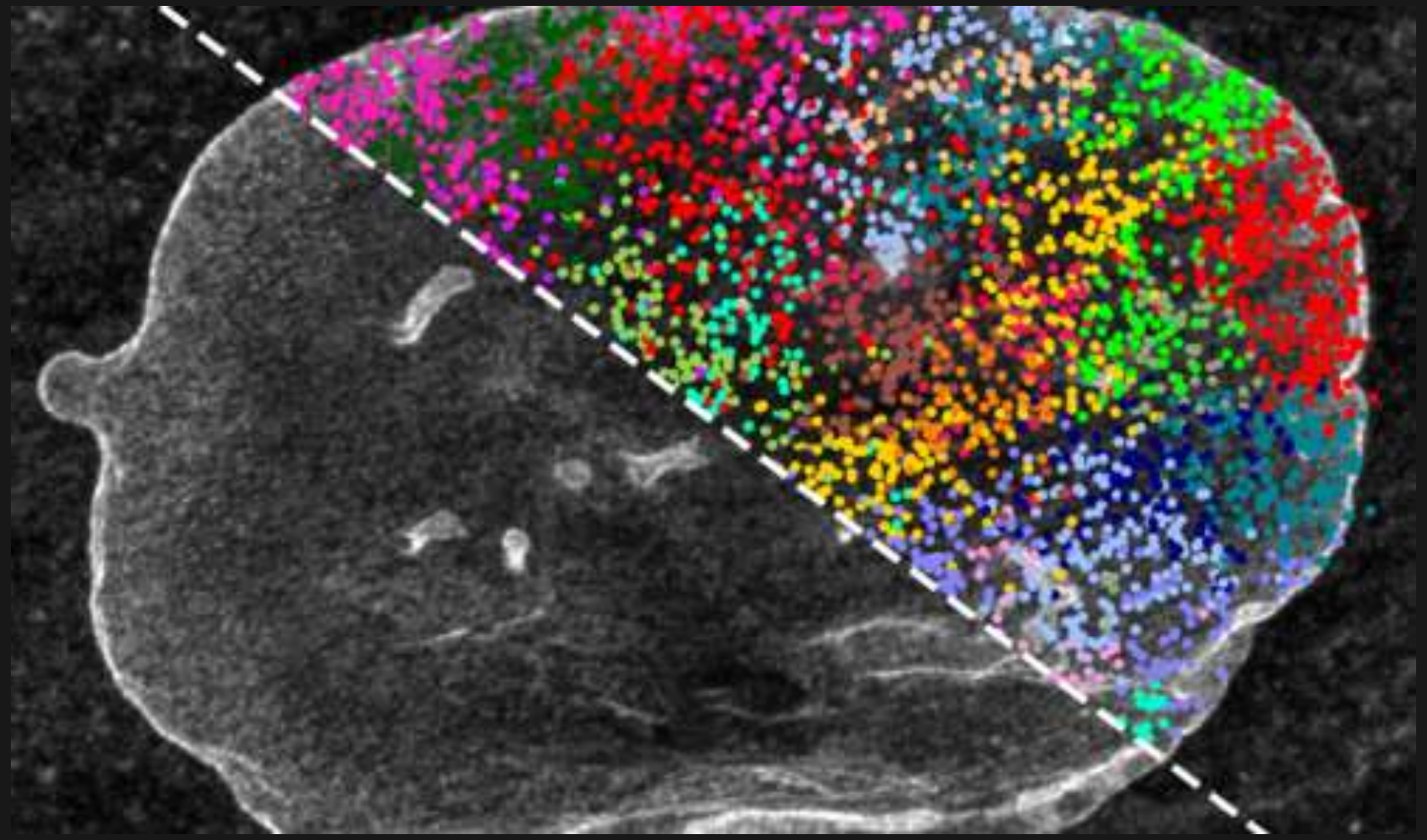
Can Also *Sequence* a Live Cell: Example of Progeria / Aging

Broad Institute Press Release, May 29, 2025

Broad Institute researchers have developed a technology that provides new insight into how disruptions in the nucleus of the cell can impact health and disease.

The approach, called expansion *in situ* genome sequencing, allows scientists to sequence DNA and map its location relative to proteins within cell nuclei. The method uses a gel to expand cells while keeping them intact, enabling both sequencing and high-resolution imaging within the same cells. The research team applied their technique to cells from patients with progeria, a disorder marked by accelerated aging. The scientists found that mutated proteins in the nucleus may suppress the expression of certain genes, which may play a role in the disease and the aging process.

The findings appear today in *Science* and come from the labs of institute member Jason Buenrostro and core institute member Fei Chen at the Broad. Buenrostro and Chen are also associate professors at Harvard University, and Buenrostro is a co-leader of Broad's Gene Regulation Observatory.



Example of expansion in situ genome sequencing, showing a physically expanded cell nucleus from an individual with progeria. Greyscale image shows lamin structures in the nucleus, and colored dots represent 3D genomic reads overlaid in their original spatial locations, colored by chromosome. Source: Buenrostro Lab.

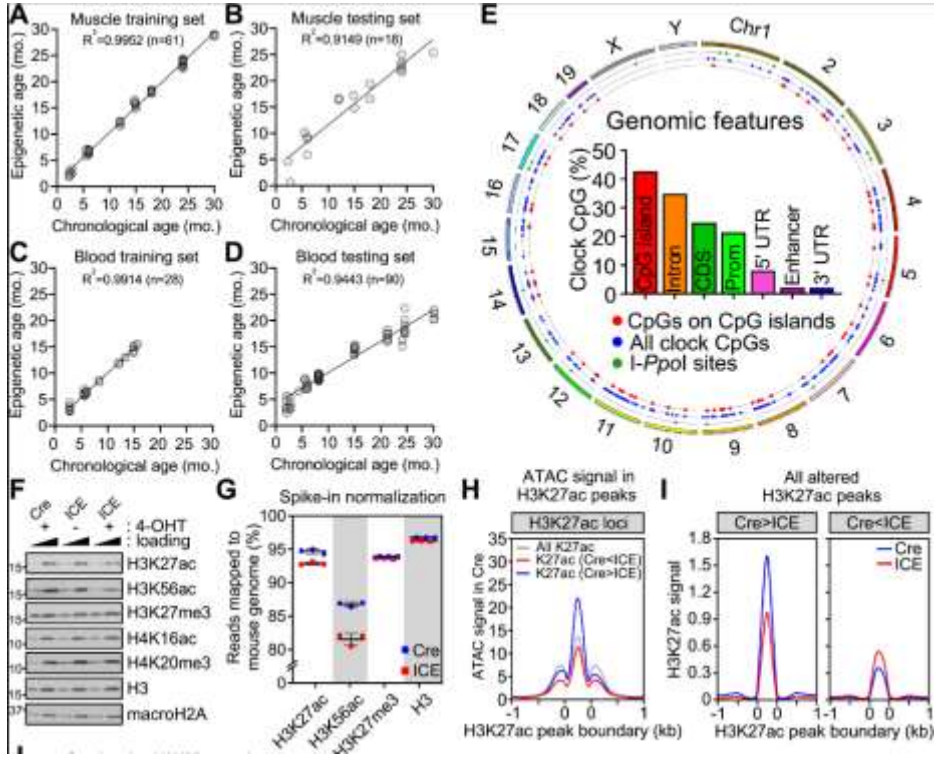
Source: https://www.broadinstitute.org/news/new-technique-expands-cells-sequence-dna-and-capture-fine-structural-details

Information Theory: David Sinclair Argues That it's the Body's Response to DNA Damage That Causes Aging – Not the Damage Itself

Yang JH et al., "Loss of epigenetic information as a cause of mammalian aging," *Cell,* Jan 19, 2023;35(3):19;186(2):305-326.e27.

David Sinclair and colleagues developed a novel "ICE" (Inducible Changes to the Epigenome) system in mice to test whether erasure or disruption of epigenetic information itself can cause aging rather than merely accompany it. By inducing double-strand DNA breaks (DSBs) at frequencies mimicking chronic physiological damage (but avoiding gene-coding regions), they observed that chromatin-modifying proteins became mislocalized from their canonical positions to sites of damage, leading to an erosion of chromatin organization, a collapse of heterochromatin, transcriptional de-differentiation, accumulation of senescent cells, activation of the DNA-methylation aging clock, and early onset of aging phenotypes (metabolic decline, cognitive impairment, organ dysfunction) in otherwise healthy mice. These results support the "information theory of aging" by showing that loss of epigenetic fidelity is sufficient to drive aging in mammals.

Crucially, the authors further demonstrated that this induced aging process can be reversed by transient expression of Yamanaka factors (OSK: Oct4, Sox2, Klf4) in vivo without erasing cellular identity. OSK expression restored youthful chromatin marks, suppressed aging-associated transcriptional drift, improved tissue and organ function, and extended lifespan in the ICE mice. The work thus positions epigenetic information loss not just as a correlator but as a potentially causal and reversible hallmark of aging, offering strong mechanistic support for interventions targeting chromatin state and epigenetic plasticity as longevity strategies.



(A–D) Muscle and blood training (A and C) and testing sets (B and D) of the clock CpG sites in WT C57BL/6J mice. (E) Circos plot of genomic locations of I-*Ppo*I cut sites (green), clock GpG sites in CpG islands (red), and all muscle clock sites (blue). (F) Western blotting for histone modifications in 96-h post-treated ICE cells. Histone H3 and macroH2A serve as loading and internal controls. (G) Spike-in normalization of ChIP-seq data. (H) ATAC signal in loci with altered H3K27ac peaks. (I) Aggregation plots of H3K27ac signal in H3K27ac changed regions (padj ‹ 0.01).

See: https://www.cell.com/cell/fulltext/S0092-8674(22)01570-7, https://hms.harvard.edu/news/loss-epigenetic-information-can-drive-aging-restoration-can-reverse

Teefy / Benayoun Critique Sinclair's Information Theory of Aging Based on the ICE Mouse

Teefy BB, Benayoun BA, "Putting aging on ICE," *Cell Metabolism,* Mar 7, 2023;35(3):383-385.

A recent report by Yang et al. in *Cell* demonstrates that faithful DNA double-strand breaks and repair cycles phenocopy many aspects of aging in mice. Whether this progeroid phenotype is caused by a loss of epigenetic information remains to be conclusively determined.

A recent paper by Yang and colleagues2 attempts to test a unifying theory of aging, dubbed the "information theory of aging." Central to this theory is the notion that cellular identity is determined by a precise epigenomic landscape. As a by-product of cellular metabolism and exposure to external insults, DNA damage inevitably accumulates with time. Repair of DNA damage is coordinated by chromatin modifiers, which also play a key role in maintaining cellular epigenomes and, thus, cell identity. Based on this theory, the repeated relocalization of chromatin modifiers to DNA-damage sites over a lifetime leads to progressive loss of epigenomic identity, ultimately manifesting in what we know as aging at the organismal level. Crucially, the theory distinguishes itself from prior DNA-based theories of aging in that it posits that the loss of epigenomic, rather than genomic, information is the primary driver of aging.

In order to test this theory, the authors use a mouse model expected to scramble epigenetic information while keeping genetic information intact, dubbed ICE for inducible changes to the epigenome.2 In this model, mice carry 2 transgenes: (1) a ubiquitously expressed Cre recombinase localizing to the nucleus upon exposure to tamoxifen (TAM) and (2) a TAM-stabilized and nuclear-localized I-PpoI endonuclease fusion protein transgene at the Rosa26 locus, which can only be expressed once an upstream floxed stop cassette is excised by Cre. Using this system, transgenic mouse cells exposed to TAM should inducibly express nuclear I-PpoI, which can cut 20 unique canonical sites in the mouse genome. To note, one of these sites is located within the 28S rDNA sequence, of which mice carry hundreds of genomic copies.3 Since using I-PpoI to induce double-stranded DNA breaks (DSBs) should create "sticky" 4-bp overhangs, these DSBs are expected to have low mutagenic potential.

This study makes a convincing case that the ICE model leads to accelerated organismal aging, suggesting that high mutational load after DSBs is not a necessary intermediate for progeroid effects of genomic instability.

However, the notion that progeroid phenotypes are only directly mediated by observed changes to the epigenome (the so-called information theory of aging) is not directly tested in this study. Importantly, the type of system used in this study (inducible nuclear localization of a restriction enzyme like I-PpoI or SacI) robustly induces the DNA-damage response and P53 signaling, which can lead to cell senescence. To note, senescent cells secrete a panoply of pro-inflammatory factors, leading to a deleterious state of chronic sterile inflammation that can drive aspects of aging. This study identified increased senescence markers in ICE cells, suggesting that the secretory impact of senescent cells in the ICE model may need to be accounted for. Interestingly, transient nuclear localization of I-PpoI in mouse epidermal stem cells was recently found to promote selective elimination of damaged stem cells through differentiation.

Although stem cell niches were not directly queried in this study, loss of adult stem cell populations by ICE activation-mediated attrition could explain a number of age-related phenotypes in ICE mice and can be addressed in future studies with single-cell technologies. In summary, additional evidence will be required to prove or disprove the information theory of aging. However, this study provided the field with a new model, whereby a short organism-wide burst of DSBs in adulthood can have a long-term detrimental impact on mice that resembles aging.

Source: https://www.cell.com/cell-metabolism/fulltext/S1550-4131(23)00048-7

Further Thoughts on the Information Theory of Aging

There is a lot to like about the information theory of aging. The notion that the epigenetic response to double-stranded breaks (DSB)'s in DNA is interesting and appears to rationalize the observations that some organisms with high numbers of DSB's survive a long time.

This is sort of like the story of the Nixon Administration and Watergate. It wasn't the crime that was the problem. It was the coverup that got Nixon in the end.

The results from the Yang et al. (2023) paper are indeed interesting showing that epigenetic alterations are clearly related to aging in the ICE mouse even when DNA breaks do not happen in coding regions

There are several things that make this Sinclair story beguiling. First, the Yamanaka reprogramming approach is *so much more* appealing if you buy the information theory idea. The reason is that Yamanaka reprogramming directly restores the prior epigenetic state of a cell. Sinclair likens it to reinstalling the backup of the original epigenetic state of the cell. It all just fits and makes sense. Second, the theory also explains the strong correlation between chronological age and epigenetic methylations patterns found in aging clock literature.

On the other hand, appealing or not, it's hard to buy this theory. Consider these points:

1. Teefy/Benayoun's critique is quite devastating. They point out that because the non-coding DSB's created in the ICE mouse can induce senescence that it may not be epigenetics at all that create aging in this mouse.
2. A related critique of the paper by Timmons and Brenner (2024) notes that the I-PpoI mechanism used in the Yang et al. paper is well-known to be genotoxic.
3. This is highly problematic because it means that so-called DSB's in non-coding regions could easily lead to an aging type response. Timmons and Brenner write: "Nondisclosure of papers showing the genotoxic and cytotoxic mechanism of I-PpoI is a problem. Had these papers been cited, one would expect reviewers to ask for data examining p53 induction and cell elimination at time points within the first month after tamoxifen removal."
4. Timmons and Brenner are particularly skeptical about the claims that OSK rejuvenation can restore the "backup" of the correct epigenome, writing: "Their discussion concluded that 'fortunately, it is now apparent that mammals retain a back-up copy of youthful epigenetic information that can safely restore the function of old tissues, akin to reinstalling software.' However, the paper showed no data on functional rejuvenation due to OSK treatment. Figure 7S shows the effect on the eyes of the tamoxifen-induced I-PpoI: the eyes are opaque in the I-PpoI mice but there was no functional characterization of OSK-treated iDSB mice. The Cell paper does not document any old tissue with restored function in any mouse and no data in support of restoring function were provided by Dr. Sinclair when requested. Given their related manuscripts not being cited and appropriately cross-referenced, the issues around I-PpoI-induced cell death, and lack of demonstration of the major claims of the paper, we remain concerned about the validity of the published *Cell* paper."
5. As for the clock literature, we later show that these models are *not good* predictors of mortality at all. In a way, this is quite a powerful critique of all epigenetic alteration stories as we argue in this report that real world predictors of age should give us insight into underlying biology.
6. The Bowhead whale story in this section is quite a powerful one. The Bowhead Whale gets plenty of DNA breaks but is really good at repairing them. If you bought the Sinclair story that whale should have a short life. The mole rat story is similar. While the rat gets plenty of DSB's it can repair them super well due to a reverse cGAS mechanism (relative to us humans).
7. A recent 2023 review of the DNA damage theory point to both DNA damage and associated epigenetic alterations as clear contributors to aging. The reviewers are fully aware of Sinclair's work and note over a half dozen papers that convincingly point to DNA damage as a central cause of aging.

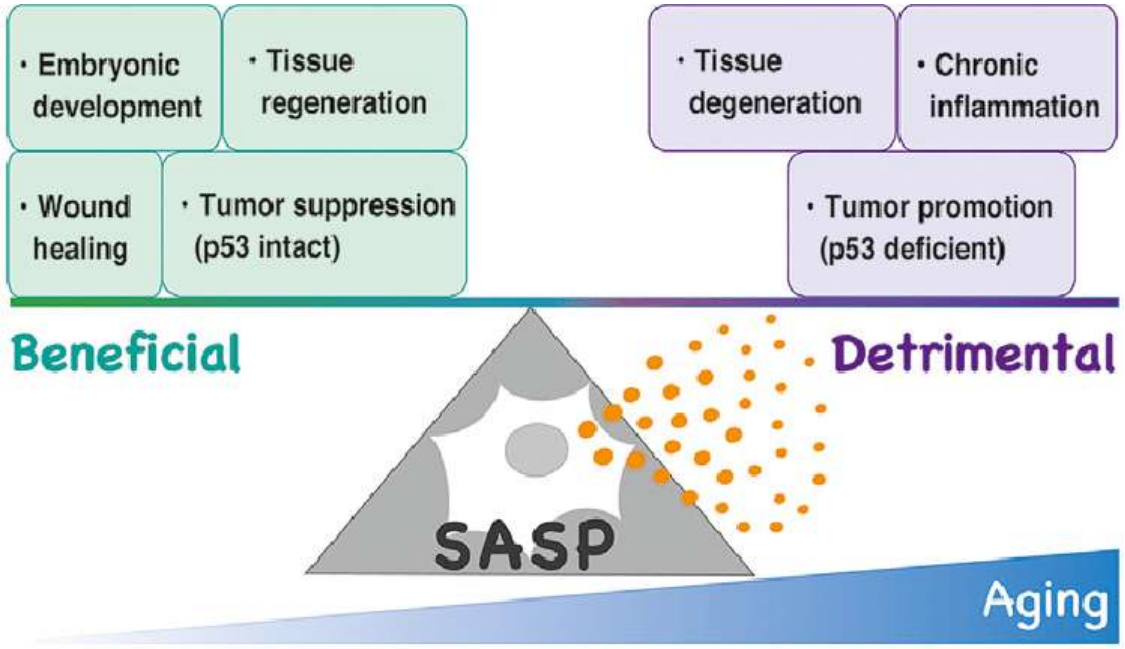
Point Nine:

Strong Evidence Supports the Idea that Cell Senescence Drives Aging

Senescent Cells are Linked to Age-Related Disease

Definition

Senescent cells are non-dividing cells that can secrete high levels of inflammatory cytokines, immune modulators, growth factors, and proteases



Concept of SASP

- Cells that have stopped dividing and are no longer functioning properly but have not undergone programmed cell death (apoptosis).
- Can accumulate over time and contribute to aging and age-related diseases by secreting inflammatory and tissue-degrading molecules, a phenomenon known as the senescence-associated secretory phenotype (SASP).

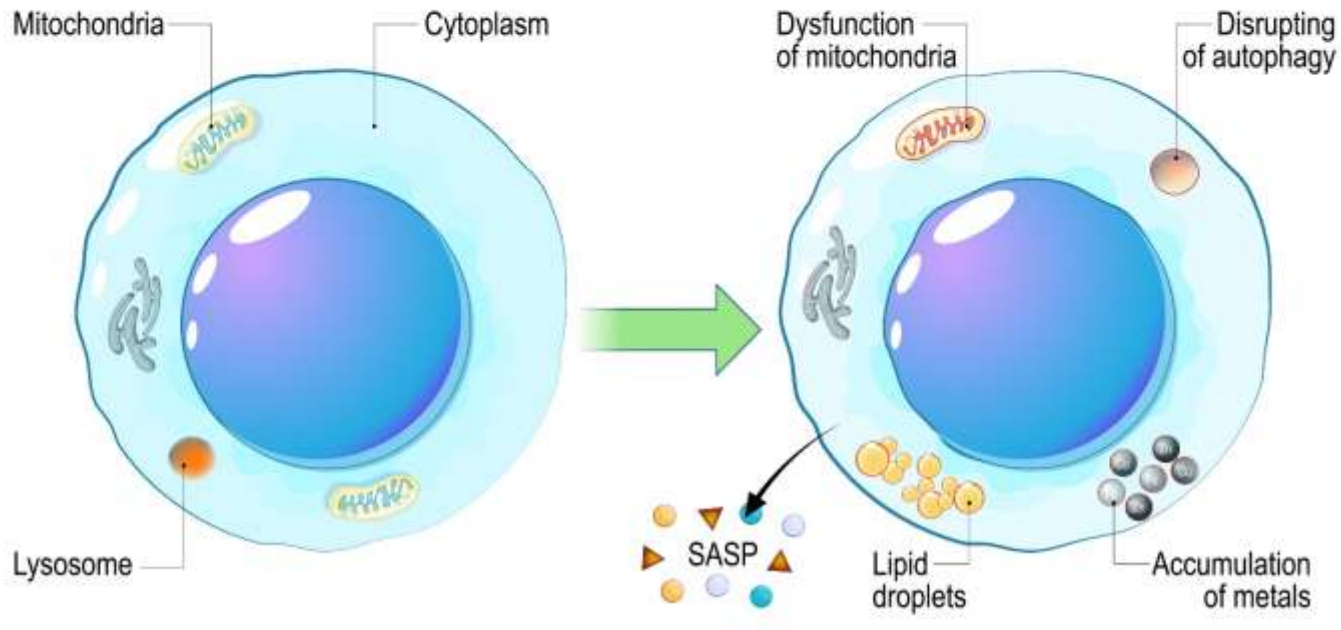
Associated Age-Related Diseases

- Cancer
- Osteoporosis and Osteoarthritis
- Cardiovascular Disease
- Covid-19 Severity in Older Adults
- Liver and Kidney Diseases
- Ocular Diseases

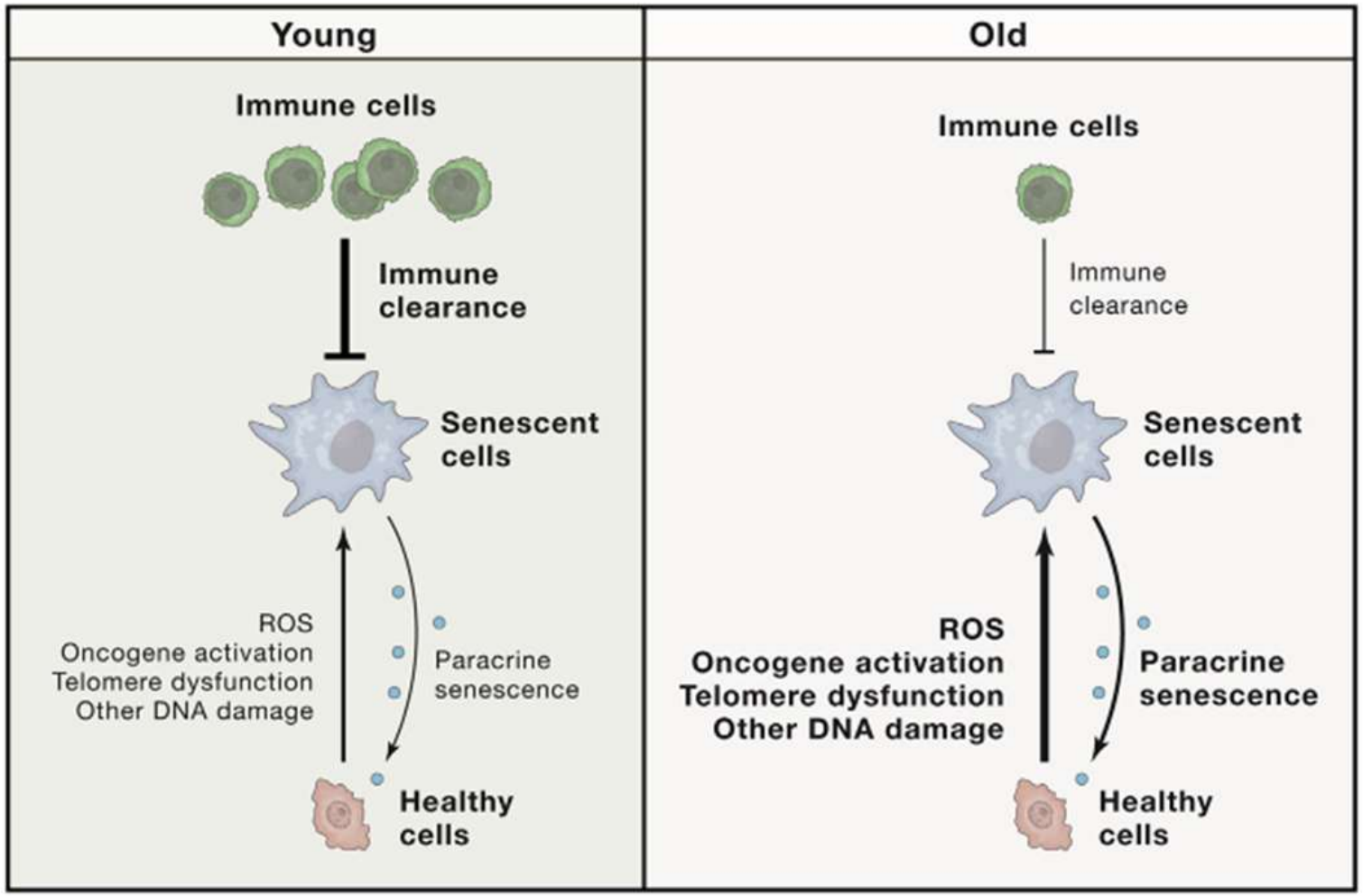
Cell Senescence

A senescent cell ceases to replicate, is characterized by disrupted autophagy, mitochondrial disruption and release of secretory proteins (SASP)

Senescent Cells Characterized by Dysfunctional Mitochondria



Senescent Cell Accumulation Triggered by Oxidative Stress and in Aging Can Impact Healthy Cells



Younger organisms are able to use the immune system to remove senescent cells while older organisms struggle to remove such cells. These cells release various markers that enhance the damage from ROS, oncogene activation and DNA damage.

Sources:

https://pubmed.ncbi.nlm.nih.gov/24138928/
https://www.nature.com/articles/s41576-018-0004-3

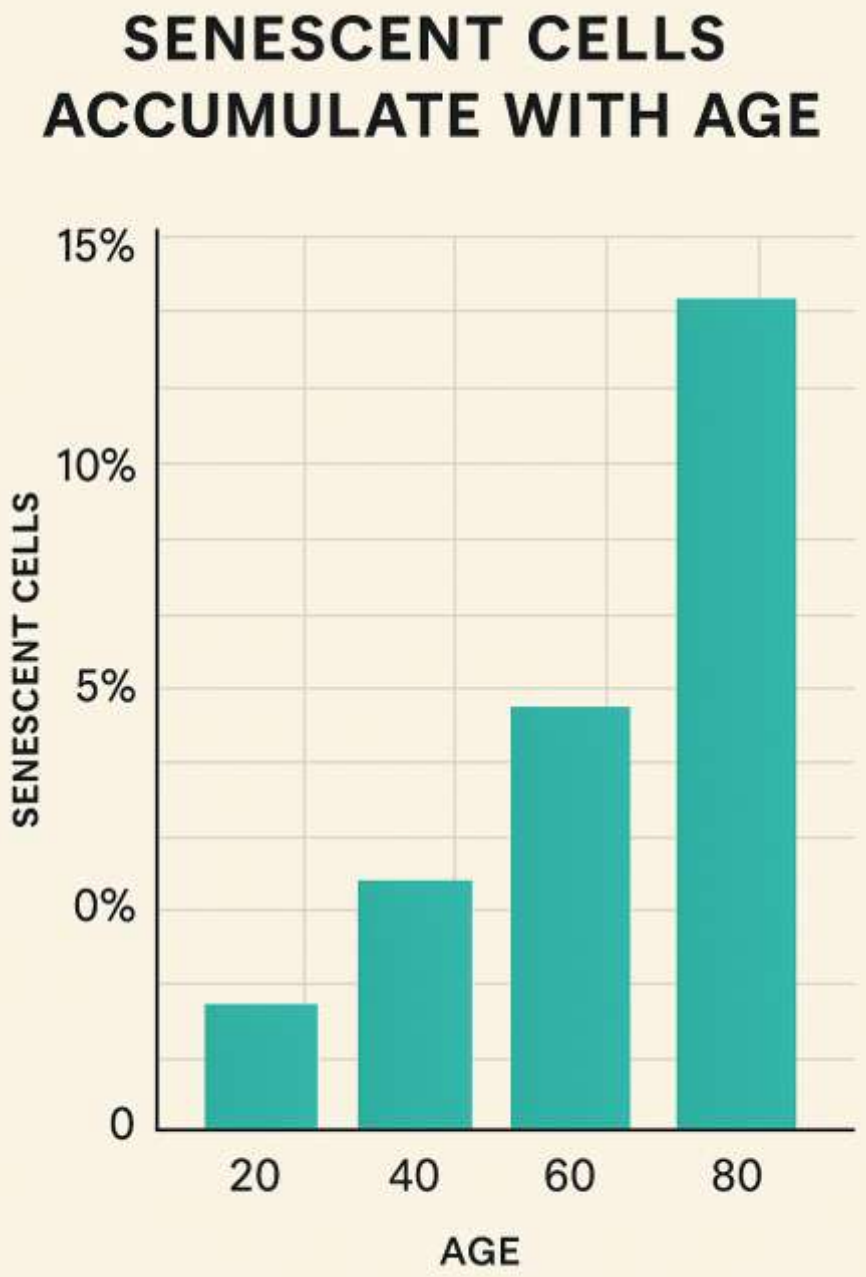
Senescent Cells Accumulate with Age

Dimri et al., 1995 (PNAS)
The key study showing senescence-associated β-galactosidase (SA-β-gal) activity in aged human skin fibroblasts and epidermis. Senescent fibroblasts increased from ~1–3% in young adults to >15% in elderly skin. This provided the first in vivo evidence that senescent cells accumulate with chronological age. (link)

Herbig et al., 2006 (Aging Cell)
Using p16^INK4a and γH2AX staining, they demonstrated that senescent fibroblasts and keratinocytes increase in human dermis with age, showing persistent DNA-damage foci and telomere dysfunction. Quantified senescent-cell markers rose sharply after age 60, independent of photoaging. (link)

Jeyapalan et al., 2008 (Mech Ageing Dev)
Extended these findings to non-skin tissues (liver, kidney, lung, vascular wall), confirming that senescence markers (p16^INK4a, SA-β-gal) increase with age in multiple organs.

Coppé et al., 2011 (Journal of Biological Chemistry)
Found that p16^INK4a expression increases exponentially with age in human T cells and skin. This became one of the most robust molecular correlates of chronological age. Showed that cell senescence as measured by this marker is independent of SASP. (link)



Diverse Stimuli Trigger Senescence

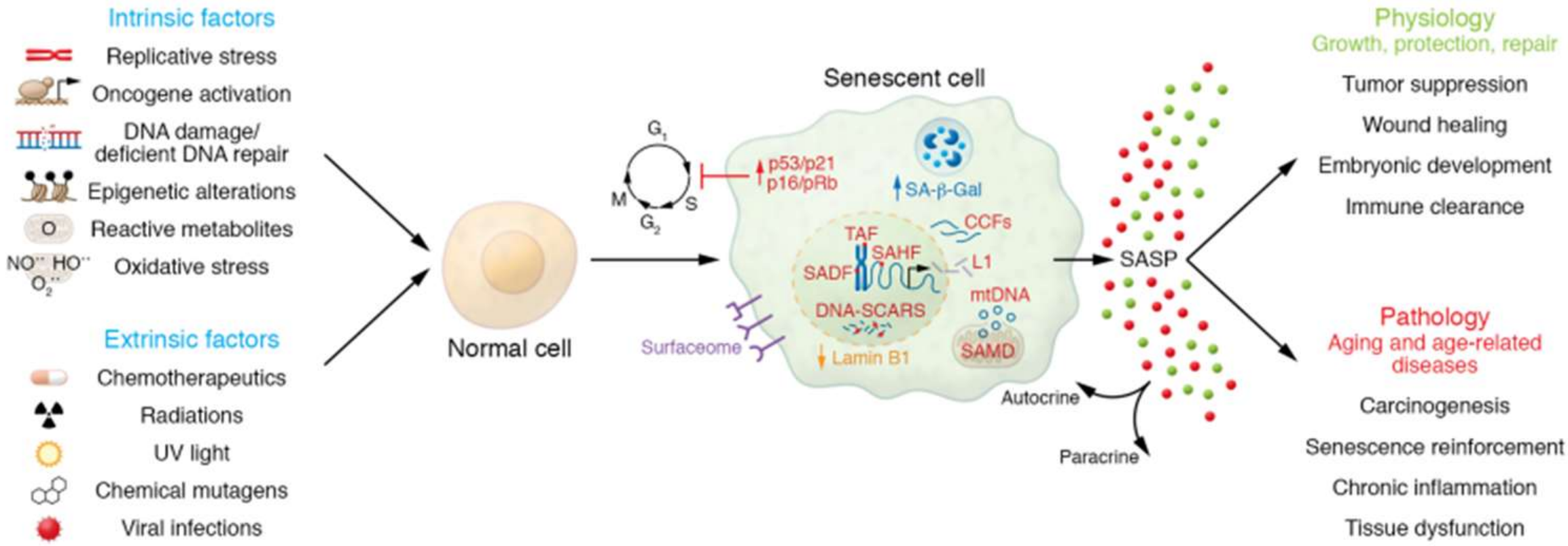
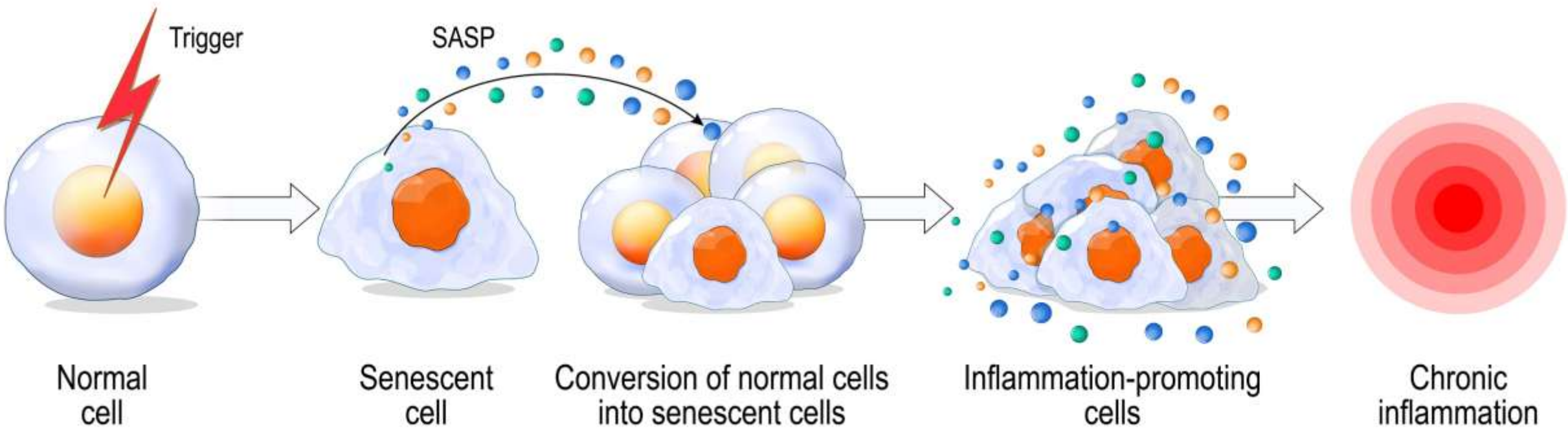


Figure 1. Diverse stress stimuli can induce cellular senescence and lead to generation of senescent cells, which play pleiotropic roles in both physiology and pathology. CCF, cytoplasmic chromatin fragment; DNA-SCARS, DNA segments with chromatin alterations reinforcing senescence; mtDNA, mitochondrial DNA; SADF, senescence-associated DNA damage foci; SAHF, senescence-associated heterochromatin foci; SAMD, senescence-associated mitochondrial dysfunction; SASP, senescence-associated secretory phenotype; TAF, telomere-associated foci.

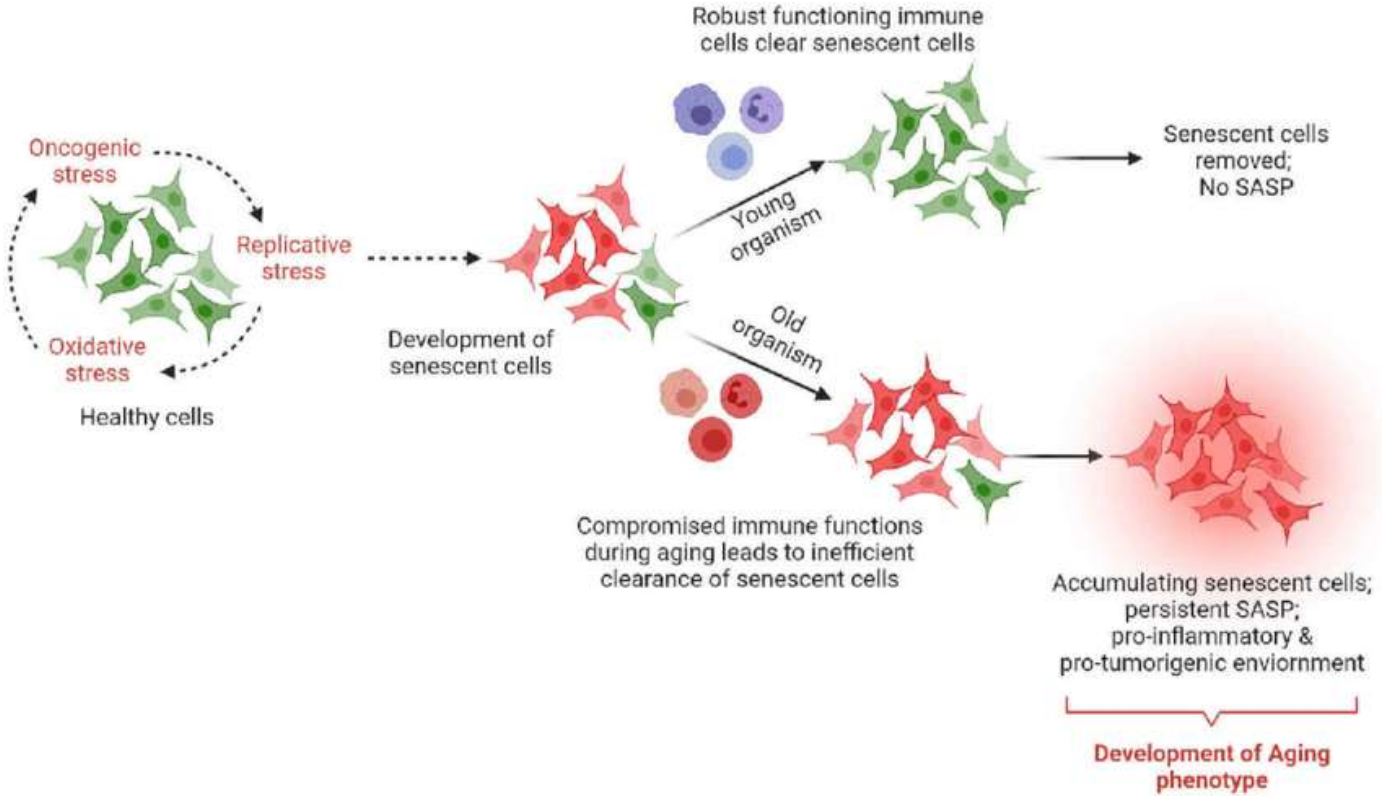
See: https://pubmed.ncbi.nlm.nih.gov/24138928/, https://www.nature.com/articles/s41576-018-0004-3

Senescent Cells Self-Propagate and Spread Inflammation

Senescent Cells Spread and Contribute to Chronic Inflammation



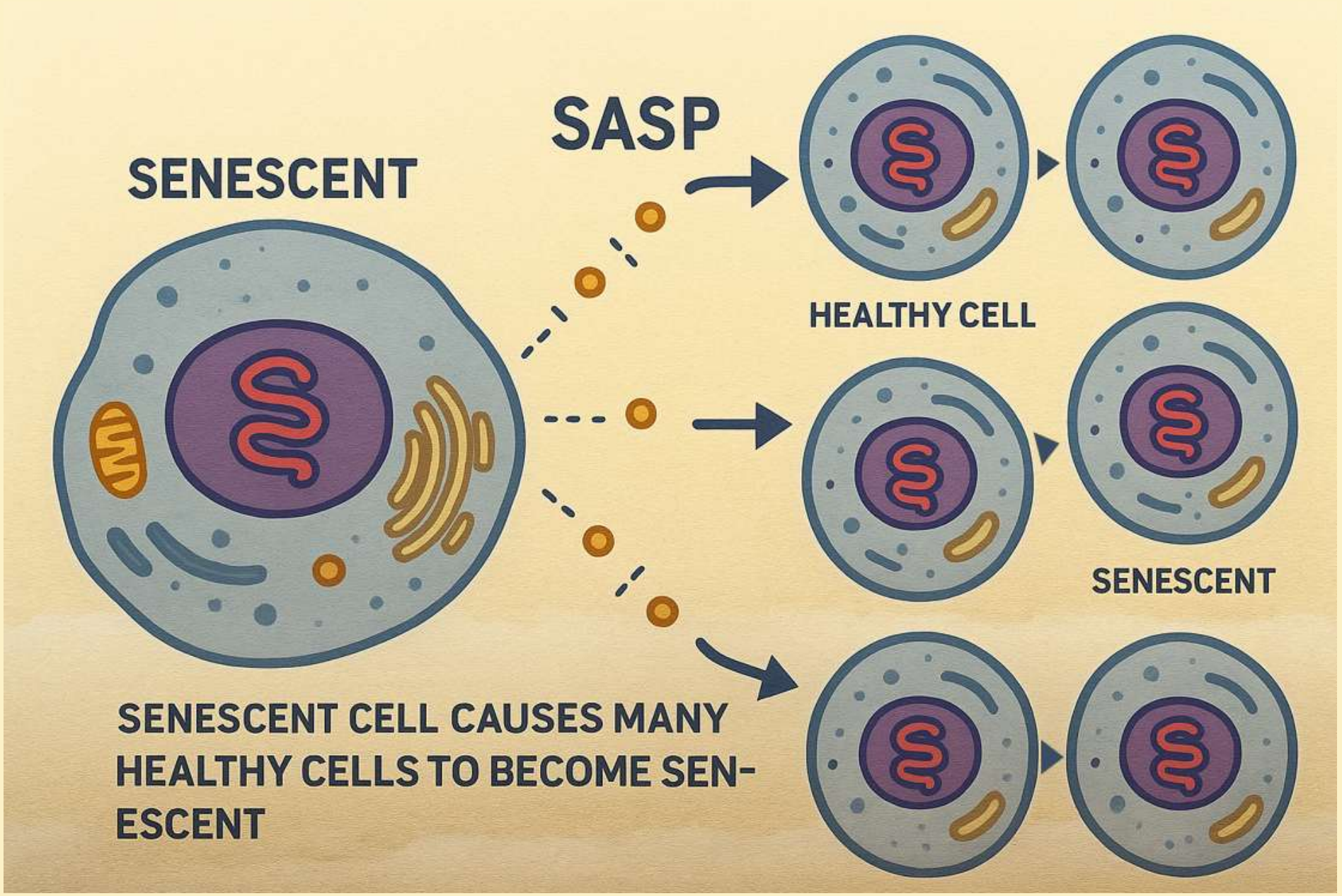
Aging Phenotype Characterized by Persistent Inflammatory Environment with Many Senescent Cells



Schematic illustration of the development and accumulation of senescent cells in mammals. Chronic exposure to intrinsic and extrinsic cellular stressors initiates cell cycle arrest and the development of senescent cells which are recognized and removed by immune cells in younger organisms. During aging, impaired immunosurveillance and related functions of the immune cells result in inefficient clearance of the senescent cells leading to their gradual accumulation. The resulting SASP of senescent cells creates a pro-tumorigenic and pro-inflammatory environment that confers deleterious bystander effects on nearby healthier cells thereby promoting tissue dysfunction and predisposition to inflammatory disorders characteristic of aging.

Source: https://www.researchgate.net/figure/Schematic-illustration-of-the-development-and-accumulation-of-senescent-cells-in-mammals_fig1_359919452

SASP from Senescent Cells Converts Healthy Cells to Senescent Cells



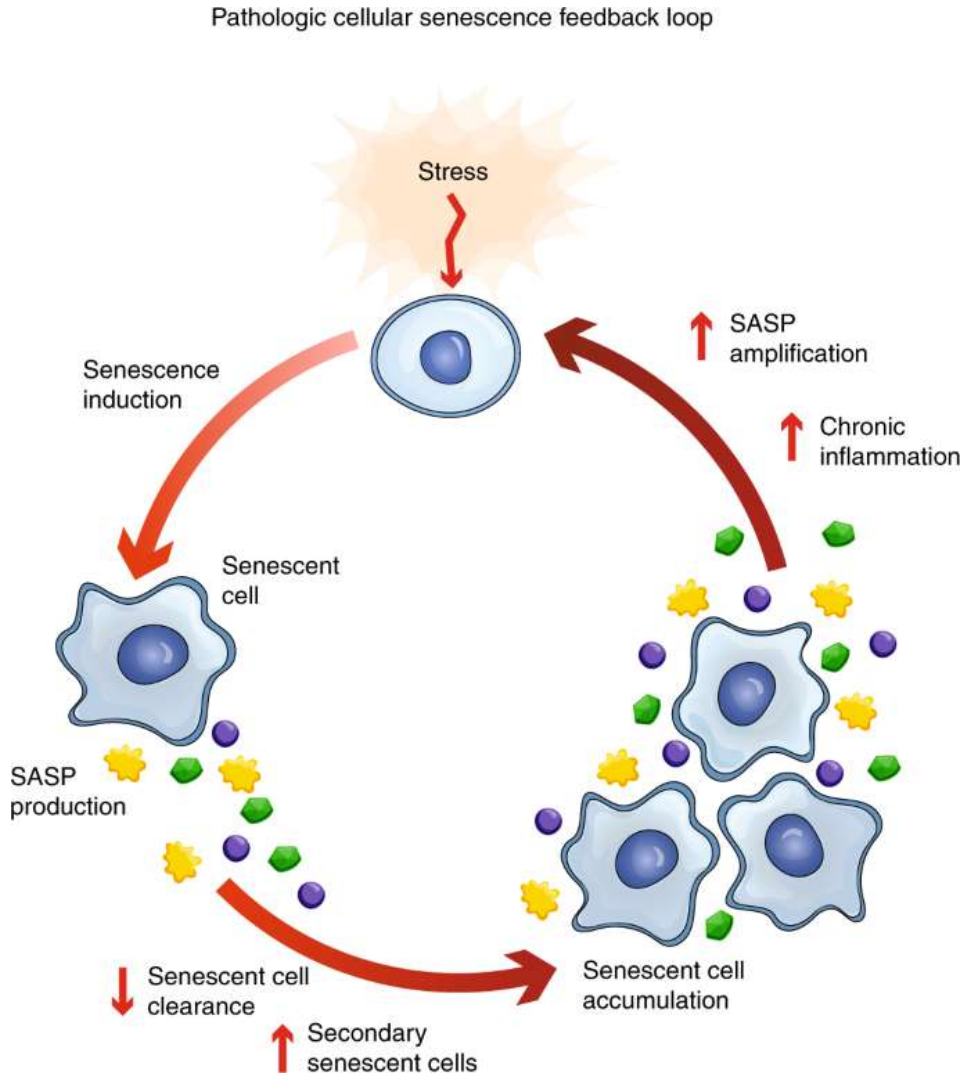
Senescent Cells Negatively Impact the Cellular Environment

Senescent cells secrete a variety of pro-inflammatory cytokines, chemokines, proteases, and growth factors, collectively known as the SASP. The SASP can have several effects on the cellular environment:

Inflammation: Chronic inflammation due to the SASP can lead to tissue dysfunction and promote diseases such as arthritis and atherosclerosis.

Altered Tissue Microenvironment: SASP factors can degrade the extracellular matrix, impacting tissue structure and function.

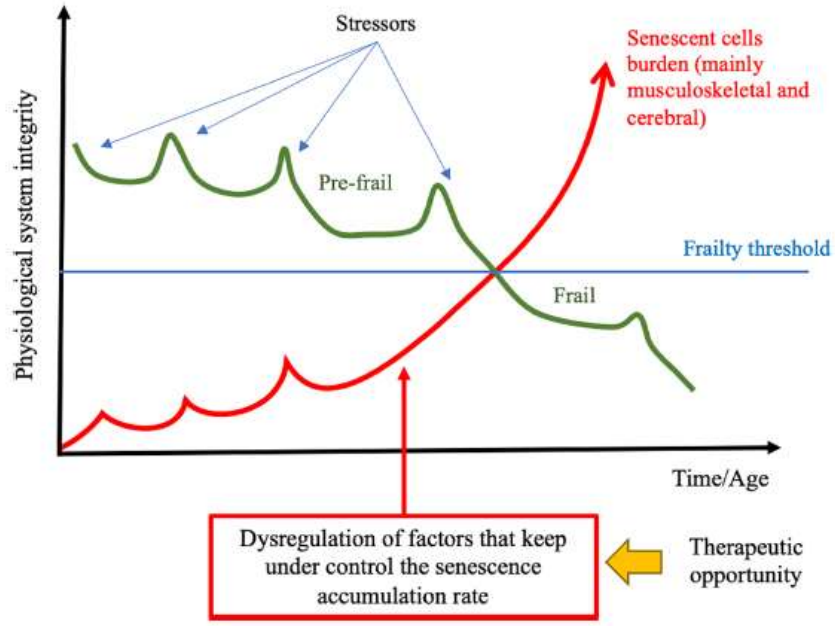
Stem Cell Function: SASP can negatively affect stem cell niches, impairing tissue regeneration and repair.



Senescent Cells Associated with Frailty

Marcozzi S, Bigossi G, Giuliani ME, Giacconi R, Piacenza F, Cardelli M, Brunetti D, Segala A, Valerio A, Nisoli E, Lattanzio F, Provinciali M, Malavolta M., "Cellular senescence and frailty: a comprehensive insight into the causal links," *Geroscience*. Dec 2023; 45(6):3267-3305.

Senescent cells may have a prominent role in driving inflammation and frailty. The impact of cellular senescence on frailty varies depending on the assessment tool used, as it is influenced by the criteria or items predominantly affected by senescent cells and the varying weights assigned to these items across different health domains. To address this challenge, we undertook a thorough review of all available studies involving gain- or loss-of-function experiments as well as interventions targeting senescent cells, focusing our attention on those studies that examined outcomes based on the individual frailty phenotype criteria or specific items used to calculate two human (35 and 70 items) and one mouse (31 items) frailty indexes. Based on the calculation of a simple "evidence score," we found that the burden of senescent cells related to musculoskeletal and cerebral health has the strongest causal link to frailty. We deem that insight into these mechanisms may not only contribute to clarifying the role of cellular senescence in frailty but could additionally provide multiple therapeutic opportunities to help the future development of a desirable personalized therapy in these extremely heterogeneous patients.

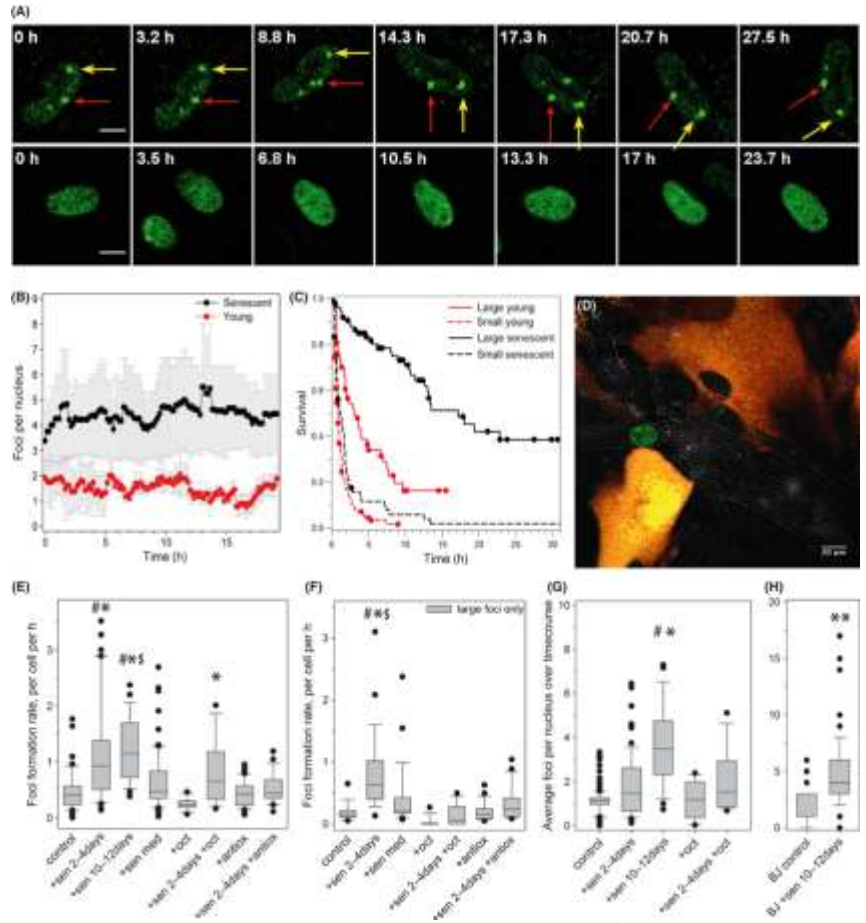


Source: https://link.springer.com/article/10.1007/s11357-023-00960-w

Senescent Cell Bystander Effect Doesn't Work Just Through SASP

Nelson G, Wordsworth J, Wang C, Jurk D, Lawless C, Martin-Ruiz C, von Zglinicki T. A senescent cell bystander effect: senescence-induced senescence. Aging Cell. 2012 Apr;11(2):345-9.

Senescent cells produce and secrete various bioactive molecules including interleukins, growth factors, matrix-degrading enzymes and reactive oxygen species (ROS). Thus, it has been proposed that senescent cells can damage their local environment, and a stimulatory effect on tumour cell growth and invasiveness has been documented. However, it was unknown what effect, if any, senescent cells have on their normal, proliferation-competent counterparts. We show here that senescent cells induce a DNA damage response, characteristic for senescence, in neighbouring cells via gap junction-mediated cell–cell contact and processes involving ROS. Continuous exposure to senescent cells induced cell senescence in intact bystander fibroblasts. Hepatocytes bearing senescence markers clustered together in mice livers. Thus, senescent cells can induce a bystander effect, spreading senescence towards their neighbours *in vitro* and, possibly, *in vivo*.



Senescent founder cells induce a senescence-like DDR in bystander cells. (A) Representative images of 53BP1 reporter fluorescence in a senescent (top) or young (bottom) MRC5 cell nucleus with time. Yellow and red arrows indicate two large foci that remain stable over › 27.5 h in the senescent cell. Images are compressed z stacks over 4.5 μm to capture the entire nuclear volume. (B) Mean 53BP1 foci frequencies over time in proliferating (red) and senescent (black) MRC5 cells. Data are mean ± SD of at least 25 nuclei, from three independent experiments. (C) Kaplan–Meier survival curves (censored data) for large (solid lines) and small (dotted lines) 53BP1 foci in proliferating (red) and senescent (black) MRC5 fibroblasts. Foci numbers are 202 (young) and 138 (senescent) from two independent experiments.

Source: https://onlinelibrary.wiley.com/doi/10.1111/j.1474-9726.2012.00795.x

Senescent Cells Associated with Mortality and Disease

Nathan Basisty et al., The Buck Institute for Aging Research, A proteomic atlas of senescence-associated secretomes for aging biomarker development, *PLoS Biol.* 2020 Jan; 18(1): e3000599.

Aging phenotype is associated with cellular senescence. Cellular senescence is a complex stress response that causes an essentially irreversible arrest of cell proliferation and development of a multicomponent senescence-associated secretory phenotype (SASP).

The SASP consists of a myriad of cytokines, chemokines (CXCLs), growth factors, and proteases that initiate inflammation, wound healing, and growth responses in nearby cells. In young healthy tissues, the SASP is typically transient and tends to contribute to the preservation or restoration of tissue homeostasis. However, senescent cells increase with age, and a chronic SASP is known or suspected to be a key driver of many pathological hallmarks of aging, including chronic inflammation, tumorigenesis, and impaired stem cell renewal.

Data from several laboratories, including our own, strongly support the idea that senescent cells and the SASP drive multiple age-related phenotypes and pathologies, including atherosclerosis, osteoarthritis, cancer metastasis, cardiac dysfunction, myeloid skewing, kidney dysfunction, and overall decrements in health span…

In this study, we demonstrate that the SASP is not a single phenotype but rather is highly complex, dynamic, and dependent on the senescence inducer and cell type.

Source: https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3000599

João Passos: Mitochondrial Damage Can Trigger Senescence

The FEBS Journal

FEBS PRESS science publishing by scientists

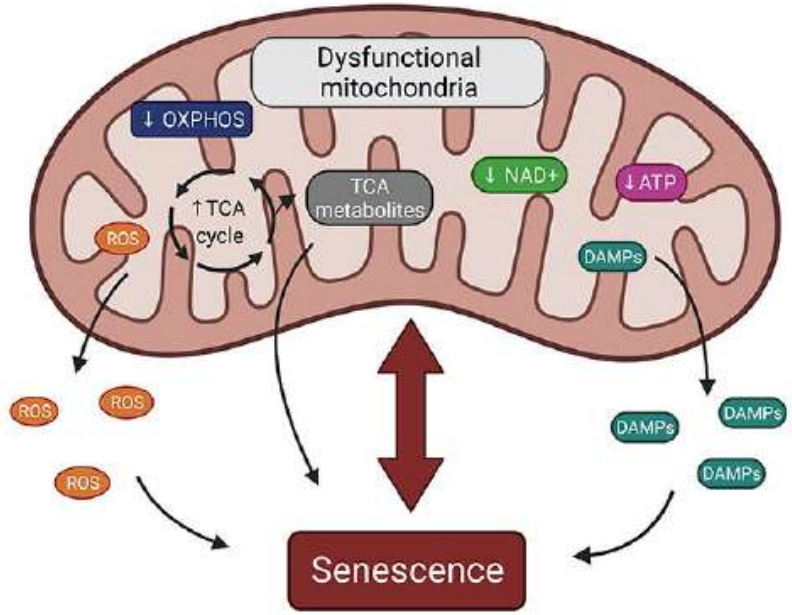
REVIEW

The FEBS Journal 290 (2023) 1186–1202

Cellular senescence: all roads lead to mitochondria

Hélène Martini[1,2] and João F. Passos[1,2]

1 Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN, USA
2 Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, MN, USA



Mitochondria play a central role in the development of cellular senescence. Senescence is characterized by several mitochondrial functional changes such as a decrease in OXPHOS, reduced levels of NAD+ and ATP and accumulation of TCA cycle metabolites, DAMPs, and ROS. Here, we provide an overview of the recent findings demonstrating how these mitochondrial changes can contribute to the senescence-associated growth arrest and the SASP.

Senescence is a multi-functional cell fate, characterized by an irreversible cell-cycle arrest and a pro-inflammatory phenotype, commonly known as the senescence-associated secretory phenotype (SASP). Emerging evidence indicates that accumulation of senescent cells in multiple tissues drives tissue dysfunction and several age-related conditions. This has spurred the academic community and industry to identify new therapeutic interventions targeting this process. Mitochondrial dysfunction is an often-unappreciated hallmark of cellular senescence which plays important roles not only in the senescence growth arrest but also in the development of the SASP and resistance to cell-death. Here, we review the evidence that supports a role for mitochondria in the development of senescence and describe the under-lying mechanisms. Finally, we propose that a detailed road map of mitochondrial biology in senescence will be crucial to guide the future development of senotherapies.

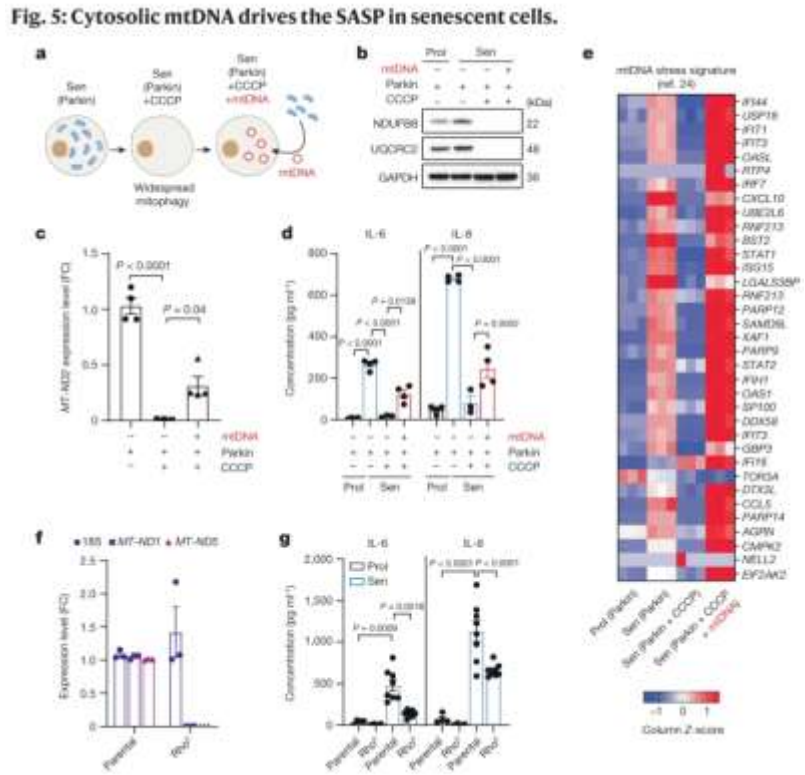
Release of Mitochondrial DNA When Cells Undergo Apoptotic Stress Triggers SASP Release

Victorelli S, Salmonowicz H, Chapman J, Martini H, Vizioli MG, Riley JS, Cloix C, Hall-Younger E, Machado Espindola-Netto J, Jurk D, Lagnado AB, Sales Gomez L, Farr JN, Saul D, Reed R, Kelly G, Eppard M, Greaves LC, Dou Z, Pirius N, Szczepanowska K, Porritt RA, Huang H, Huang TY, Mann DA, Masuda CA, Khosla S, Dai H, Kaufmann SH, Zacharioudakis E, Gavathiotis E, LeBrasseur NK, Lei X, Sainz AG, Korolchuk VI, Adams PD, Shadel GS, Tait SWG, Passos JF., "Apoptotic stress causes mtDNA release during senescence and drives the SASP," *Nature, October* 2023; 622(7983):627-636.

"Senescent cells drive age-related tissue dysfunction partially through the induction of a chronic senescence-associated secretory phenotype (SASP). Mitochondria are major regulators of the SASP; however, the underlying mechanisms have not been elucidated. Mitochondria are often essential for apoptosis, a cell fate distinct from cellular senescence. During apoptosis, widespread mitochondrial outer membrane permeabilization (MOMP) commits a cell to die.

Here we find that MOMP occurring in a subset of mitochondria is a feature of cellular senescence. This process, called minority MOMP (miMOMP), requires BAX and BAK macropores enabling the release of mitochondrial DNA (mtDNA) into the cytosol. Cytosolic mtDNA in turn activates the cGAS-STING pathway, a major regulator of the SASP. We find that inhibition of MOMP in vivo decreases inflammatory markers and improves healthspan in aged mice.

Our results reveal that apoptosis and senescence are regulated by similar mitochondria-dependent mechanisms and that sublethal mitochondrial apoptotic stress is a major driver of the SASP. We provide proof-of-concept that inhibition of miMOMP-induced inflammation may be a therapeutic route to improve healthspan."



Source: https://www.nature.com/articles/s41586-023-06621-4

Communication with João Passos in 2025

The two papers shown thus far indicate that mitochondrial stress is a *sufficient* condition to trigger release of SASP proteins.

In forthcoming work Dr. Passos and colleagues at the Mayo Clinic will show that mitochondrial stress is also a necessary condition for the release of SASP proteins.

This is quite an important point: the negative aging effects of SASP are triggered by mitochondrial damage in the first place.

This points to mitochondrial respiration and associated stress in time as the central cause of cell stress and the associated senescent phenotype.

Point Ten:

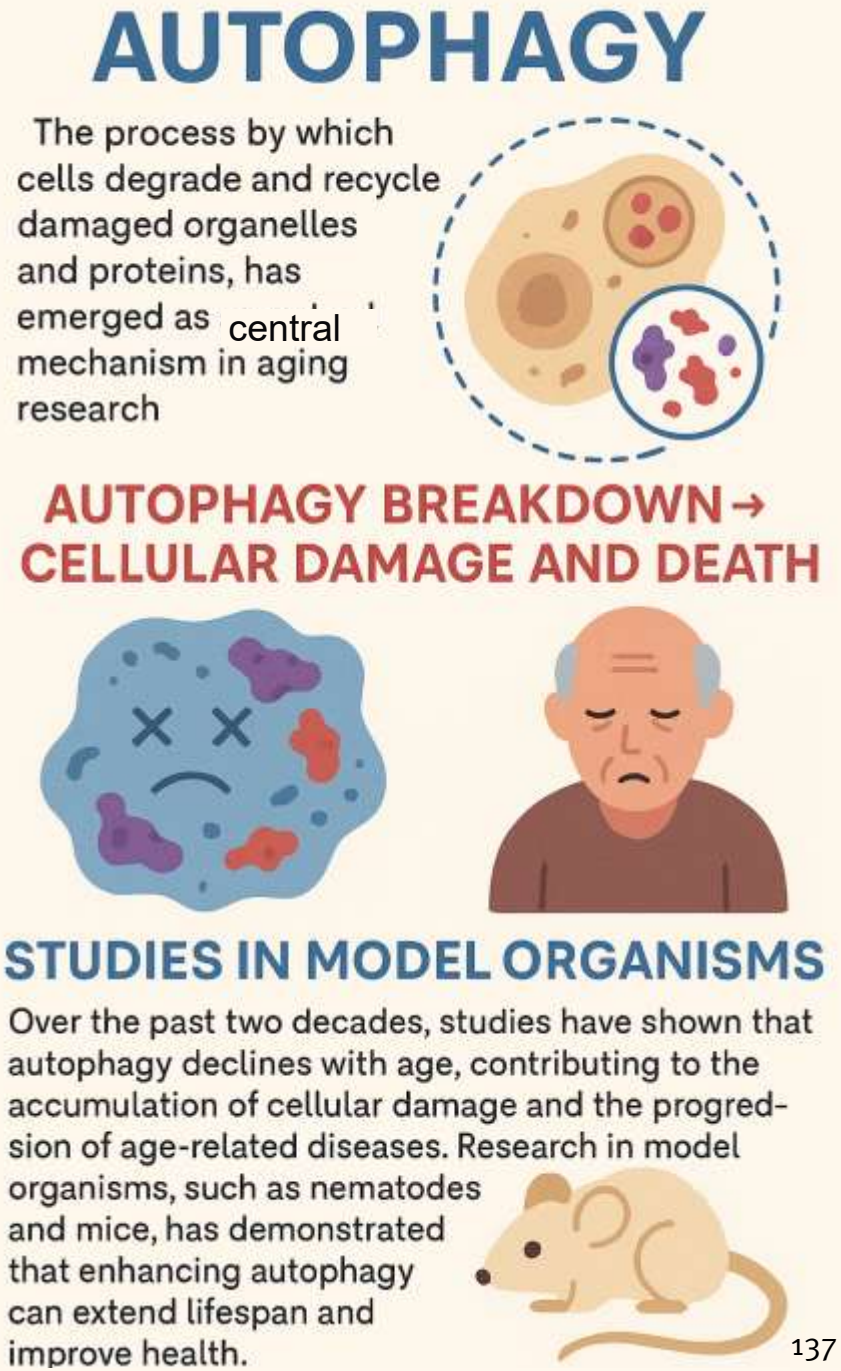
Breakdown in Autophagy is an Important Driver of Aging

We believe that autophagy is not an independent driver of aging but rather is mainly a byproduct of mitochondrial and cell damage.

Autophagy is a Key Cell Process Involved in Aging

Autophagy is a fundamental cellular process that acts as the body's internal recycling system, allowing cells to degrade and reuse damaged organelles, misfolded proteins, and other unwanted components. Think of this as the cell's natural vacuum cleaner. Through a sequence of tightly regulated steps, autophagy maintains cellular homeostasis by enclosing defective materials in double-membraned vesicles called autophagosomes, which then fuse with lysosomes for degradation. This process is essential for clearing toxic cellular debris, preventing the buildup of dysfunctional mitochondria, and maintaining energy balance under stress conditions.

Macroautophagy has emerged as a central mechanism in aging research. The evidence linking autophagy breakdown to cellular damage and death obtained in the last two decades has been remarkably strong. Importantly, caloric restriction, a well-known longevity intervention, has been shown to upregulate autophagy, thereby reducing cellular stress and damage. Pharmacological agents like rapamycin, which inhibits mTOR (a key regulator of autophagy), have also been shown to promote autophagy and extend lifespan in animal models. These findings have spurred interest in developing autophagy-enhancing therapies for age-related conditions.



What is Macroautophagy?

Autophagy is a cellular process that involves the degradation and recycling of cellular components.

Relation to Aging

- Form of cellular housekeeping
- Maintaining cellular homeostasis and function
- As organisms age, the efficiency of autophagy tends to decline

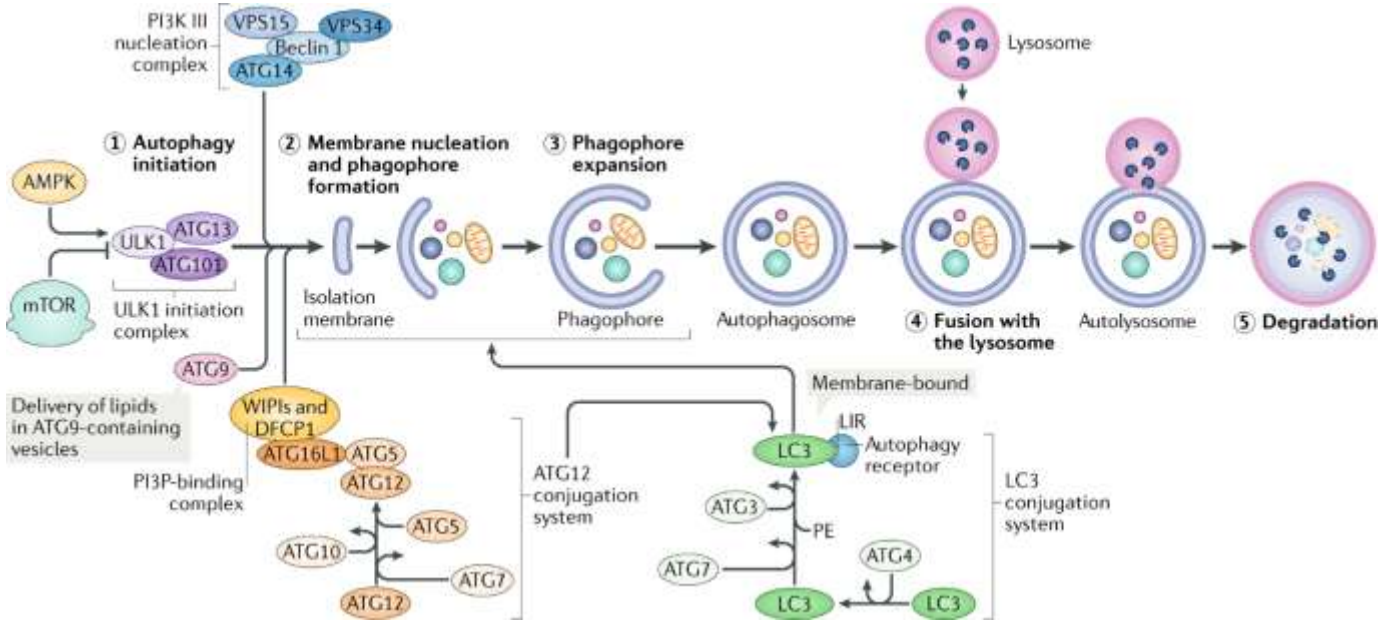
  ↳ Association with age-related diseases and conditions

Autophagy agonists --› extend human lifespans?

- Good scientific evidence
- Maintenance of cellular health and function
- Less risk of age-related diseases

How the Autophagy Process Works

Malene Hansen, DC Rubinsztein, DW Walker, "Autophagy as a promoter of longevity: insights from model organisms," *Nature Reviews Molecular Cell Biology,* Sep 2018; 19(9):579-593.



A schematic depicting the process and main regulatory machinery of macroautophagy (referred to as autophagy) is shown. The conserved metabolic sensors and longevity determinants mTOR and AMP-activated kinase (AMPK) are the main regulators of autophagy, with mTOR acting as an inhibitor and AMPK as an activator. When autophagy is induced, cytoplasmic material (the autophagic cargo) is engulfed by double membranes, starting from the formation of a cup-shaped structure called the phagophore to the sequestration into double-membrane vesicles, called autophagosomes, which subsequently fuse with acidic lysosomes and form autolysosomes, where cargo is degraded. Autophagy is a multistep process that includes (1) initiation, (2) membrane nucleation and phagophore formation, (3) phagophore expansion, (4) fusion with the lysosome, and (5) degradation, which correspondingly are regulated by multiple proteins, referred to as autophagy-related proteins (ATGs). ATGs assemble into several complexes: the Unc-51-like kinase 1 (ULK1; Atg1 in yeasts) initiation complex, the class III PI3K nucleation complex and the phosphatidylinositol 3-phosphate (PI3P)-binding complex, which directs the distribution of the machinery that enables autophagosome formation, and includes the ATG12 and the microtubule-associated protein light chain 3/γ-aminobutyric acid receptor-associated proteins (LC3/GABARAPs; Atg8 in yeasts) conjugation systems (for simplicity, only LC3 is noted in the figure). In the ATG12 conjugation system, ATG12 is attached to ATG5, which is then attached to ATG16L1 (Atg16 in yeasts), followed by dimerization (not shown) and interaction with the PI3P-binding complex (formed by WD repeat domain phosphoinositide-interacting proteins (WIPIs; Atg18 in yeasts) and zinc-finger FYVE domain-containing protein 1 (DFCP1). The ATG12–ATG5–ATG16L1 complex then promotes conjugation of LC3 (or GABARAP), whereby LC3 is cleaved by the protease ATG4 to form LC3-I, which is then conjugated with phosphatidylethanolamine (PE) to form LC3-II. This conjugate is incorporated into pre-autophagosomal and autophagosomal membranes, where LC3 can interact with cargo receptors, which harbour LC3-interacting motifs (LIRs). Membranes for phagophore expansion are delivered, at least in part, by ATG9-containing vesicles. For simplicity, only the names of vertebrate ATGs are shown. VPS15, PI3K regulatory subunit 4 (also known as PIK3R4 in humans); VPS34, phosphatidylinositol 3-kinase catalytic subunit type 3 (also known as PIK3C3 in humans).

Source: https://www.nature.com/articles/s41580-018-0033-y

Autophagy Breakdown Linked to Neurodegeneration

Palmer JE, Wilson N, Son SM, Obrocki P, Wrobel L, Rob M, Takla M, Korolchuk VI, Rubinsztein DC., "Autophagy, aging, and age-related neurodegeneration," *Neuron*, Jan 8, 2025; 113(1):29-48.

Autophagy is a conserved mechanism that degrades damaged or superfluous cellular contents and enables nutrient recycling under starvation conditions. Many neurodegeneration-associated proteins are autophagy substrates, and autophagy upregulation ameliorates disease in many animal models of neurodegeneration by enhancing the clearance of toxic proteins, proinflammatory molecules, and dysfunctional organelles. Autophagy inhibition also induces neuronal and glial senescence, a phenomenon that occurs with increasing age in non-diseased brains as well as in response to neurodegeneration-associated stresses. However, **aging and many neurodegeneration-associated proteins and mutations impair autophagy. This creates a potentially detrimental feedback loop whereby the accumulation of these disease-associated proteins impairs their autophagic clearance, facilitating their further accumulation and aggregation.** Thus, understanding how autophagy interacts with aging, senescence, and neurodegenerative diseases in a temporal, cellular, and genetic context is important for the future clinical application of autophagy-modulating therapies in aging and neurodegeneration.

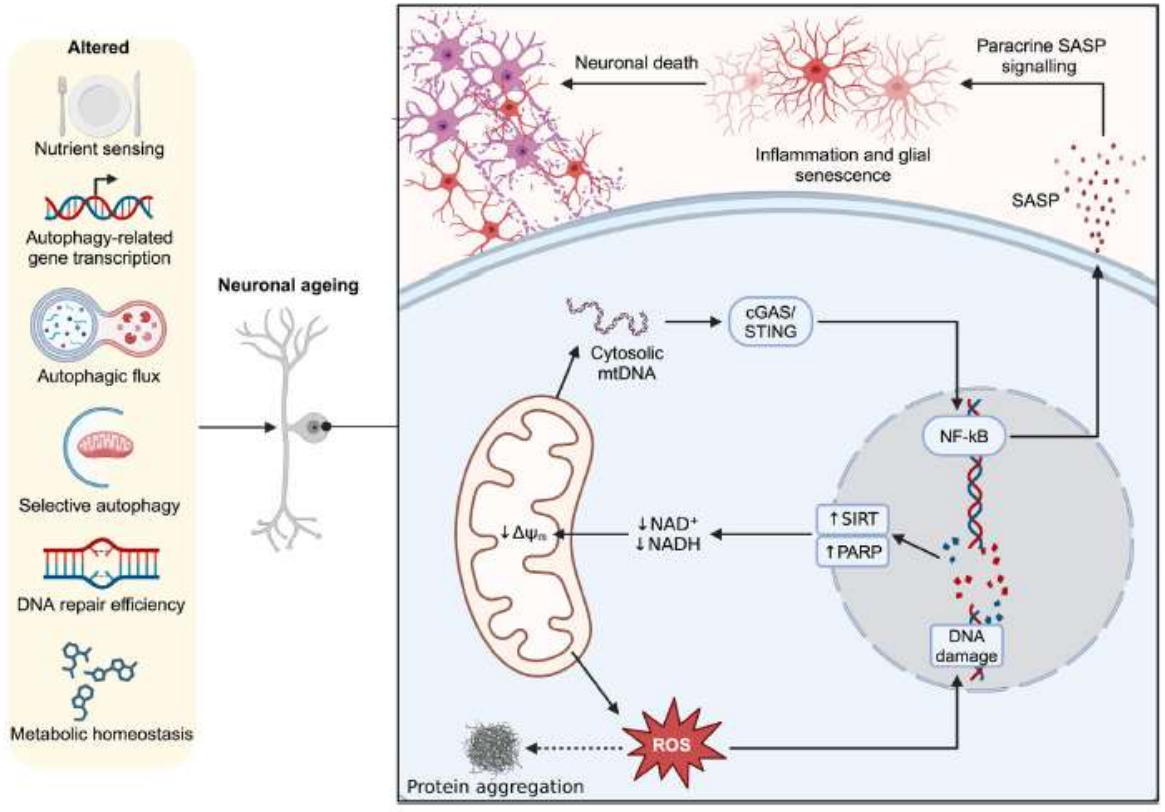


Figure 2. Simplified schematic of the role of aging in neurodegeneration
Changes to cellular homeostasis and autophagy activity contribute to the accumulation of dysfunctional mitochondria in aged neurons. Reactive oxygen species (ROS) leakage from damaged mitochondria damages nuclear DNA, which has been shown to induce both protein aggregation and sirtuin (SIRT)- and PARP-mediated NAD^+/NADH depletion in autophagy-deficient models. Cytosolic release of mitochondrial DNA (mtDNA) also contributes to the activation of the cyclic GMP-AMP synthase/stimulator of interferon genes (cGAS/STING) pathway and the secretion of proinflammatory senescence-associated secretory phenotype (SASP) factors, which may participate in the spread of senescent phenotypes in the aging brain.

Source: https://www.cell.com/neuron/fulltext/S0896-6273(24)00663-9

Autophagy is Linked to Diseases of Aging

Ren J, Zhang Y. Targeting Autophagy in Aging and Aging-Related Cardiovascular Diseases. *Trends Pharmacol Sci.* Dec 2018:1064-1076

"Aging, an irreversible biological process, serves as an independent risk factor for chronic disease including cancer, pulmonary, neurodegenerative and cardiovascular diseases. In particular, high morbidity and mortality has been associated with cardiovascular aging although effective clinical therapeutic remedy is suboptimal for the ever-rising aging population.

Recent evidence suggests a unique role for aberrant aggregate clearance and protein quality control machinery - the process of autophagy in shortened lifespan, compromised healthspan, onset and development of aging-associated cardiovascular diseases.

Autophagy degrades and removes long-lived or damaged cellular organelles and proteins, the functions of which decline with advanced aging. Induction of autophagy … delays aging, prolongs lifespan and improves cardiovascular function in aging. Given the ever-rising human lifespan and aging population as well as the prevalence of cardiovascular disease provoked with increased age, it is pertinent to understand the contribution and underlying mechanisms for autophagy and organelle-selective autophagy (e.g., mitophagy) in the regulation of lifespan, healthspan and cardiovascular aging. Here we will dissect the mechanism of action for autophagy failure in aging and discuss the potential rationale of targeting autophagy."

We have reviewed dozens of papers on aging biology and stories regarding modifiable risk factors.

The evidence suggesting that autophagy enhancement would make a major difference emerged as particularly strong from our review.

Source: https://pubmed.ncbi.nlm.nih.gov/30458935/

The Relationship Between Autophagy Proteins in the Serum and Mortality in the DECODE (2021) Paper is Weak at Best

Protein	Biological Role in Autophagy	Observed Circulating Change (vs. Controls / Healthy Aging)	Is This Protein Highly Ranked as a Predictor of Mortality in Decode (2021)	Clinical Context Studied	Interpretation	Key References
ATG5	Essential component of autophagosome formation	↓ Decreased in serum of Alzheimer's disease (AD) and mild cognitive impairment (MCI) patients	No. This protein has zero correlation with mortality experience in Iceland.	Neurodegeneration / cognitive aging	Suggests systemic decline of autophagy with aging and neurodegeneration	Nuzzo et al., *Sci Rep* 2019
Parkin (PARK2)	Ubiquitin ligase mediating mitophagy (removal of damaged mitochondria)	↓ Decreased in AD and MCI serum	This protein is very slightly negative correlated with mortality risk in Iceland.	Neurodegeneration / mitochondrial dysfunction	Indicates impaired mitophagy during brain aging	Nuzzo et al., *Sci Rep* 2019
Beclin-1 (BECN1)	Initiates autophagosome formation (Beclin-1 complex with Vps34)	↑ Higher in centenarians vs. younger or diseased subjects	Yes. This protein is in the top quartile of those which are positively ranked with mortality experience in Iceland. HR=1.05 (not that high)	Longevity / cardiovascular aging	Suggests preserved autophagy initiation in healthy aging	Front. Cardiovasc. Med. 2023

Source: Stifel Investment Banking Department.

Summary:

1. Decreased **ATG5**, **Parkin**, and **Beclin-1** are most reproducibly linked with impaired autophagy/mitophagy in human aging and neurodegeneration.
2. The relationship between serum levels of these proteins and mortality is weak at best.
3. No single circulating protein yet provides a reliable quantitative measure of autophagy decline; these are *proxy indicators* within broader aging networks.

Summary of Empirical Evidence Regarding Autophagy Linkage to Aging and Mortality

Mouse Loss of Function Data

- In mice, tissue-specific deletion of essential autophagy genes such as **Atg5** in neurons causes progressive protein aggregation, neurodegeneration, and early death even in the absence of any mutant disease proteins.
- This implies that baseline autophagy is required for normal lifespan and nervous-system integrity.

Mouse Gain of Function Data

- Conversely, moderate whole-body overexpression of Atg5 increases autophagic activity and extends median mouse lifespan by ~17%, while improving insulin sensitivity, leanness, and motor function.
- This is one of the clearest demonstrations that up-tuning autophagy can delay aging phenotypes in a mammal.

Human Neurodegeneration Data

- Extensive links between impaired autophagy and major human diseases (neurodegeneration, metabolic disease, cancer), support calling autophagy a **central hub** in the aging network.

But… Human Data Linking Autophagy to Mortality Are Missing

- There is currently no human study showing that pharmacologic enhancement of autophagy (e.g., via mTOR inhibition) definitively lowers all-cause mortality or dramatically extends lifespan.
- Nonetheless, there are promising signals in age-related disease models.

…And Proteomic Validation is Absent

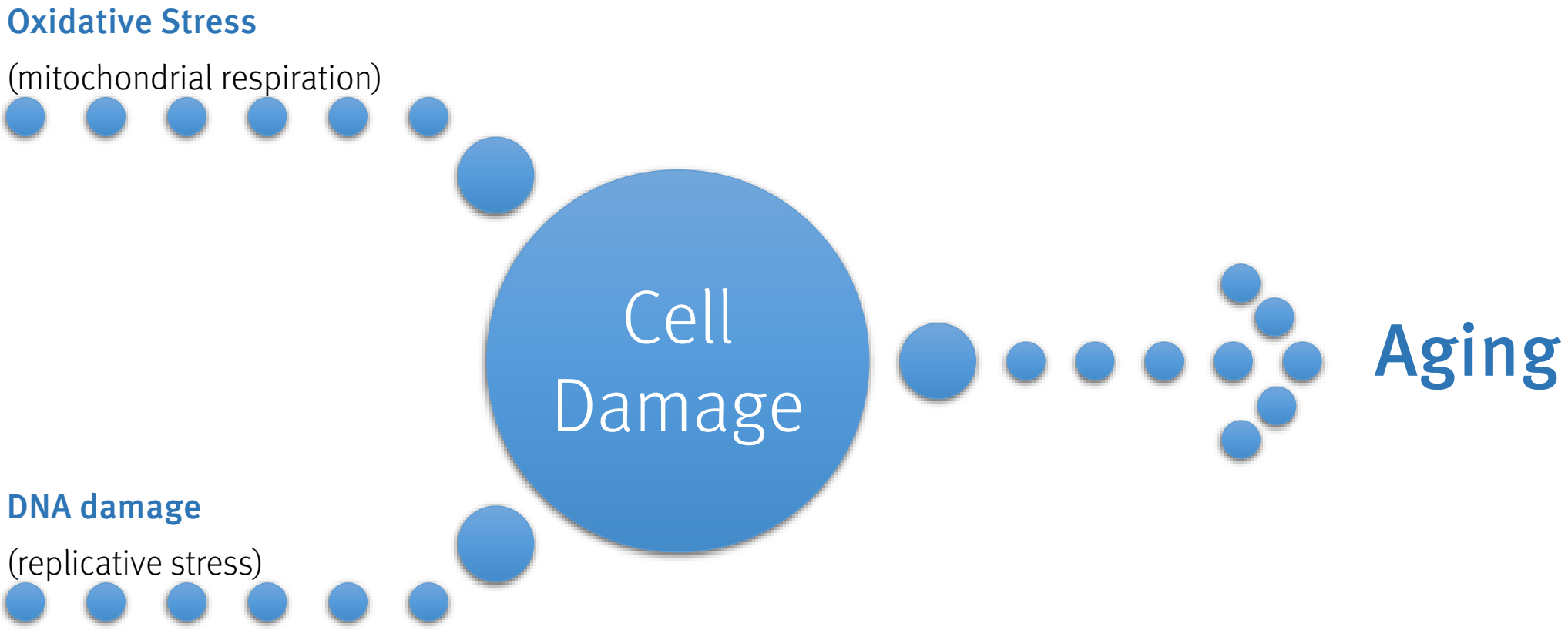
- Unlike the mitochondrial story – which stands out strongly in blood proteomics, autophagy proteins do not stand out
- This does not necessarily imply that autophagy is not relevant to human mortality risk, but if it is relevant then autophagy processes do not shed proteins into the bloodstream.

Point Eleven:

We Propose an Integrated Model of Aging Biology

A Simple General Model of Cellular Aging

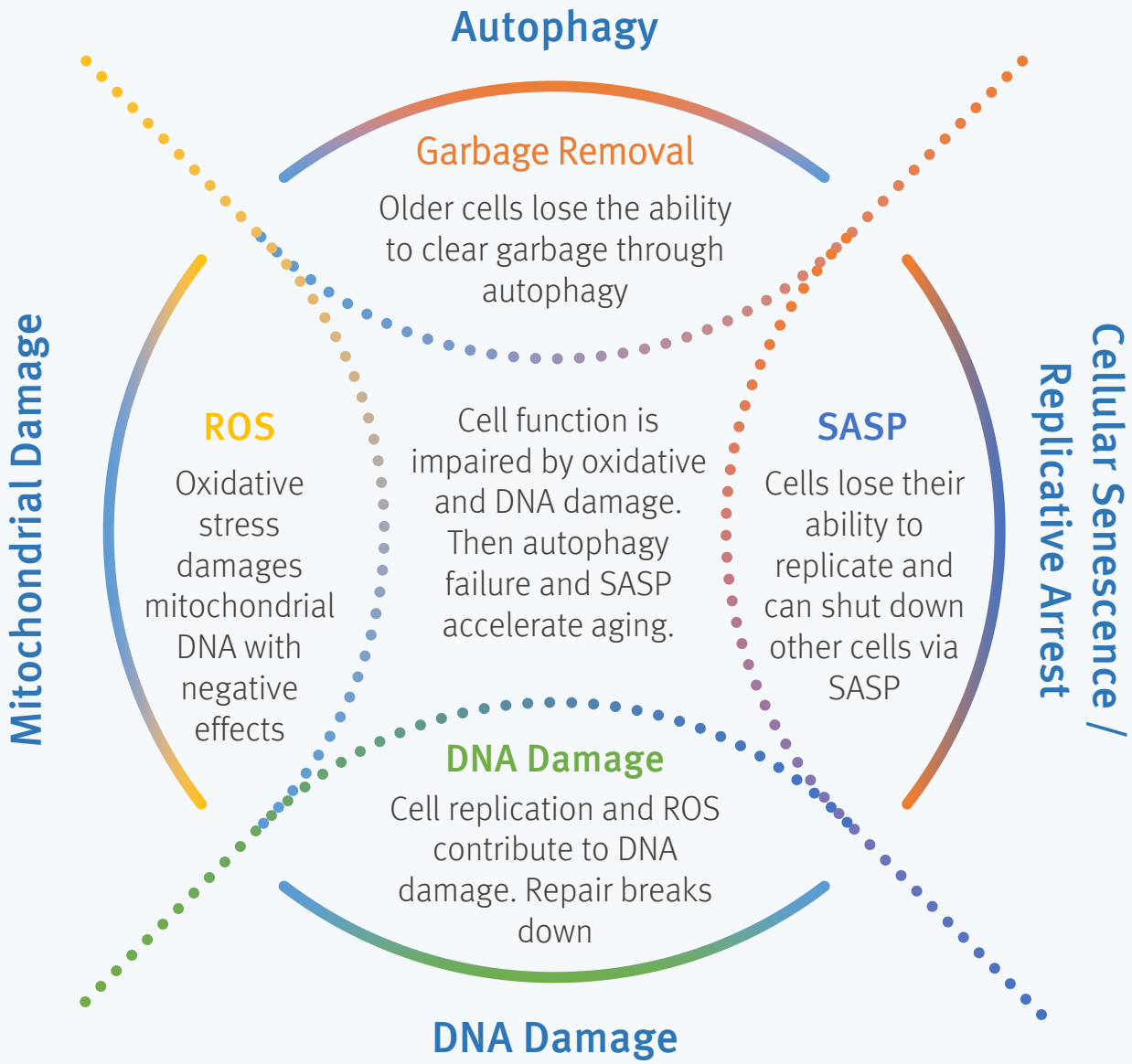
We argue that the core causes of aging are caused by mitochondrial respiration (energy burning) which leads to oxidative stress and DNA damage caused by replicative stress in the cell. Oxidative stress can also induce DNA damage. There are “recovery and repair” systems in cells including the stress response system (ISR), the DNA damage repair system and the autophagy system (garbage disposal). These repair systems also break down as the cell is subject to stress.



A General Model of Aging Biology

Four Driver Model of Aging

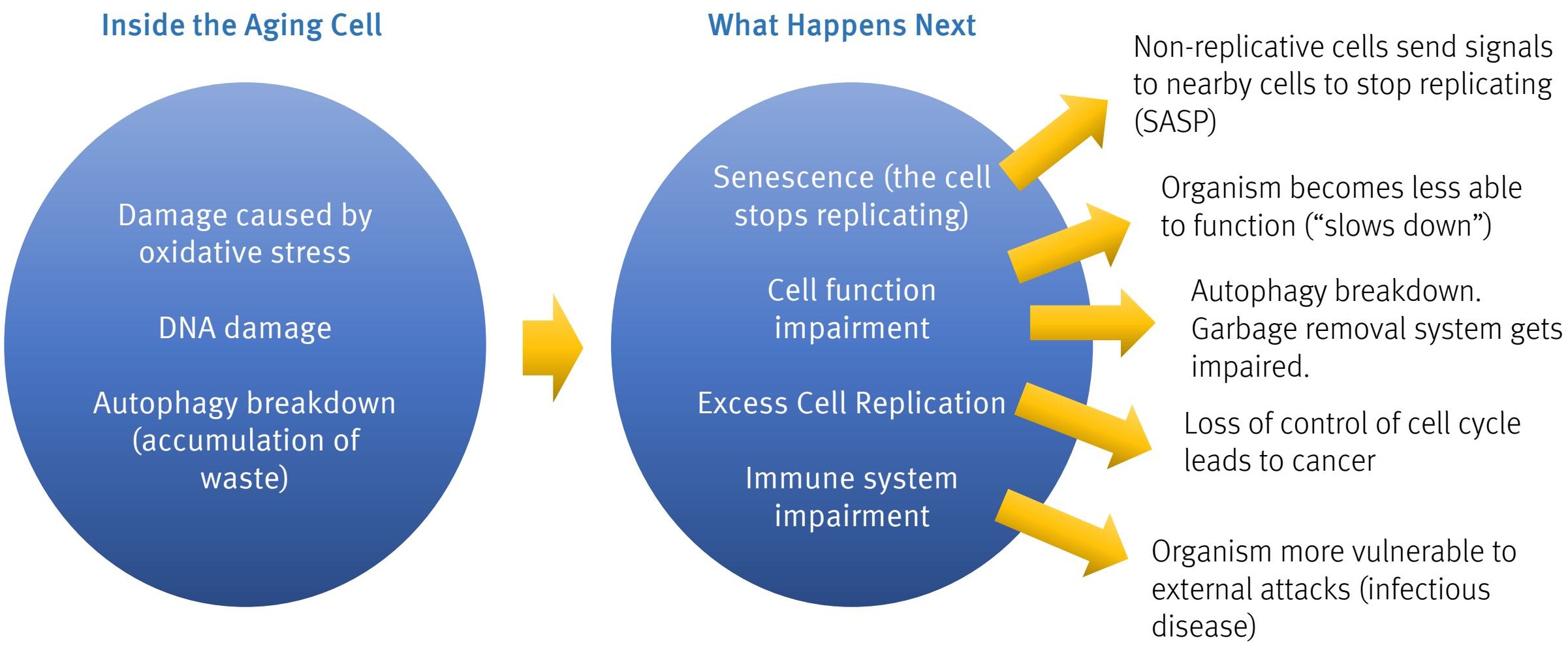
The core idea of the four-driver model of aging shown here is that cells naturally create oxidative stress through mitochondrial respiration. Over time, this damages mitochondrial DNA and, ultimately, many other cellular functions. DNA damage caused by replicative stress also is an independent source of damage to cell function. As cellular functions break down over time due to accumulated damage, the organism begins to experience issues with many organ systems.



This model suggested here is synthesized from Ramakrishnan's review and our own read of the literature.

A key factor that governs the extent of this damage is the autophagy breakdown. At some point the cell becomes less able to remove damaged elements. Interestingly, the body retains the ability to make new cells (depending on the cell type). One important opportunity to do this involves the removal of so-called senescent cells – those that can no longer replicate.

Causal Architecture: How the Aging Process Works



Snowballing of Aging Process

The acceleration of aging is a remarkable fact of life after the age of 85 when the probability of death rises exponentially following Gompertz Law. The chance of living past age 115 is approximately one in one hundred million and the chance of living past age 125 is zero. Aging processes are clearly cumulative, leading to the inevitable breakdown of the human organism.

Looking at the chart on the previous page we see multiple simultaneous negative feedback loops arise:

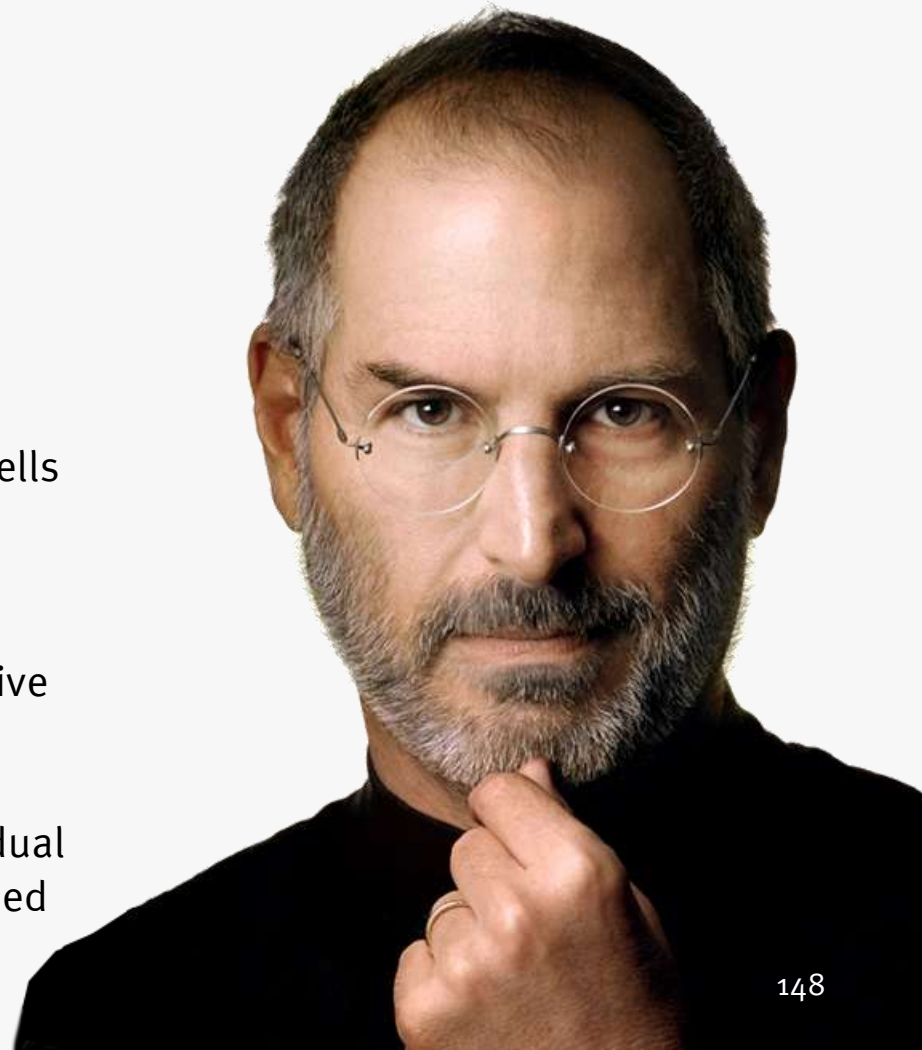
(1) Senescent cells beget more senescent cells through SASP
(2) Mitochondrial oxidative damage is self-perpetuating
(3) Breakdown of cell cycle function can trigger cancer
(4) Breakdown of autophagy triggers worsening of status of remaining functioning cells
(5) Damage accumulation within the cell triggers multiple negative feedback loops
(6) Weakening of immune cell function increases vulnerability of organism

An obvious and difficult question is how might one slow this "snowballing" of negative feedback loops. Presumably, prevention and early intervention will matter.

It strikes us that this topic has not received enough attention. In other words, individual researchers have tried senolytics and antioxidants in isolation, but we haven't focused enough on managing cumulative aging stress.

"Death is the destination we all share."

Steve Jobs



Point Twelve:

There are Many Downstream Aspects of Aging Resulting from Core Drivers of Cell Damage

Immunosenescence / Inflammaging

An aged immune system drives senescence and ageing of solid organs

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Matthew J. Yousefzadeh[1,2,14], Rafael R. Flores[1,2,14], Yi Zhu[3], Zoe C. Schmiechen[4], Robert W. Brooks[5], Christy E. Trussoni[6], Yuxiang Cui[7], Luise Angelini[1,2], Kyoo-A Lee[1,2], Sara J. McGowan[1,2], Adam L. Burrack[4], Dong Wang[8], Qing Dong[8], Aiping Lu[9], Tokio Sano[5], Ryan D. O'Kelly[1,2], Collin A. McGuckian[1,2], Jonathan I. Kato[5], Michael P. Bank[5], Erin A. Wade[5], Smitha P. S. Pillai[10], Jenna Klug[11], Warren C. Ladiges[11], Christin E. Burd[12], Sara E. Lewis[13], Nicholas F. LaRusso[6], Nam V. Vo[8], Yinsheng Wang[7], Eric E. Kelley[13], Johnny Huard[9], Ingunn M. Stromnes[4], Paul D. Robbins[1,2]✉ & Laura J. Niedernhofer[1,2]✉

Ageing of the immune system, or immunosenescence, contributes to the morbidity and mortality of the elderly[1,2]. To define the contribution of immune system ageing to organism ageing, here we selectively deleted *Ercc1*, which encodes a crucial DNA repair protein[3,4], in mouse haematopoietic cells to increase the burden of endogenous DNA damage and thereby senescence[5–7] in the immune system only. We show that *Vav-iCre*$^{+/-}$*;Ercc1*$^{-/fl}$ mice were healthy into adulthood, then displayed premature onset of immunosenescence characterized by attrition and senescence of specific immune cell populations and impaired immune function, similar to changes that occur during ageing in wild-type mice[8–10]. Notably, non-lymphoid organs also showed increased senescence and damage, which suggests that senescent, aged immune cells can promote systemic ageing. The transplantation of splenocytes from *Vav-iCre*$^{+/-}$*;Ercc1*$^{-/fl}$ or aged wild-type mice into young mice induced senescence *in trans*, whereas the transplantation of young immune cells attenuated senescence. The treatment of *Vav-iCre*$^{+/-}$*;Ercc1*$^{-/fl}$ mice with rapamycin reduced markers of senescence in immune cells and improved immune function[11,12]. These data demonstrate that an aged, senescent immune system has a causal role in driving systemic ageing and therefore represents a key therapeutic target to extend healthy ageing.

Nature, June 3, 2021

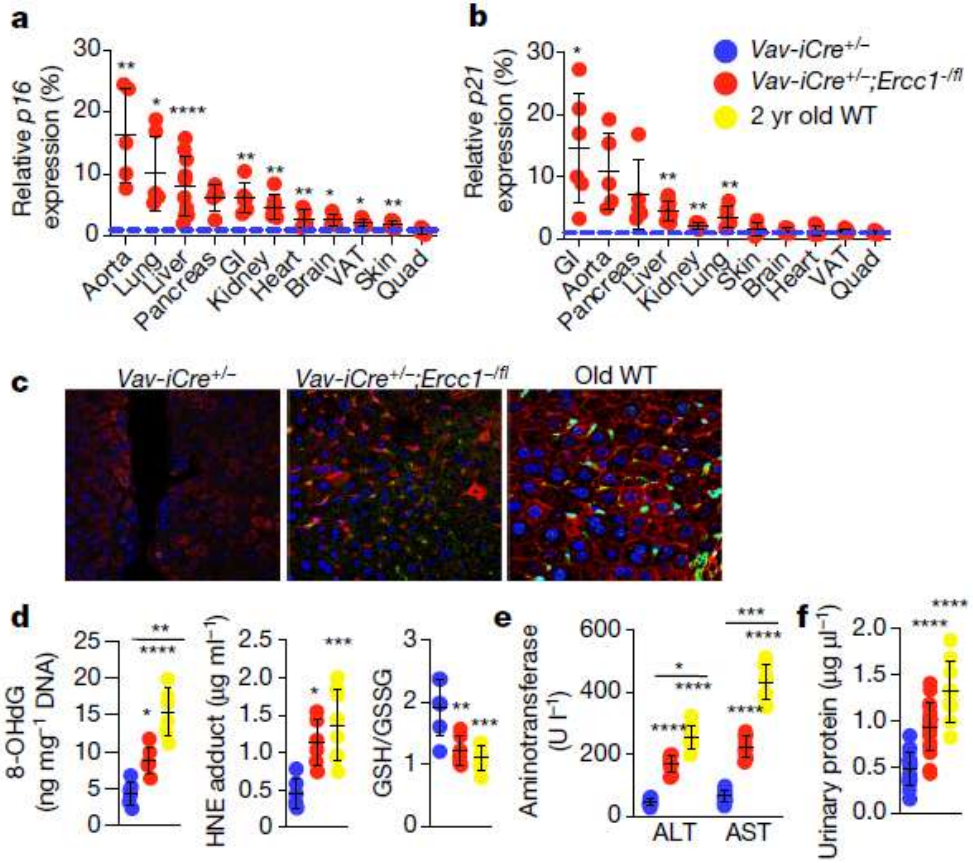


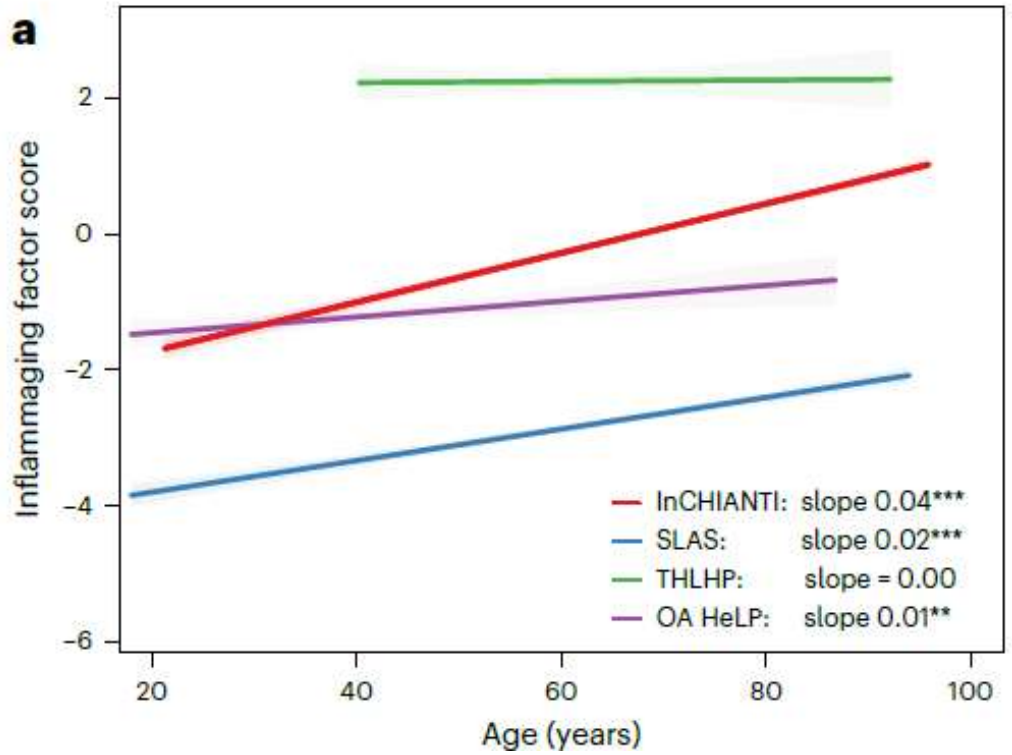
Fig. 3 | An aged immune system drives senescence and loss of tissue homeostasis in non-lymphoid organs. Several senescence and tissue damage markers were measured in 8–11-month-old Vav-iCre mice and old wild-type mice. a, b, Expression of p16 (a) and p21 (b) (n = 5–10 mice) in mutant mice was normalized to Vav-iCre+/– controls (blue line). GI, gastrointestinal; VAT, visceral adipose tissue. c, representative images of in situ hybridization on hepatic sections for p16 mRNA (green), albumin (red) to detect hepatocytes, and DAPI (blue nuclei). Hepatic 8-oxo-guanine DNA adducts and HNE protein adducts measured by ELISA (n = 6–8 mice per group). Glutathione rat in livers of Vav-iCre+/–;Ercc1–/fl mice (n = 6), Vav-iCre+/– controls (n = 6) and aged wild-type mice (n = 7). e, Serum aminotransferase levels (n = 9 mice per group). ALT, alanine aminotransferase; AST, aspartate transaminase f, Urinary protein levels from Vav-iCre (n = 18) and old wild-type (n = 9) mice measured by Bradford assay.

Source: https://www.nature.com/articles/s41586-021-03547-7

Inflammaging is Culturally Specific: It's Not Inevitable

M. Frank et al., "Nonuniversality of inflammaging across human populations," *Nature Aging*, June 30, 2021

Inflammaging, an age-associated increase in chronic inflammation, is considered a hallmark of aging. However, there is no consensus approach to measuring inflammaging based on circulating cytokines. Here we assessed whether an inflammaging axis detected in the Italian InCHIANTI dataset comprising 19 cytokines could be generalized to a different industrialized population (Singapore Longitudinal Aging Study) or to two indigenous, nonindustrialized populations: the Tsimane from the Bolivian Amazon and the Orang Asli from Peninsular Malaysia. We assessed cytokine axis structure similarity and whether the inflammaging axis replicating the InCHIANTI result increased with age or was associated with health outcomes. The Singapore Longitudinal Aging Study was similar to InCHIANTI except for IL-6 and IL-1RA. The Tsimane and Orang Asli showed markedly different axis structures with little to no association with age and no association with age-related diseases. Inflammaging, as measured in this manner in these cohorts, thus appears to be largely a byproduct of industrialized lifestyles, with major variation across environments and populations.

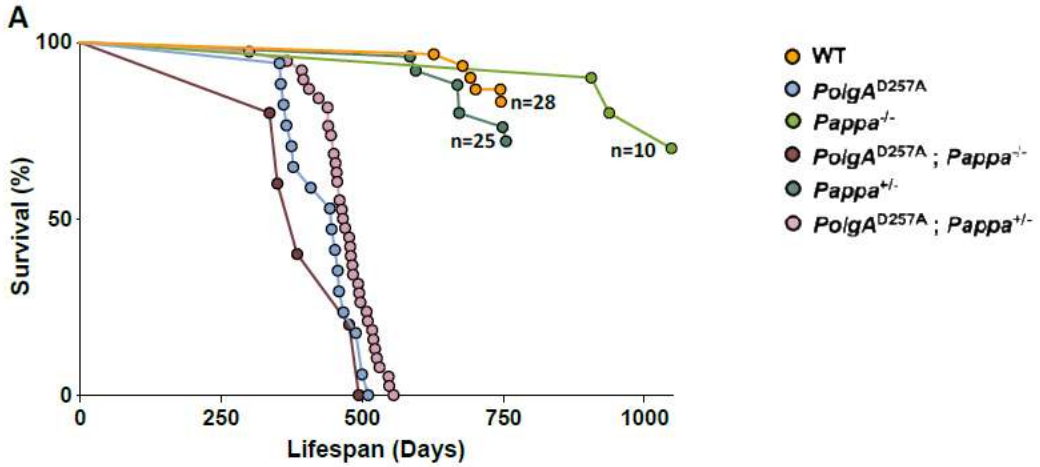


Source: https://www.nature.com/articles/s43587-025-0

IGF-1 Effects Appear Linked to the Mitochondrial Theory of Aging

Sarah Shemtov, et.al, "The longevity effects of reduced IGF-1 signaling depend on the stability of the mitochondrial genome," *BioRxiv*, June 6, 2025

Suppression of insulin-like growth factor-1 (IGF-1) signaling extends mammalian lifespan and protects against a range of age-related diseases. Surprisingly though, we found that reduced IGF-1 signaling fails to extend the lifespan of mitochondrial mutator mice. Accordingly, most of the longevity pathways that are normally initiated by IGF-1 suppression were either blocked or blunted in the mutator mice. These observations suggest that the pro-longevity effects of IGF-1 suppression critically depend on the integrity of the mitochondrial genome and that mitochondrial mutations may impose a hard limit on mammalian lifespan. Together, these findings deepen our understanding of the interactions between the hallmarks of aging and underscore the need for interventions that preserve the integrity of the mitochondrial genome.



Lifespan, weight, size and appearance of WT, PolgAD257A and Pappa mutant mice. A. The lifespan of PolgAD257A is not rescued by deletion of the Pappa gene.

There is quite a large literature on IGF-1 signaling and aging. It does not appear that this effect is independent of mitochondrial / DNA damage theories of aging. In the above experiment, the PolgAD257a mouse has genetic deletions that increase its rate of mitochondrial mutations. The Pappa +/- mouse has mutations that reduce IGF-1 signaling – which improves longevity. The benefit of the latter mutation goes away completely in mice with elevated mitochondrial mutations. This suggests but does not prove the notion that the well-known effect of IGF signaling on longevity is dependent on mitochondrial DNA integrity. Separately, note a very interesting PAPP-A antibody in development at Calico with AbbVie.

Source: https://www.biorxiv.org/content/10.1101/2025.06.03.656903v1

Dysregulated Proteasome and Ubiquitination System

Nature, Aug 12, 2021

Rewiring of the ubiquitinated proteome determines ageing in *C. elegans*

https://doi.org/10.1038/s41586-021-03781-z

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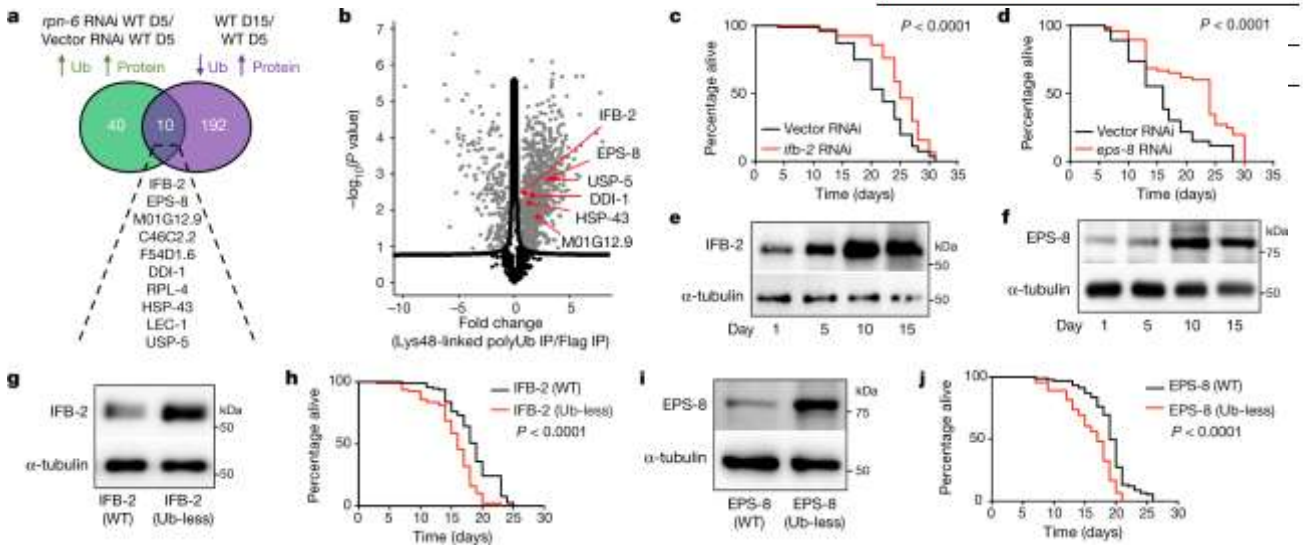
Accepted: 29 June 2021

Seda Koyuncu[1], Rute Loureiro[1], Hyun Ju Lee[1], Prerana Wagle[1], Marcus Krueger[1,2] & David Vilchez[1,2,3]✉



Age-related deubiquitination impairs targeted degradation of longevity regulators.

Ageing is driven by a loss of cellular integrity[1]. Given the major role of ubiquitin modifications in cell function[2], here we assess the link between ubiquitination and ageing by quantifying whole-proteome ubiquitin signatures in *Caenorhabditis elegans*. We find a remodelling of the ubiquitinated proteome during ageing, which is ameliorated by longevity paradigms such as dietary restriction and reduced insulin signalling. Notably, ageing causes a global loss of ubiquitination that is triggered by increased deubiquitinase activity. Because ubiquitination can tag proteins for recognition by the proteasome[3], a fundamental question is whether deficits in targeted degradation influence longevity. By integrating data from worms with a defective proteasome, we identify proteasomal targets that accumulate with age owing to decreased ubiquitination and subsequent degradation. Lowering the levels of age-dysregulated proteasome targets prolongs longevity, whereas preventing their degradation shortens lifespan. Among the proteasomal targets, we find the IFB-2 intermediate filament[4] and the EPS-8 modulator of RAC signalling[5]. While increased levels of IFB-2 promote the loss of intestinal integrity and bacterial colonization, upregulation of EPS-8 hyperactivates RAC in muscle and neurons, and leads to alterations in the actin cytoskeleton and protein kinase JNK. In summary, age-related changes in targeted degradation of structural and regulatory proteins across tissues determine longevity.

Source: https://www.nature.com/articles/s41586-021-03781-z

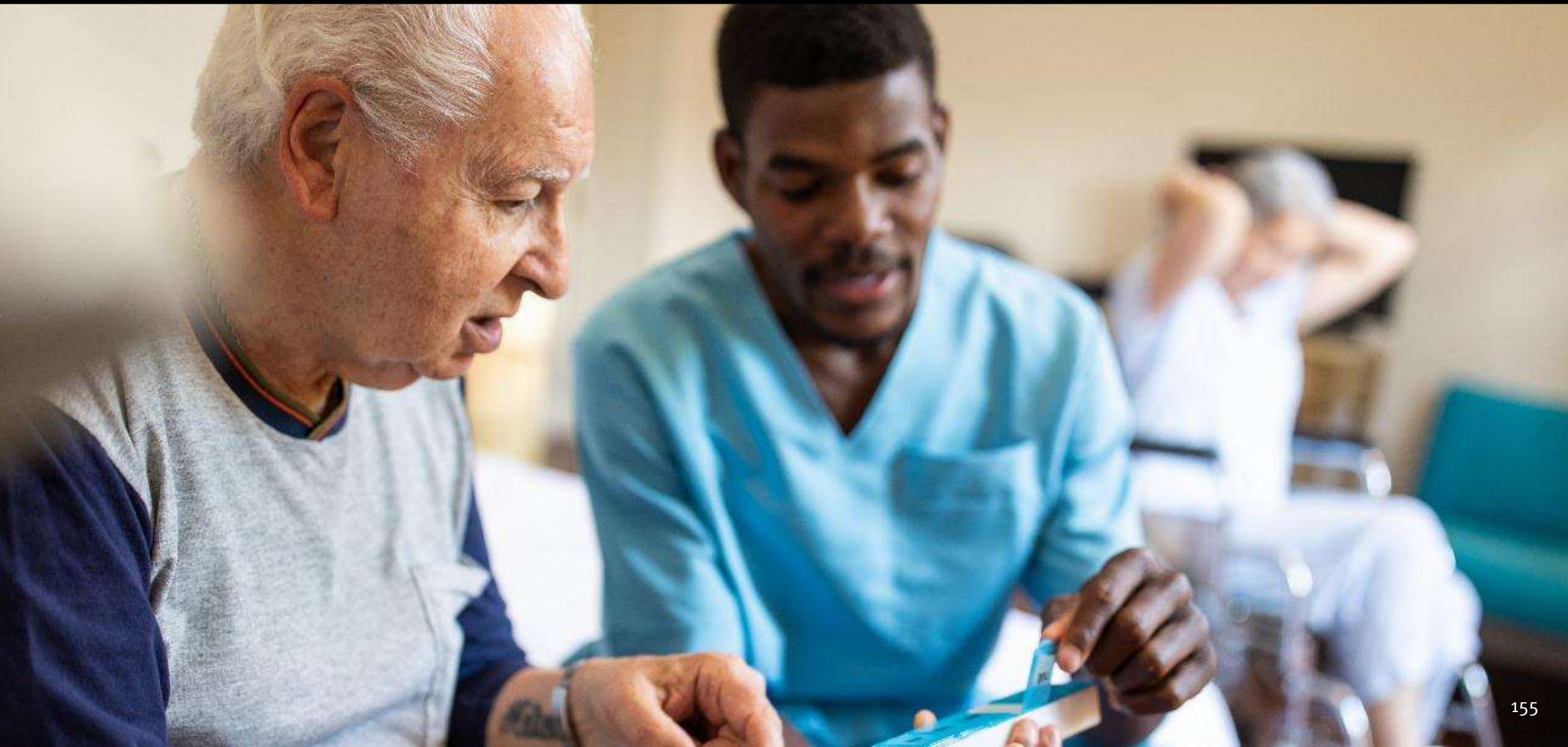
Aging and the Microbiome

Badal VD, Vaccariello ED, Murray ER, Yu KE, Knight R, Jeste DV, Nguyen TT. The Gut Microbiome, Aging, and Longevity: A Systematic Review. *Nutrients*, Dec 7, 2020; 12(12):3759.

Aging is determined by complex interactions among genetic and environmental factors. Increasing evidence suggests that the gut microbiome lies at the core of many age-associated changes, including immune system dysregulation and susceptibility to diseases. The gut microbiota undergoes extensive changes across the lifespan, and age-related processes may influence the gut microbiota and its related metabolic alterations. The aim of this systematic review was to summarize the current literature on aging-associated alterations in diversity, composition, and functional features of the gut microbiota. We identified 27 empirical human studies of normal and successful aging suitable for inclusion. Alpha diversity of microbial taxa, functional pathways, and metabolites was higher in older adults, particularly among the oldest-old adults, compared to younger individuals. Beta diversity distances significantly differed across various developmental stages and were different even between oldest-old and younger-old adults. Differences in taxonomic composition and functional potential varied across studies, but Akkermansia was most consistently reported to be relatively more abundant with aging, whereas Faecalibacterium, Bacteroidaceae, and Lachnospiraceae were relatively reduced. Older adults have reduced pathways related to carbohydrate metabolism and amino acid synthesis; however, oldest-old adults exhibited functional differences that distinguished their microbiota from that of young-old adults, such as greater potential for short-chain fatty acid production and increased butyrate derivatives. Although a definitive interpretation is limited by the cross-sectional design of published reports, we integrated findings of microbial composition and downstream functional pathways and metabolites, offering possible explanations regarding age-related processes.

Source: https://www.mdpi.com/2072-6643/12/12/3759

Arguments 2 & 3: There are Good Opportunities to Drug Aging



Each Axis of the Four Driver Age Model is Open to Pharmacologic Intervention

Oxidative Stress / Mitochondria

There are a number of drugs in development that help preserve mitochondrial integrity like Stealth's elamipreitide.

Another example of a drug is Tisento's Zagociguat which stimulates an enzyme known as soluble guanylate cyclase (sGC). This helps to strengthen a cell's mitochondrial function.

Another idea would be to use mitochondrial uncouplers.

Cell and DNA Damage

There is a long history of the development of drugs that protect cells against damage from reactive oxygen species.

There are direct ROS scavengers such as vitamin C and E. Another example would be superoxide dismutase mimetics.

There are a variety of pathways that could confer protection against DNA damage like cGAS / STING

Cell Senescence

There are numerous strategies designed to eliminate non-dividing senescent cells or to limit their damage.

Senescent cells often resist apoptosis by upregulating pro-survival pathways. Senolytics work by disrupting these pathways, forcing apoptosis. Key drug targets include BCL-2 and PI3K/AKT.

Another strategy would be to target cell surface markers like GPRC5A or uPAR.

Autophagy Decline

There are multiple targets available here.

Mammalian Target of Rapamycin (mTOR) is a key regulator of autophagy. Rapamycin can be used here.

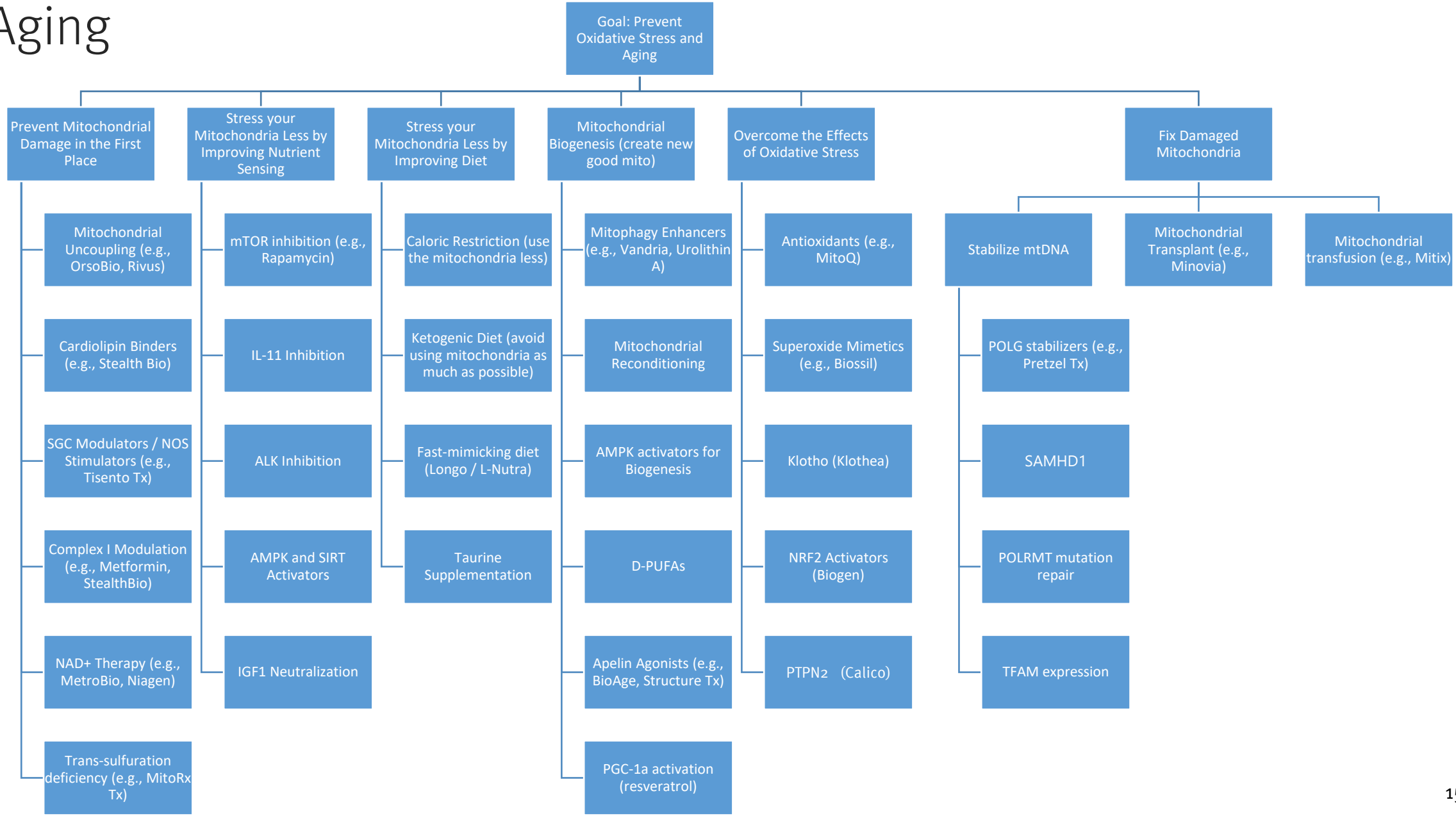
AMPK activators like metformin are another strategy.

Other options include calorie restriction mimetics, autophagy-inducing peptides, autophagy modulators and HDAC inhibitors.

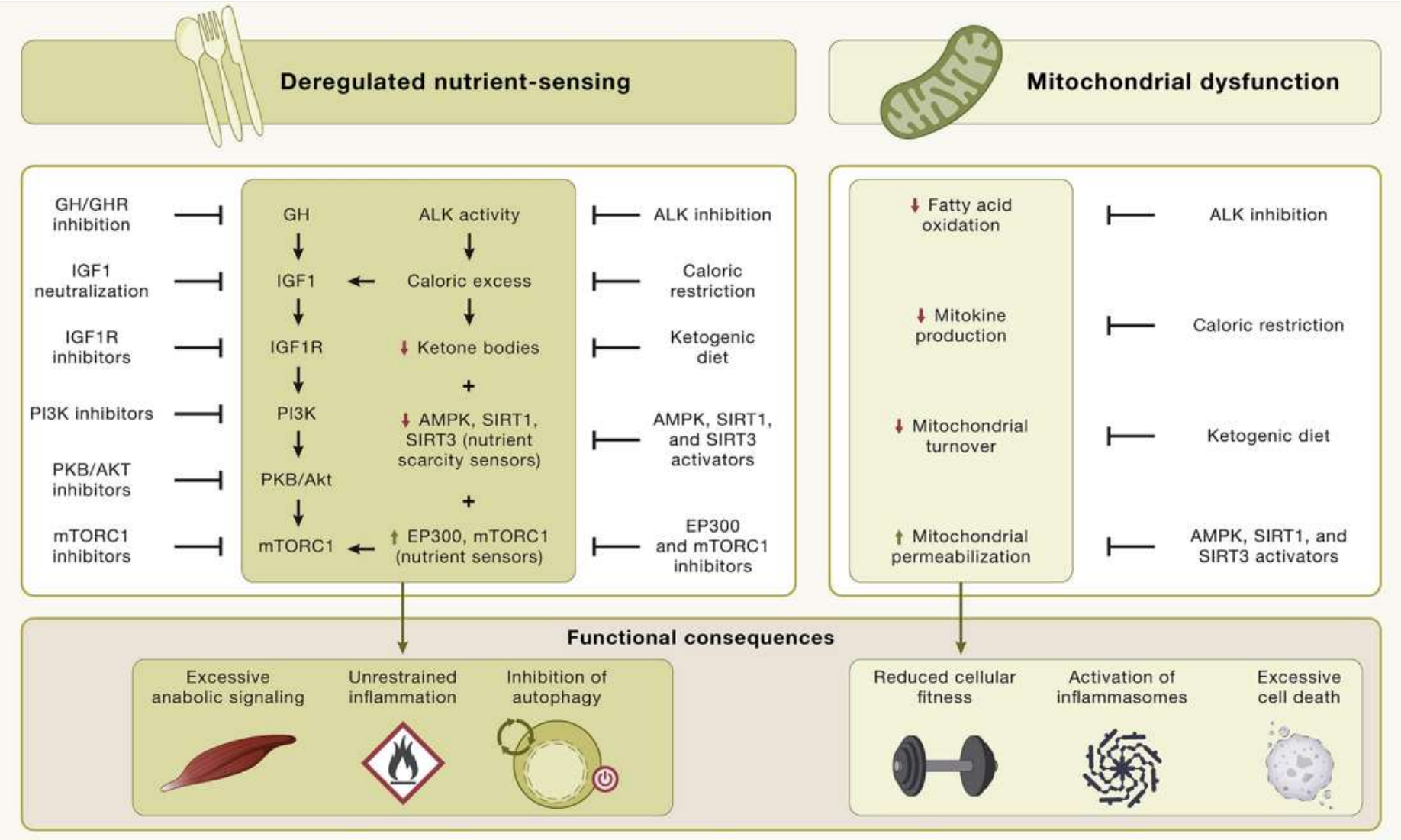
First Area:

Oxidative Stress and Mitochondrial Damage

Dendrogram of Therapeutic Options for Mitochondrial Damage / Aging



Pathways to Manage Oxidative Stress Highlighted in the Hallmarks of Aging (2023) Paper



Source: https://www.cell.com/cell/fulltext/S0092-8674(22)01377-0

Multiple Therapeutic Options Available to Manage Mitochondrial Damage / Oxidative Stress

Strategy	Example Drug(s) / Class	How It Modulates Mito Respiration / ROS	Evidence for Lifespan Extension / Health Improvement	Key Limitations / Risks
Mild inhibition of mitochondrial respiration (complex I)	Metformin, other biguanides, SBT-585 (StealthBio)	Partially inhibits complex I ⟶ ⇣ electron flux and ΔΨm ⟶ less electron leak ⟶ ⇣ ROS; also shifts metabolism toward glycolysis and AMPK activation	In worms and some rodent studies, metformin extends lifespan and improves healthspan; in humans, associated with reduced incidence of age-related diseases (T2D, CVD, some cancers) but no proven lifespan extension yet	GI side effects, B12 deficiency risk, lactic acidosis in susceptible patients; effect size on aging per se in humans still unproven
mTOR inhibition (reducing metabolic demand and mitochondrial ROS indirectly)	Rapamycin, analogues like everolimus	Inhibits mTORC1 ⟶ reduces anabolic metabolism, protein synthesis and mitochondrial activity ⟶ ⇣ ROS production and enhanced autophagy/mitophagy	Robust lifespan extension in yeast, worms, flies, and multiple mouse strains; improved healthspan features (immune, cardiac, cognitive) in animals	Immunosuppression, metabolic side effects (hyperlipidemia, glucose intolerance), mouth ulcers; dosing and schedules for humans as "anti-aging" still unclear
Mitochondria-targeted antioxidants	MitoQ, SkQ1, SS-31/ Elamipretide, CoQ10 variants	Antioxidant moieties conjugated to lipophilic cations or peptides ⟶ selectively accumulate in mitochondria and neutralize ROS at the source	Some rodent studies show protection against age-related cardiac, renal, or neurodegenerative changes; limited or mixed human data mostly on surrogate endpoints (endothelial function, exercise capacity)	Long-term safety and true lifespan benefit unproven; may blunt beneficial ROS signaling (mitohormesis) if overdosed
NAD^+ boosters & sirtuin activators	NMN, NR, MIB-626 (MetroBiotech), other NAD^+ analogs	Increase NAD^+ ⟶ enhance sirtuin-mediated mitochondrial maintenance, DNA repair, and antioxidant responses; can improve mito efficiency and reduce ROS per unit ATP	In rodents, NAD^+ repletion improves mitochondrial function, insulin sensitivity, and some age-related traits; early human trials show ⇡ NAD^+ and modest functional improvements (e.g., walking tests) but no proven lifespan effect	Long-term efficacy and safety unknown; possible interactions with cancer biology; many trials small and short
SOD mimetics & ROS scavenging small molecules	MnSOD mimetics (e.g., MnTBAP, MitoTEMPOL),	Mimic superoxide dismutase or directly scavenge superoxide / peroxynitrite ⟶ ⇣ oxidative damage to DNA, lipids, proteins	In some models, overexpression of SOD or treatment with SOD mimetics improves healthspan and sometimes lifespan; effects are context-dependent and not universally pro-longevity	Global ROS suppression can interfere with redox signaling; potential off-target toxicity; dose, timing, and tissue selectivity are critical
NRF2 activators (boost endogenous antioxidant defenses)	Bardoxolone, dimethyl fumarate, sulforaphane-like molecules	Activate NRF2 ⟶ increased transcription of antioxidant and detox genes (SOD, catalase, glutathione synthesis, phase II enzymes) ⟶ better handling of mito-derived ROS	In animals, NRF2 activation improves stress resistance and delays onset of age-related phenotypes; some human drugs (e.g., DMF) improve outcomes in specific diseases but not validated as lifespan-extending	Chronic NRF2 activation may have complex metabolic effects. Biogen has achieved approval of a NRF2 activator from Reata for F. Ataxia.
Uncouplers / controlled mitochondrial uncoupling	Low-dose uncouplers (e.g., DNP analogs), BAM15 (preclinical)	Mildly dissipate proton gradient ⟶ ⇣ ΔΨm ⟶ less electron leak and ROS; increase energy expenditure and reduce ectopic lipid accumulation	In rodents, carefully titrated uncoupling can reduce obesity, improve insulin sensitivity, and lower hepatic steatosis; some data suggest improved healthspan	Narrow therapeutic window, historical toxicity (DNP); overheating, weight loss, and organ toxicity if overdosed; Several drugs of this type in development for obesity management.
Mitophagy enhancers & mitochondrial quality-control drugs	Urolithin A, spermidine, mTOR-independent autophagy inducers	Promote selective removal of damaged mitochondria via mitophagy ⟶ lowers ROS output from dysfunctional organelles	Urolithin A improves muscle function and mitochondrial markers in animals and early human trials; spermidine extends lifespan in multiple model organisms	Human data mostly short-term, functional (muscle endurance) rather than hard aging endpoints; optimal dosing and long-term safety not fully known
Caloric restriction mimetics (indirectly ⇣ mito load & ROS)	Resveratrol, SIRT1 activators, some AMPK activators	Shift metabolism toward efficient substrate use, increase mitochondrial biogenesis but also tighten QC; modulate sirtuin pathways that improve antioxidant defenses and DNA repair	Lifespan extension in some lower organisms and certain mouse studies; human data show modest metabolic benefits but inconsistent	Resveratrol's in-vivo potency and bioavailability are modest; high doses may have off-target effects; "CR mimetic" label often oversold

Source: Stifel Investment Banking Department.

Despite Multiple Clinical Studies, There Have Been No Trials Testing These Aging Drug Candidates for Lifespan Extension

Mechanism / Drug	Trial / Citation	Population (n, age)	Design / Dose / Duration	Primary Endpoint(s)	Mortality / Lifespan Data?	Main Results	Aging-Relevance & Notes
mTOR inhibition RAD001 (everolimus)	Mannick et al., Sci Transl Med 2014	264 elderly adults	Randomized, double-blind, placebo-controlled; low-dose RAD001 for 6 weeks	Serologic response to influenza vaccine; safety	No	Improved immune response (~20% ↑); well-tolerated	Proof that TORC1 inhibition reverses immunosenescence in humans
mTOR inhibition RTB101	Mannick et al., Lancet Healthy Longev 2021	Thousands of adults ≥65 y	Phase 2b/3 RCTs; RTB101 ± everolimus for 16 weeks	Respiratory infection rate; immune gene expression	No	Improved immune gene expression; mixed infection results	Some infection reduction; mixed Phase 3 results
NAD^+ booster – Nicotinamide riboside (NR)	Martens et al., Nat Commun 2018	24 middle-aged & older adults (55–79 y)	Double-blind crossover; 1000 mg/day NR for 6 weeks	NAD^+ metabolism; aortic stiffness	No	↑ blood NAD^+; reduced aortic stiffness	Good PD signal; small, short-term study
NAD^+ booster NMN (prediabetes)	Yoshino et al., Science 2021	25 overweight postmenopausal women with prediabetes	Double-blind RCT; 250 mg/day NMN for 10 weeks	Muscle insulin sensitivity (clamp test)	No	Improved muscle insulin sensitivity; ↑ insulin signaling	Strong metabolic PD; small study
NAD^+ booster – NMN (healthy older men)	Igarashi et al., npj Aging 2022	108 healthy older men (~65 y)	12-week RCT; 250–500 mg/day NMN	Blood NAD^+, gait speed, grip strength	No	↑ NAD^+; modest gait and grip improvements	Good PD + functional hints; short-term
Mito-targeted antioxidant – MitoQ	Rossman et al., Hypertension 2018	20 older adults (age 60–79 y)	Crossover RCT; 20 mg/day MitoQ for 6 weeks	Brachial artery FMD, aortic stiffness	No	↑ FMD (~42%); ↓ aortic stiffness	Nice mechanistic proof-of-concept; small n
Mito-targeted antioxidant – MitoQ	Murray et al., Front Physiol 2022	90 older adults (≥60 y)	Parallel-group RCT; 3 months of oral MitoQ	FMD, arterial stiffness, oxidative markers	No	Improved FMD and oxidative markers	Confirms Rossman; still surrogate endpoints
Mitophagy enhancer – Urolithin A (older adults)	Liu et al., JAMA Netw Open 2022	66 adults (65–90 y)	4-month RCT; 1000 mg/day UA	6-min walk distance, muscle endurance	No	No primary difference; improved muscle endurance and mito biomarkers	Functional + mito benefit; missed primary endpoint
Mitophagy enhancer – Urolithin A (middle-aged adults)	Singh et al., Cell Rep Med 2022	88 middle-aged adults (40–64 y)	4-month RCT; 500–1000 mg/day UA	Muscle strength, mitochondrial biomarkers	No	↑ Leg muscle strength and mito gene expression	Best human mitophagy data to date; still midlife cohort

Source: Stifel Investment Banking Department.

NAD+ is an Interesting Therapeutic Option to Combat Mitochondrial Stress

NAD^+ (nicotinamide adenine dinucleotide) is a fundamental molecule that sustains life by transferring electrons in cellular metabolism. It participates in key energy-producing pathways such as glycolysis, the tricarboxylic acid (TCA) cycle, and mitochondrial oxidative phosphorylation. When NAD^+ accepts electrons, it becomes NADH, which donates those electrons to generate ATP — the cell's main energy currency. As NAD^+ levels decline with age, mitochondrial efficiency falls, energy output decreases, and reactive oxygen species accumulate, contributing to cellular fatigue and oxidative damage that accelerate aging.

Beyond its role in energy metabolism, NAD^+ serves as a critical cofactor for enzymes involved in DNA repair and gene regulation. PARP enzymes use NAD^+ to fix DNA strand breaks, while the sirtuin family of enzymes relies on NAD^+ to regulate stress resistance, inflammation, and chromatin stability. Low NAD^+ levels therefore weaken genomic maintenance, reduce sirtuin activity, and promote the buildup of damaged DNA and mis regulated genes — features closely tied to aging, metabolic decline, and neurodegeneration. This depletion forms a feedback loop: DNA damage activates NAD^+-consuming enzymes, further draining NAD^+ stores and impairing cellular resilience.

Restoring NAD^+ has emerged as a key strategy in aging research. Supplementing precursors such as NMN or NR can raise cellular NAD^+, improving mitochondrial performance, and dampening chronic inflammation. Additional approaches target enzymes that degrade NAD^+, like CD38 or PARP, or boost the salvage pathway through NAMPT activation. While animal studies show improvements in energy metabolism, vascular function, and lifespan, human trials so far mainly demonstrate biochemical rejuvenation without confirmed extension of healthspan. There is still much to do and certain hurdles to overcome in bringing NAD-based therapies to human use. Indeed, some research questions the value of NAD+ for muscle and aging.

Several Companies Developing NAD+ Products for Aging

Company	Public / Private	Lead NAD⁺-Related Agent(s)	Development Status / Notes
Niagen Bioscience (Ticker: NAGE)	Public	Nicotinamide riboside (NR) branded Niagen® / Tru Niagen®	Already sold as a supplement/ingredient; recently licensed rights for a pharmaceutical-NR therapy (for e.g., Parkinson's) under regulatory path.
MetroBiotech	Private	MIB-626 (novel NAD+ booster), MIB-725 (next-gen NAD+ precursor)	MIB-626 is in Phase 2 for Alzheimer's, chronic kidney disease, muscle strength. MIB-725 has commenced Phase 1a dose-escalation.
MetaShape Pharma	Private	MS 001 – an inhibitor of PNP (purine nucleoside phosphorylase) aiming to boost NAD⁺ by blocking precursor degradation	Early stage (pre-clinical/initial development) targeting age-related diseases (cognitive decline, cholesterol, neurodegeneration) via NAD+ modulation.

Source: Stifel Investment Banking Department.

METROBIOTECH

Most NAD⁺ boosters on the market (like nicotinamide riboside [NR] or nicotinamide mononucleotide [NMN]) are sold as dietary supplements, not as rigorously tested drugs. MetroBiotech is pursuing FDA-regulated drug development with its lead candidate MIB-626.

MetroBiotech's innovation centers on chemical form and delivery: MIB-626 is not merely NMN, but a refined, proprietary salt/crystalline form that exhibits higher oral absorption, plasma stability, and NAD⁺ conversion efficiency in animal and early human studies.

In Phase 1 trials, MIB-626 showed dose-dependent increases in whole-blood NAD⁺ and improved mitochondrial function markers, suggesting true pharmacologic control rather than nutritional supplementation. Rather than claiming to "reverse aging," MetroBiotech focuses on disease indications with clear regulatory endpoints that are mechanistically tied to NAD⁺ decline such as Neurodegeneration (Alzheimer's, Parkinson's), mitochondrial myopathy and muscle weakness and chronic kidney disease.

Some Clinical Benefit of Supplements that Increase NAD Shown in a Small Indian Study (But No Mortality Gain)

Yi L, Maier AB, Tao R, Lin Z, Vaidya A, Pendse S, Thasma S, Andhalkar N, Avhad G, Kumbhar V. The efficacy and safety of β-nicotinamide mononucleotide (NMN) supplementation in healthy middle-aged adults: a randomized, multicenter, double-blind, placebo-controlled, parallel-group, dose-dependent clinical trial. *Geroscience*. 2023 Feb;45(1):29-43.

In animal studies, β-nicotinamide mononucleotide (NMN) supplementation increases nicotinamide adenine dinucleotide (NAD) concentrations and improves healthspan and lifespan with great safety. However, it is unclear if these effects can be transferred to humans. This randomized, multicenter, double-blind, placebo-controlled, parallel-group, dose-dependent clinical trial included 80 middle-aged healthy adults being randomized for a 60-day clinical trial with once daily oral dosing of placebo, 300 mg, 600 mg, or 900 mg NMN. The primary objective was to evaluate blood NAD concentration with dose-dependent regimens. The secondary objectives were to assess the safety and tolerability of NMN supplementation, next to the evaluation of clinical efficacy by measuring physical performance (six-minute walking test), blood biological age (Aging.Ai 3.0 calculator), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and subjective general health assessment [36-Item Short Form Survey Instrument (SF-36)]. Statistical analysis was performed using the Per Protocol analysis with significant level set at $p = 0.05$. All 80 participants completed the trial without trial protocol violation. Blood NAD concentrations were statistically significantly increased among all NMN-treated groups at day 30 and day 60 when compared to both placebo and baseline (all $p \leq 0.001$). Blood NAD concentrations were highest in the groups taking 600 mg and 900 mg NMN. No safety issues, based on monitoring adverse events (AEs), laboratory and clinical measures, were found, and NMN supplementation was well tolerated. Walking distance increase during the six-minute walking test was statistically significantly higher in the 300 mg, 600 mg, and 900 mg groups compared to placebo at both days 30 and 60 (all $p < 0.01$), with longest walking distances measured in the 600 mg and 900 mg groups. The blood biological age increased significantly in the placebo group and stayed unchanged in all NMN-treated groups at day 60, which resulted in a significant difference between the treated groups and placebo (all $p < 0.05$).

Source: https://pubmed.ncbi.nlm.nih.gov/36482258/

This is a good start. However, this study has a small sample size, a short duration, and imperfect endpoints. It would be interesting to shift from surrogate endpoints (e.g., NAD^+ level, walking test) to hard "aging" endpoints (mortality, frailty, cognition over years) in larger studies done over longer time periods.

Stealth Biotherapeutics Focused on Preservation of Mitochondrial Health

Stealth BioTherapeutics is a clinical-stage biopharmaceutical company focused on the discovery, development, and commercialization of novel therapies for age-related and rare genetic diseases involving mitochondrial dysfunction.

Elamipretide was tested in a Phase 3 clinical trial in primary mitochondrial myopathy, a rare skeletal myopathic disease, and was recently approved by the FDA for Barth syndrome, an ultra-rare cardioskeletal disease. It's called FORZINITY.

Elamipretide is in Phase 3 in dry age-related macular degeneration, where Stealth saw a 43% protective effect on the photoreceptors (a prespecified endpoint) and a significant number of patients gaining 2 or more lines of low light best corrected visual acuity in Phase 2, despite no signal on GA (which was the primary endpoint). Stealth has gained FDA alignment on photoreceptor death, measured by OCT, as an approvable endpoint, and it is the key endpoint in its fully-enrolled ReNEW Phase 3 study.

Elamipretide is also in an aging study at the University of Washington.

Mitochondrial Inner Membrane Targeting: Elamipretide binds to cardiolipin, a lipid located in the inner membrane of mitochondria. Cardiolipin is crucial for maintaining the structure and function of the inner mitochondrial membrane, including the organization of proteins involved in the electron transport chain (ETC).

Reducing Reactive Oxygen Species (ROS) Production: Mitochondrial dysfunction often leads to an overproduction of reactive oxygen species (ROS), which can cause oxidative damage to the mitochondrial membrane, proteins, and DNA. By stabilizing the inner mitochondrial membrane, Elamipretide reduces ROS production, preventing oxidative stress.

Improving Electron Transport Chain (ETC) Efficiency: By interacting with cardiolipin and stabilizing the mitochondrial membrane, Elamipretide helps improve the function of the ETC. This enhances the efficiency of energy (ATP) production, leading to better cellular energy management and reducing the impact of mitochondrial diseases where ATP production is impaired.

Preventing Mitochondrial Swelling and Cytochrome c Release: Elamipretide helps maintain mitochondrial integrity by preventing the swelling of mitochondria and the release of cytochrome c, which are steps involved in the initiation of programmed cell death (apoptosis). This can protect cells from premature death due to mitochondrial dysfunction.

Elamipretide Can Correct Imbalances Caused by Oxidative Stress

GeroScience (2023) 45:3529–3548
https://doi.org/10.1007/s11357-023-00861-y

ORIGINAL ARTICLE

The mitochondrially targeted peptide elamipretide (SS-31) improves ADP sensitivity in aged mitochondria by increasing uptake through the adenine nucleotide translocator (ANT)

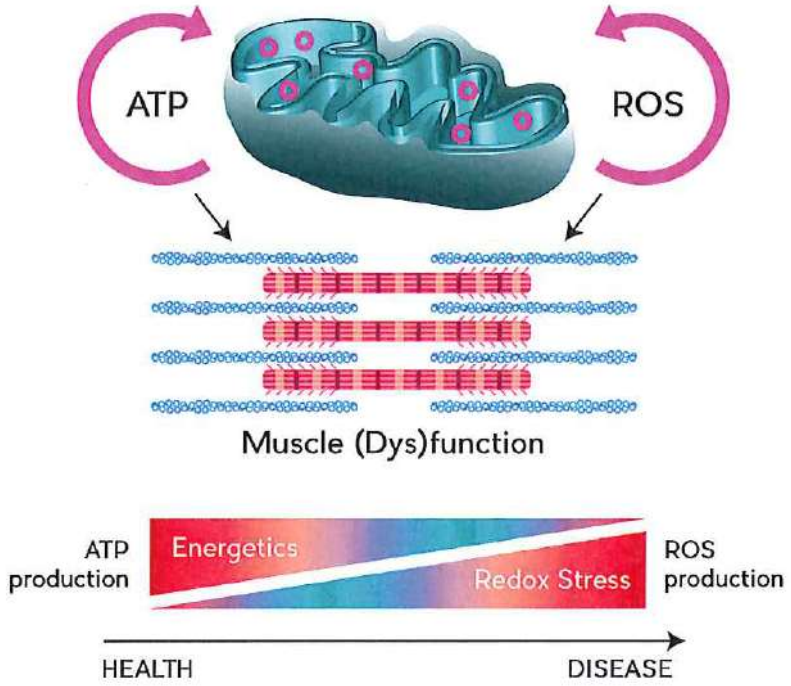
Gavin Pharaoh · Varun Kamat · Sricharan Kannan · Rudolph S. Stuppard · Jeremy Whitson · Miguel Martín-Pérez · Wei-Jun Qian · Michael J. MacCoss · Judit Villén · Peter Rabinovitch · Matthew D. Campbell · Ian R. Sweet · David J. Marcinek

Received: 18 April 2023 / Accepted: 23 June 2023 / Published online: 18 July 2023

Abstract Aging muscle experiences functional decline in part mediated by impaired mitochondrial ADP sensitivity. Elamipretide (ELAM) rapidly improves physiological and mitochondrial function in aging and binds directly to the mitochondrial ADP transporter ANT. We hypothesized that ELAM improves ADP sensitivity in aging leading to rescued physiological function. We measured the response to ADP stimulation in young and old muscle mitochondria with ELAM treatment, in vivo heart and muscle function, and compared protein abundance, phosphorylation, and S-glutathionylation of ADP/ATP pathway proteins. ELAM treatment increased ADP sensitivity in old muscle mitochondria by increasing uptake of ADP through the ANT and rescued muscle force and heart systolic function. Protein abundance in the ADP/ATP transport and synthesis pathway was unchanged, but ELAM treatment decreased protein s-glutathionylation incuding of ANT. Mitochondrial ADP sensitivity is rapidly modifiable. This research supports the hypothesis that ELAM improves ANT function in aging and links mitochondrial ADP sensitivity to physiological function.

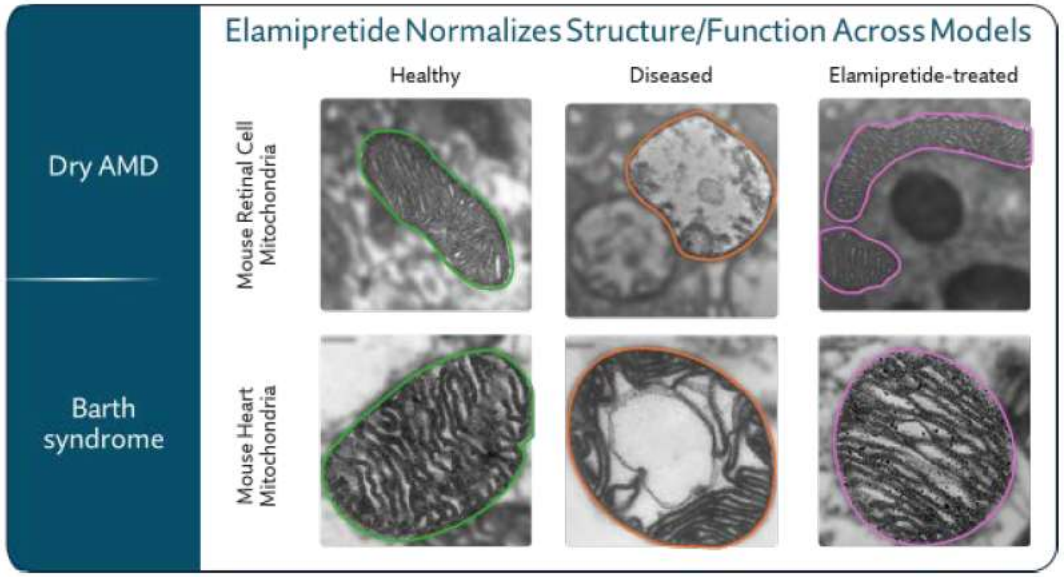
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11357-023-00861-y

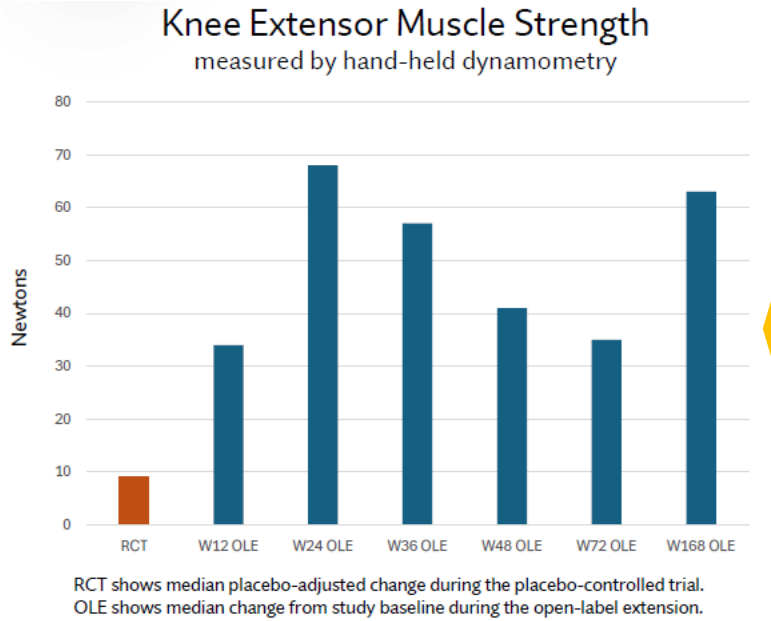
'Our research focuses on how changes in mitochondria energetics and oxidative stress affect the pathological and adaptive signalling in skeletal muscle. We have found that some pathological conditions associated with ageing may be more dynamic than previously thought and could be rapidly reversed by targeted intervention with agents such as elamipretide to restore redox or energetic balance.'



Also see https://pubmed.ncbi.nlm.nih.gov/39554099/

Stealth Bio Building up a Pipeline of Mitochondrial Drugs





Barth Syndrome Data

1. No changes in knee extensor muscle strength, which FDA considers an intermediate clinical endpoint (ICE), were observed in the placebo-controlled portion of the TAZPOWER clinical trial.
2. Improvements ranged from median increases of 34 to 68 newtons (approximately 7.5 to 15 pounds) during the open-label extension (OLE) through week 168.
3. FDA determined that improvements in knee extensor muscle strength are reasonably likely to predict clinical benefit in Barth syndrome, such as an ability to stand more easily or walk farther.

Forzinity™ (elamipretide) injection
1st approved mitochondrial medicine

Elamipretide
Healthspan insights from X-prize funded Phase 1B trial

Elamipretide
Approved or in pivotal trial for POLG-related disorders

Phase 3 ReNEW data seeds dAMD partnership opportunity

Bevemipretide *topical drops*
Partner-ready for dry AMD

Potential to improve vision for intermediate dAMD

Bevemipretide *exploring QW Phase 2 for PD*

SBT-255 *in Phase 2 development (DMD?)*

SBT-589 *in Phase 1 development (FA/Leigh?)*

Source: Stealth Biotherapeutics Corporate Presentation, November 2025

Mitochondrial Uncoupler Drugs Have High Potential

Mitochondrial uncoupler drugs—agents that mildly dissipate the proton gradient across the inner mitochondrial membrane—have long been theorized to slow aging by lowering mitochondrial membrane potential, reducing reactive oxygen species (ROS) generation, and promoting mitochondrial renewal.

Three key studies across different biological systems support this “uncoupling to survive” hypothesis that was enunciated by Martin Brand in 2000.

Speakman et al. (2004) showed that mice with naturally higher metabolic intensity and greater intrinsic uncoupling lived dramatically longer—about 36%—than mice with lower metabolic rates, suggesting that mild uncoupling is not simply energetically costly but may instead be protective.

This concept was further validated experimentally by Caldeira da Silva et al. (2008), who used controlled, low-dose DNP (a classical uncoupler) to induce mild uncoupling in mice. Treated animals displayed reduced oxidative damage to DNA and proteins, improved metabolic markers, and a measurable extension of mean lifespan. Importantly, the doses were far below toxic thresholds, highlighting that “therapeutic uncoupling”—as opposed to the extreme uncoupling historically associated with DNP toxicity—can enhance mitochondrial efficiency and reduce cumulative oxidative stress.

Nicholatos et al. (2019) extended the observation to natural variation in dogs: fibroblasts from long-lived small breeds exhibited higher uncoupling, lower membrane potential, and greater respiratory capacity than those from large breeds with shorter lifespans.

Fielder et al. (2024) notes that uncouplers can synergize with other aging drug approaches including senolytics.

Biotechs Developing Mitochondrial Uncouplers in the Clinic Include:*

Rivus PHARMACEUTICALS

orsobio

There are also efforts underway at Mitochon.

Taurine Shows Promise in a Recent Study

Singh P, et al., "Taurine deficiency as a driver of aging," *Science*, June 9, 2023; 380(6649):eabn9257.

Aging is associated with changes in circulating levels of various molecules, some of which remain undefined. We find that concentrations of circulating taurine decline with aging in mice, monkeys, and humans. A reversal of this decline through taurine supplementation increased the health span (the period of healthy living) and life span in mice and health span in monkeys. Mechanistically, taurine reduced cellular senescence, protected against telomerase deficiency, suppressed mitochondrial dysfunction, decreased DNA damage, and attenuated inflammaging. In humans, lower taurine concentrations correlated with several age-related diseases and taurine concentrations increased after acute endurance exercise. Thus, taurine deficiency may be a driver of aging because its reversal increases health span in worms, rodents, and primates and life span in worms and rodents. Clinical trials in humans seem warranted to test whether taurine deficiency might drive aging in humans.

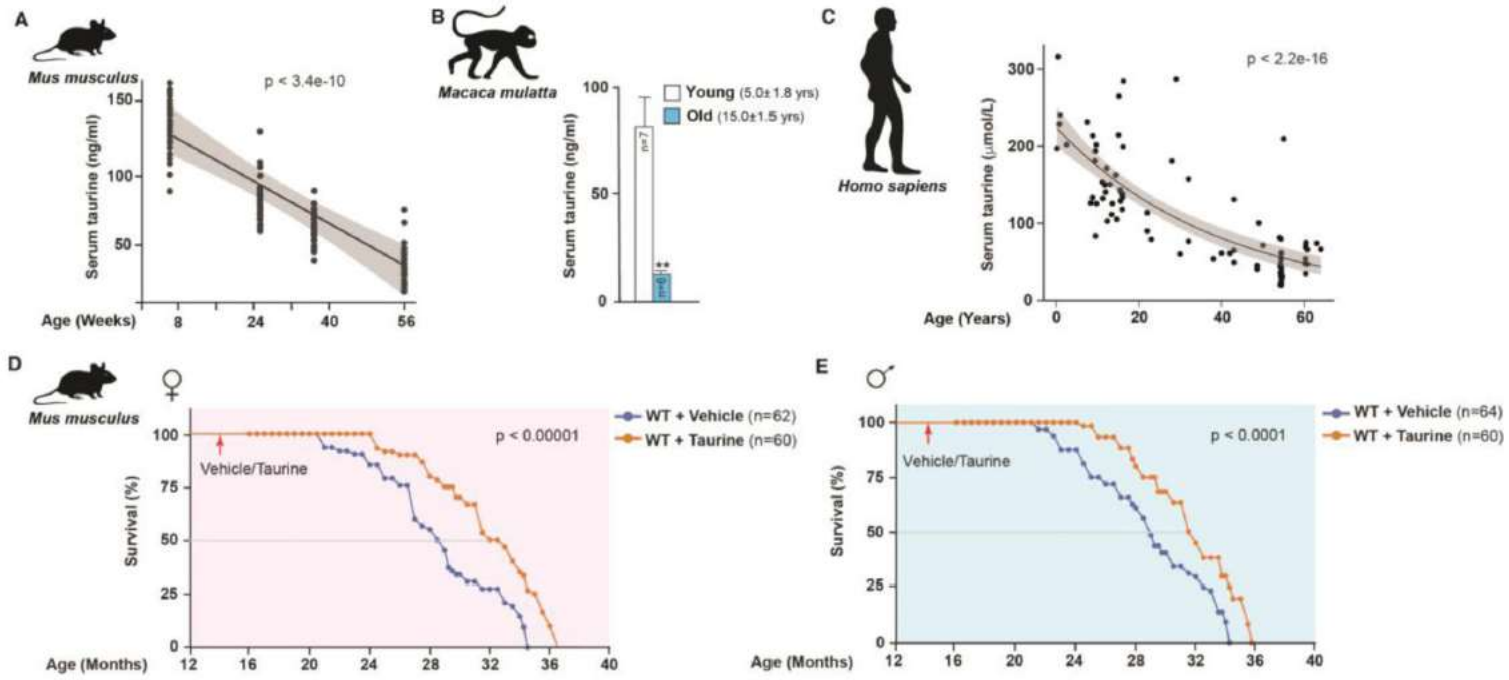


Fig. 1. Taurine deficiency is a driver of aging in evolutionarily divergent species. (A-C) Serum taurine levels in female mice at different ages (A), in young (5-year-old) and old (15-year-old) female monkeys (B), and in humans at different ages (C). (D-E)

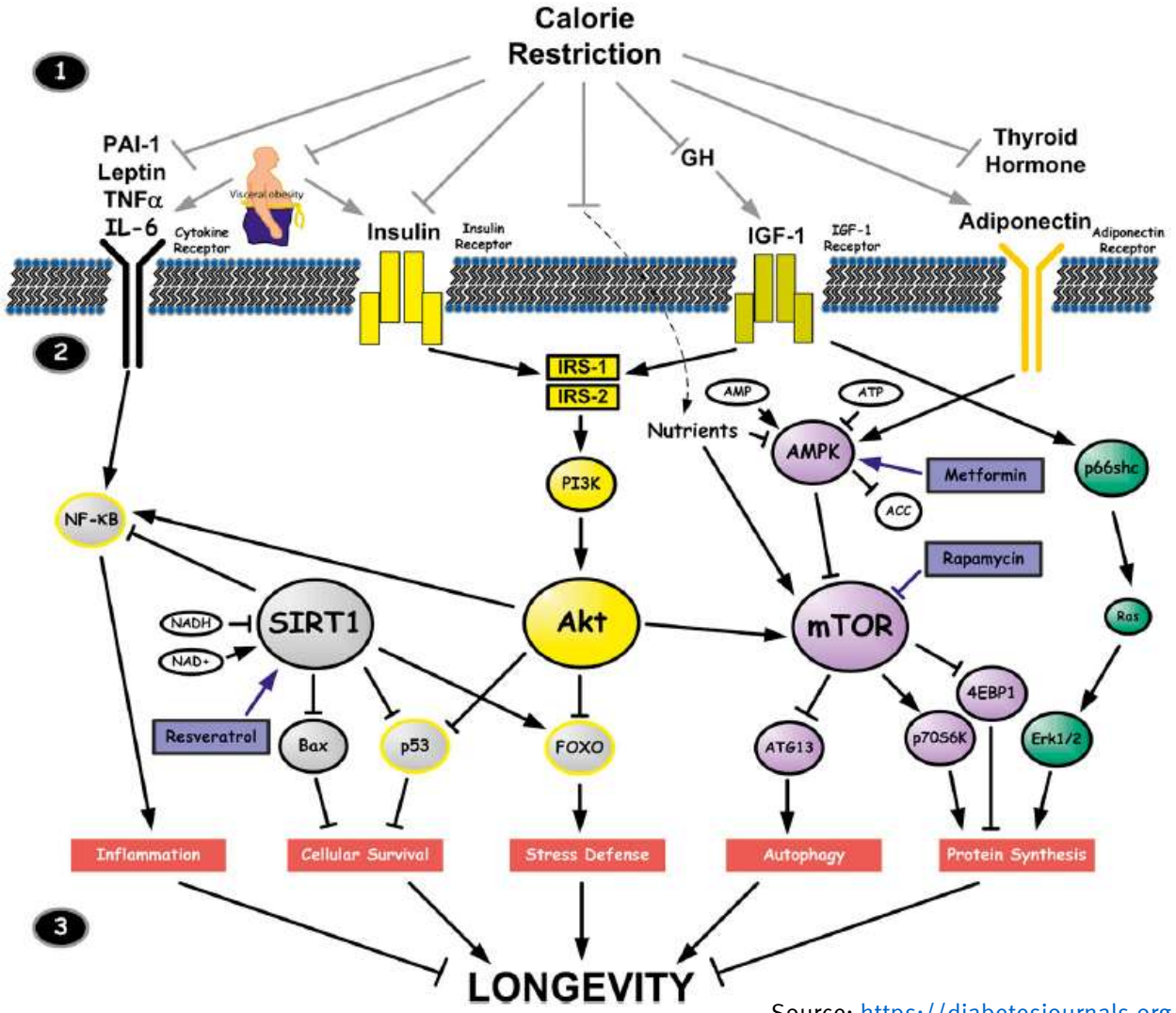
Source: https://www.science.org/doi/10.1126/science.abn9257

Classic Treatments for Mitochondrial Disease May be Relevant in the Aging Context

There are many aspect of mitochondrial disease and there may be ways of treating it using drugs and supplements that are already known to have utility in specific contexts as noted in the table. It strikes us as evident that one could benefit from treating specific disorders of mitochondrial function in aging persons.

Product	Mechanism of Action	Targeted Disease Aspect/Symptom
L-Carnitine	Transports long-chain fatty acids into the mitochondria for beta-oxidation (fat energy production).	**Energy Production:** Supports fat metabolism, an alternative energy source to glucose.
	Helps detoxify the cell by binding to and removing accumulated toxic acyl-CoA groups that can inhibit mitochondrial enzymes.	**Secondary Deficiency:** Addresses the secondary carnitine deficiency often seen in mitochondrial patients.
CoEnzyme Q10	Acts as a crucial electron carrier between Complexes I/II and Complex III in the Electron Transport Chain (ETC).	**Energy Production:** Improves the efficiency of the ETC, helping to maximize ATP production.
	Functions as a powerful lipid-soluble antioxidant, protecting mitochondrial membranes and DNA from oxidative damage.	**Primary CoQ10 Deficiency:** Disease-specific treatment for this rare genetic cause. **Oxidative Stress:** Reduces cell damage from free radicals.
L-Arginine	L-Arginine is the precursor to Nitric Oxide (NO). In conditions like MELAS syndrome, NO production is impaired.	**MELAS Stroke-like Episodes:** Used intravenously during acute episodes to restore NO, improving blood flow (vasodilation) to the affected areas of the brain.
		Prevention: Used orally (prophylactically) to reduce the frequency and severity of stroke-like episodes in MELAS patients.

Multiple Pathways Link Calorie Restriction to Longevity Including SIRT1, AKT, FOXO and mTOR



Nir Barzilai et.al, *Diabetes*, May 14, 2012

FIG. 1. Major metabolic pathways that regulate mammalian longevity. Life span has been verifiably modulated by genetic, pharmacologic, and dietary interventions in model systems. 1: CR represents the most robust intervention to extend both mean and maximum life span in mammals, perhaps due to the magnitude of pathways affected by CR, including reduced cytokine levels, adiposity, IIS signaling, thyroid hormone levels, and increased adiponectin. 2: In response to these changes, numerous downstream cellular pathways are engaged, including SIRT1 activation (gray), IIS/phosphatidylinositol 3-kinase (PI3K)/Akt signaling (yellow), AMPK/mTOR signaling (purple), and extracellular signal-regulated kinase ½ (Erk1/2) signaling (green). 3: The collective response of these pathways to CR is believed to promote cellular fitness and ultimately longevity via activation of autophagy, stress defense mechanisms, and survival pathways while attenuating proinflammatory mediators and cellular growth. Furthermore, there is evidence supporting that life span extension can be achieved with pharmacologic approaches, such as rapamycin, via mTOR signaling blockade, resveratrol, by activating SIRT1 activity, and metformin, which seems to be a robust stimulator of AMPK activity. Arrows indicate a directional and stimulatory relationship, whereas blunt-ended lines indicate an inhibitory effect. Please note that there is some evidence that Akt activation of NF-kB may be mTOR-dependent, whereas SIRT1 may be a direct stimulator of AMPK activity and autophagy (not shown). TNFa, tumor necrosis factor-a; IL-6, interleukin-6; NF-kB, nuclear factor-kB; PAI-1, plasminogen activator inhibitor 1; IRS-1, insulin receptor substrate-1.

Source: https://diabetesjournals.org/diabetes/article/61/6/1315/15367/The-Critical-Role-of-Metabolic-Pathways-in-Aging

Several Other Types of Interventions Proposed to Extend Lifespan in Humans

Kritchevsky SB, Cummings SR., "Geroscience: A Translational Review," *JAMA*, Sep 23 2025; 334(12):1094-1102.

ROS Pathway

ROS Pathway

Table 1. Select Interventions Hypothesized to Have Benefits Related to Effects on the Biology of Aging in Humans

Pathways/targets	Aging-related pathways affected	Observations from preclinical models	Potential interventions	Summary of human data
Caloric restriction	Increased autophagy Decreased reactive oxygen species Decreased inflammation Decreased cellular senescence Increased DNA repair Preserved mitochondrial function	Lifespan extension in multiple animal species Delay in onset of age-related disease	Voluntary caloric restriction GLP-1 receptor agonists (eg, semaglutide, tirzepatide, liraglutide) Other pharmacologic interventions to decrease caloric intake Bariatric surgery	Meta-analysis of weight loss trials showed a reduction in all-cause mortality Caloric restriction slowed aging according to various measures of biologic age
Metformin	Increased autophagy Decreased reactive oxygen species Decreased inflammation Increased DNA repair Decreased mammalian target of rapamycin	Lifespan extension in some animal species and mouse strains Preserved physical function	Metformin	Observational data were consistent with multiple health benefits such as neurodegenerative disease and COVID-19 infection severity; Clinical trial data are mixed
Rapamycin/ rapalogs	Decreased mammalian target of rapamycin Increased autophagy	Lifespan extension in multiple animal species Delay in onset of age-related disease	Sirolimus Everolimus Temsirolimus RTB101	Evidence of improved vaccine efficacy; improved symptoms in patients with rheumatoid arthritis
Senolytics	Decreased burden of senescent cells targeting p16 and p53/p21 Decreased inflammation	Lifespan extension Reduction of age-related organ dysfunction	Dasatanib plus quercitin Fisetin	Early-phase studies indicate that treatments are well-tolerated

Source: https://jamanetwork.com/journals/jama/fullarticle/2837435

There is Some Data Showing Benefits of Rapamycin for Lifespan of Mice

Kritchevsky SB, Cummings SR., "Geroscience: A Translational Review," *JAMA*, Sep 23 2025; 334(12):1094-1102.

ROS Pathway

Table 2. Lifespan Effects of Select Compounds Evaluated by the Interventions Testing Program Evaluation in Genetically Heterogeneous Mice (UM-HET3)

Compound (age started)	Mode of action	Maximal lifespan extension, %	Human indications and adverse effects	Adverse effects
Acarbose	Inhibits α-glucosidase, which breaks down ingested carbohydrates	8% Female 11% Male	Type 2 diabetes	Diarrhea and flatulence
Metformin (9 mo)	Multiple; inhibition of mitochondrial complex I, activation of adenosine monophosphate protein kinase, decreased liver gluconeogenesis, increased insulin sensitivity	No significant effect in either sex	Type 2 diabetes, ovary syndrome	Diarrhea, nausea, bloating, decreased vitamin B_{12} absorption, lactic acidosis (rare)
Rapamycin (9 mo)	Inhibition of mammalian target of rapamycin complex 1 signaling	16% Female 11% Male	Prevention of organ transplant rejection Multiple, decreased glucose tolerance, peripheral edema, dyslipidemia, stomatitis, infection	Multiple, including decreased glucose tolerance, peripheral edema, dyslipidemia, stomatitis, infection
Rapamycin (20 mo)	See above	14% Female 9% Male	See above	See above
Metformin and rapamycin (16 mo)	See above	17% Female 14% Male	See above	See above
Acarbose and rapamycin	See above	15% Female 18% Male	See above	See above
Canagliflozin	Sodium-glucose cotransporter-2 inhibitor Increased glucose excretion	No significant effect on females 10% Male	Type 2 diabetes, cardiovascular disease prevention	Multiple, including urinary tract infection, limb amputation, acute kidney injury dehydration, yeast infection, hypoglycemia, bone fractures

Observational Data Suggests that Metformin Can Reduce Mortality in Diabetics vs. Sulfonylureas

Bannister CA, Holden SE, Jenkins-Jones S, Morgan CL, Halcox JP, Schernthaner G, Mukherjee J, Currie CJ. Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls. *Diabetes Obes Metab*. 2014 Nov;16(11):1165-73.

We used retrospective observational data from the UK Clinical Practice Research Datalink (CPRD) from 2000. Subjects with type 2 diabetes who progressed to first-line treatment with metformin or sulphonylurea monotherapy were selected and matched to people without diabetes. Progression to all-cause mortality was compared using parametric survival models that included a range of relevant co-variables.

Results: We identified 78,241 subjects treated with metformin, 12,222 treated with sulphonylurea, and 90,463 matched subjects without diabetes. This resulted in a total, censored follow-up period of 503,384 years. There were 7498 deaths in total, representing unadjusted mortality rates of 14.4 and 15.2, and 50.9 and 28.7 deaths per 1000 person-years for metformin monotherapy and their matched controls, and sulphonylurea monotherapy and their matched controls, respectively. With reference to observed survival in diabetic patients initiated with metformin monotherapy [survival time ratio (STR) = 1.0], adjusted median survival time was 15% lower (STR = 0.85, 95% CI 0.81-0.90) in matched individuals without diabetes and 38% lower (0.62, 0.58-0.66) in diabetic patients treated with sulphonylurea monotherapy.

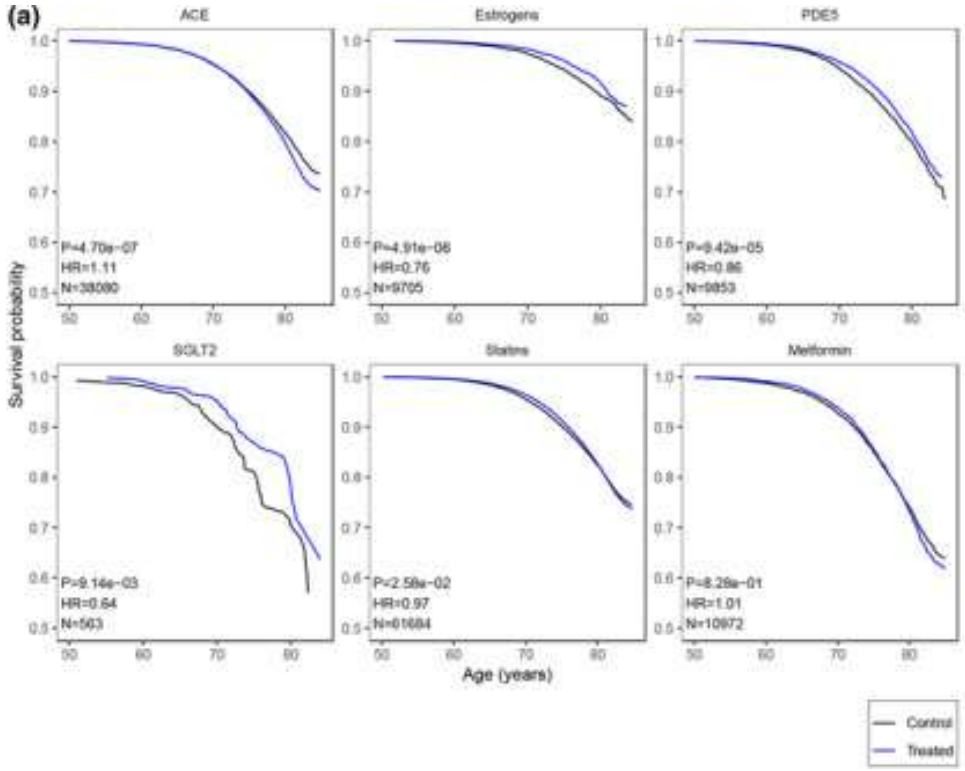
Conclusions: Patients with type 2 diabetes initiated with metformin monotherapy had longer survival than did matched, non-diabetic controls. Those treated with sulphonylurea had markedly reduced survival compared with both matched controls and those receiving metformin monotherapy. This supports the position of metformin as first-line therapy and implies that metformin may confer benefit in non-diabetes. Sulphonylurea remains a concern.

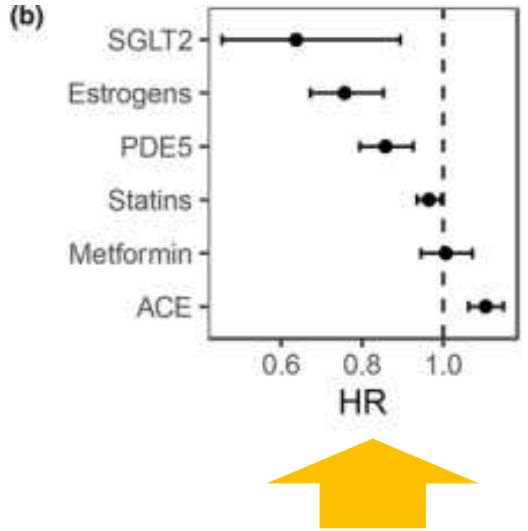
This study did not find that non-diabetics lived shorter lives than diabetics on metformin. This is not particularly informative because it is well known that diabetics live shorter lives in general.

In a Large Real World Evidence Study, Persons on SGLT2s had Remarkably Better Survival. In Contrast, There was no Survival Benefit for Those on Metformin

Morin J, Rolland Y, Bischoff-Ferrari HA, Ocampo A, Perez K. Association between prescription drugs and all-cause mortality risk in the UK population. *Aging Cell*. 2024 Dec;23(12):e14334.

The UK Biobank has collected data on prescription medications and mortality for over 500,000 participants aged 40–70 years. This study analyzed the effects of the top 406 prescribed medications on overall mortality rates in the general population. Most drugs were linked to a shortened lifespan, likely due to the life-limiting nature of the diseases they are prescribed to treat. However, a few medications, notably Sildenafil, SGLT2's Atorvastatin, Naproxen, and Estradiol, were associated with increased lifespans.





These results are quite interesting because this was a gigantic real world evidence study that was not confined to diabetics. SGLT2s have a huge mortality benefit, but much discussed metformin didn't matter at all. However, this is not a controlled study so confounding factors could be at play.

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC11634711/

A Prospective Study Failed to Find a Benefit of Metformin on Survival / Lifespan in PreDiabetics

Lee CG, Heckman-Stoddard B, Dabelea D, Gadde KM, Ehrmann D, Ford L, Prorok P, Boyko EJ, Pi-Sunyer X, Wallia A, Knowler WC, Crandall JP, Temprosa M; Diabetes Prevention Program Research Group; Diabetes Prevention Program Research Group:. Effect of Metformin and Lifestyle Interventions on Mortality in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. *Diabetes Care*. 2021 Dec;44(12):2775-2782.

Research design and methods: From 1996 to 1999, 3,234 adults at high risk for type 2 diabetes were randomized to an intensive lifestyle intervention, masked metformin, or placebo. Placebo and lifestyle interventions stopped in 2001, and a modified lifestyle program was offered to everyone, but unmasked study metformin continued in those originally randomized. Causes of deaths through 31 December 2018 were adjudicated by blinded reviews. All-cause and cause-specific mortality hazard ratios (HRs) were estimated from Cox proportional hazards regression models and Fine-Gray models, respectively.

Results: Over a median of 21 years (interquartile range 20-21), 453 participants died. Cancer was the leading cause of death (n = 170), followed by cardiovascular disease (n = 131). Compared with placebo, metformin did not influence mortality from all causes (HR 0.99 [95% CI 0.79, 1.25]), cancer (HR 1.04 [95% CI 0.72, 1.52]), or cardiovascular disease (HR 1.08 [95% CI 0.70, 1.66]). Similarly, lifestyle modification did not impact all-cause (HR 1.02 [95% CI 0.81, 1.28]), cancer (HR 1.07 [95% CI 0.74, 1.55]), or cardiovascular disease (HR 1.18 [95% CI 0.77, 1.81]) mortality. Analyses adjusted for diabetes status and duration, BMI, cumulative glycemic exposure, and cardiovascular risks yielded results similar to those for all-cause mortality.

Conclusions: Cancer was the leading cause of mortality among adults at high risk for type 2 diabetes. Although metformin and lifestyle modification prevented diabetes, neither strategy reduced all-cause, cancer, or cardiovascular mortality rates.

This prospective study and the previous UK RWE study using the UK Biobank both failed to find evidence associating metformin use with greater lifespan.

While there is still a case for a larger prospective study, our sense is that such a study would be unlikely to find a mortality benefit for using metformin. We are not the only skeptics.

Rapamycin Use in Humans is Not Benign Despite Complete Lack of Proven Survival Benefit; Biohacker Discontinued Use

Roark KM, Iffland PH 2nd., "Rapamycin for longevity: the pros, the cons, and future perspectives," *Front Aging*. June 20, 2025; 6:1628187.

However, long-term mTOR inhibition is accompanied by significant side effects. In epilepsy cohorts and transplant populations, chronic rapamycin or everolimus use is associated with mucosal ulcers, impaired wound healing, delayed tissue repair, and increased infection risk (Crino, 2016; Peterson et al., 2016; Hudson et al., 2024). Metabolic disturbances are also common, including elevated cholesterol and triglyceride levels (French et al., 2016; Lee et al., 2024). These effects are mechanistically attributed not only to mTORC1 inhibition but also the unintended suppression of mTORC2. Rapamycin induced mTORC2 inhibition has been shown to induce insulin resistance, highlighting a mechanistic trade-off between metabolic side effects and longevity benefits (Lamming et al., 2012). In female patients, hormonal side effects such as dysmenorrhea, menstrual irregularities, and ovarian dysfunction have been reported (Canpolat et al., 2018). These findings are largely derived from populations using rapamycin chronically at immunosuppressive doses. However, emerging data suggest that low-dose or intermittent rapamycin regimens may be more readily tolerated and are currently under investigation in multiple clinical trials (Kaeberlein et al., 2023; Konopka and Lamming, 2023; Mannick and Lamming, 2023; Hudson et al., 2024). Nonetheless, **until long-term data are available, caution is warranted–particularly when considering the use of rapamycin in otherwise healthy individuals.** The ethical implications of exposing such populations to even low levels of immunosuppression remain unresolved and merit careful deliberation and scrutiny.

As rapamycin gains popularity for its anti-aging potential, online longevity clinics have emerged offering access to the drug with minimal medical oversight. This semi-regulated availability raises ethical concerns regarding patient safety, misinformation, and the potential for serious harm. This is best illustrated by the widely publicized case of tech entrepreneur Bryan Johnson, who undertook an elaborate self-directed anti-aging regimen involving rapamycin, metformin, and over 100 daily supplements. **Despite extensive physiological tracking, Johnson ultimately discontinued rapamycin and expressed regret over its use citing side effects such as elevated blood glucose, susceptibility to infection, and impaired healing** (The Economic Times, 2025). This case highlights the risks of bypassing peer-reviewed science in favor of anecdotal "biohacking" culture. Clinical literature has long documented rapamycin-associated toxicities that mirror the complaints reported by Johnson and others (Peterson et al., 2016; Hudson et al., 2024; Lee et al., 2024). The use of such a powerful immunosuppressant outside established indications, especially in otherwise healthy individuals, demands stronger ethical scrutiny and public education.

Source: https://www.frontiersin.org/journals/aging/articles/10.3389/fragi.2025.1628187/full

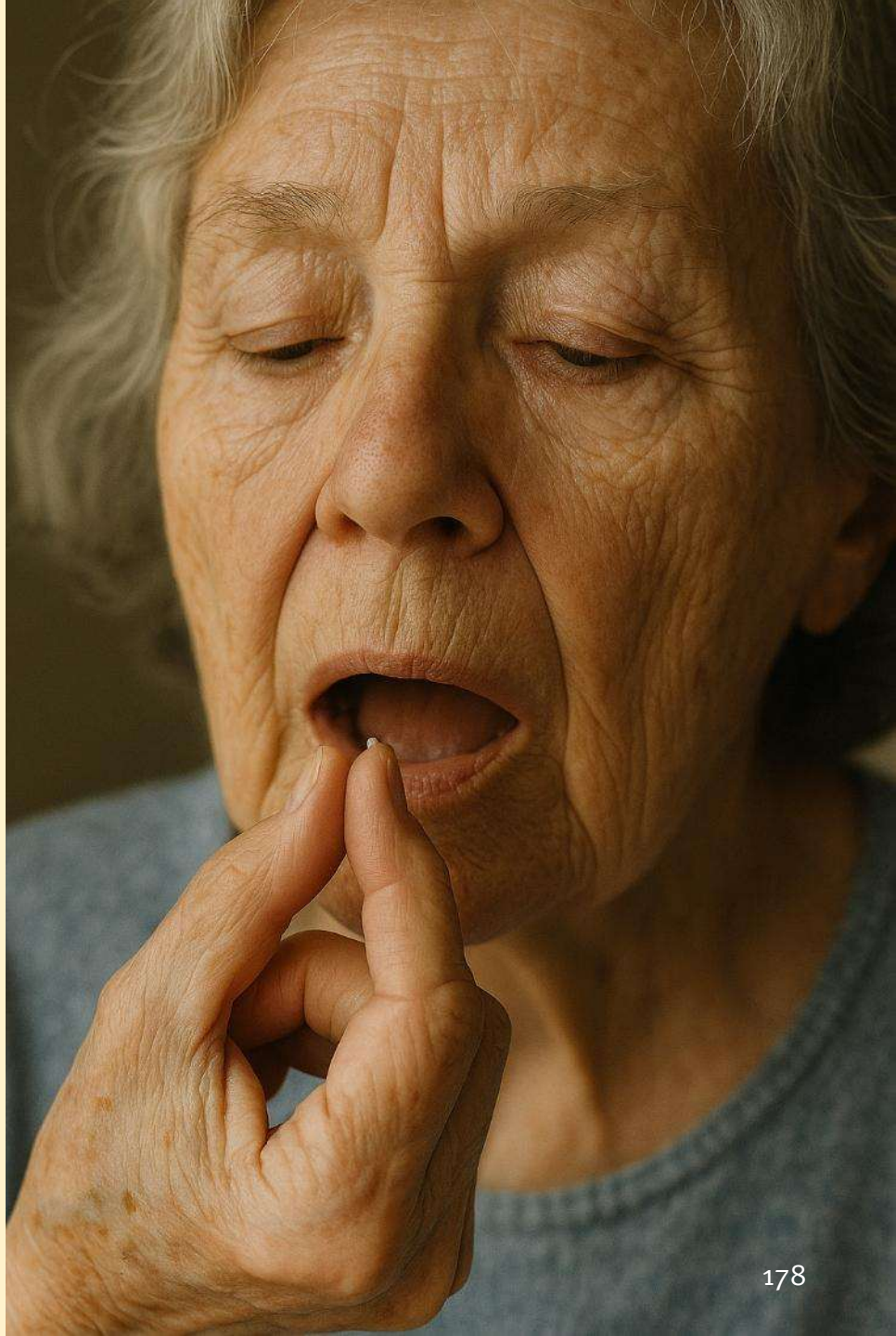
Microdosing Rapamycin Doesn't Seem to Help Much

Hands JM, Lustgarten MS, Frame LA, Rosen B., "What is the clinical evidence to support off-label rapamycin therapy in healthy adults?," *Aging* (Albany NY). Aug 7, 2025; 17(8):2079-2088.

Despite extensive preclinical evidence supporting sirolimus and other mTOR inhibitors as potential gero-therapeutics, human data have yet to demonstrate that rapamycin can extend mean or maximal lifespan or delay the onset of age-related diseases. The findings reported herein underscore the need for larger, well-designed human studies to clarify rapamycin's clinical relevance. Off-label prescribing should include vigilant monitoring for adverse effects and open discussion of knowns and unknowns with patients. Key priorities for future research include (1) establish efficacy with well-designed trials identifying relevant clinical endpoints in healthy adults, (2) identify therapeutic dose-response curves, and (3) explore synergistic interactions with other gerotherapeutics.

This paper has reviewed trials of low-dose mTOR inhibition therapy in human subjects. What emerges is a complex picture that remains insufficient to affirm or negate the longevity and healthspan extending benefits attributed to rapamycin. Despite the preclinical evidence supporting the use of sirolimus to enhance mean and maximal lifespan, the data in humans has yet to establish that rapamycin, or its analogues, is an effective seno-therapeutic to delay aging in healthy older adults.

Source: https://www.aging-us.com/article/206300/text



Aeovian is Coming at the Problem with a Selective mTORC1 Inhibitor

"Rapamycin and its previously developed analogs functionally result in nonselective inhibition of mTORC1 and mTORC2, and this nonselective profile has been associated with **tolerability issues** that limit their use in TSC and other disorders of selective mTORC1 overactivation. The nonselective mTORC1/mTORC2 inhibitor everolimus has demonstrated a partial degree of efficacy in TSC epilepsy, but its clinical use has been limited due to dose-limiting toxicities likely stemming from its undesirable off-target inhibition of mTORC2. These often result in dose reductions or interruptions which in turn limit achievable efficacy. The suboptimal safety and efficacy profile of nonselective mTORC1/mTORC2 inhibitors has resulted in a significant ongoing unmet medical need for a next-generation treatment able to achieve improved safety and efficacy by selectively targeting the mTORC1 overactivation associated with TSC. As such, we believe TSC is an exceptionally clear and compelling precision medicine target for **AV078, our first-in-class CNS-penetrant selective inhibitor of mTORC1."**

Aeovian is solving the problems of rapamycin with an mTORC1 selective agent and is now in a Phase 2 study. This company has attracted mainstream investors and strikes us having a decent change of a big pharma M&A exit. They are pursuing a good idea. Now, we just need them to run a trial for their drug to see if it impacts human lifespan.

PR Newswire (3/28/2024): Aeovian Pharmaceuticals raised $50 million to fuel clinical trials of its lead candidate, AV078, to treat a rare, genetic form of epilepsy.

The round, which was led by Hevolution, comes as Aeovian dosed the first participant in a Phase I trial assessing the safety of AV078 in healthy volunteers. The compound is a central nervous system-penetrant selective mTORC1 inhibitor in development for tuberous sclerosis complex (TSC) epilepsy. "TSC is a genetic disorder of mTORC1 hyperactivation," CEO Allison Hulme said. "AV078 has the potential to be transformative for patients with TSC refractory epilepsy, a patient population in need of therapeutic options with better efficacy and tolerability." The financing – which saw participation from existing investors Apollo Health Ventures, Sofinnova Investments, venBio, Evotec and b2venture – is expected to provide Aeovian enough runway to finish the Phase I study and prepare for a Phase II trial in adult and paediatric patients with TSC refractory epilepsy.

The Pitch for Aeovian: The argument for Aeovian's selected mTORC1 inhibitor notes first that human's can't tolerate therapeutic doses of rapamycin but can tolerate doses of an mTORC1 inhibitor. However, marmosets (a super cute type of monkey) *can* tolerate high doses of rapamycin. Adam Salmon has been running a quiet placebo-controlled rapamycin study in monkeys for eight years and is getting a much better survival rate in the rapa group. The idea/hope then is that humans will also see material longer survival on an mTORC1 inhibitor.

Source: Aeovian Web Site

IL-11 is Another Target in the mTOR Pathway

Inhibition of IL-11 signalling extends mammalian healthspan and lifespan

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Anissa A. Widjaja[1,12,13], Wei-Wen Lim[1,2,12], Sivakumar Viswanathan[1], Sonia Chothani[1], Ben Corden[2,3], Cibi Mary Dasan[1], Joyce Wei Ting Goh[1], Radiance Lim[1], Brijesh K. Singh[1], Jessie Tan[2], Chee Jian Pua[2], Sze Yun Lim[1], Eleonora Adami[4], Sebastian Schafer[1], Benjamin L. George[1], Mark Sweeney[5], Chen Xie[2], Madhulika Tripathi[1], Natalie A. Sims[6,7], Norbert Hübner[4,8,9], Enrico Petretto[1,10], Dominic J. Withers[5,11], Lena Ho[1], Jesus Gil[5,11], David Carling[5,11] & Stuart A. Cook[1,2,5,13]

For healthspan and lifespan, ERK, AMPK and mTORC1 represent critical pathways and inflammation is a centrally important hallmark[1–7]. Here we examined whether IL-11, a pro-inflammatory cytokine of the IL-6 family, has a negative effect on age-associated disease and lifespan. As mice age, IL-11 is upregulated across cell types and tissues to regulate an ERK–AMPK–mTORC1 axis to modulate cellular, tissue- and organismal-level ageing pathologies. Deletion of *Il11* or *Il11ra1* protects against metabolic decline, multimorbidity and frailty in old age. Administration of anti-IL-11 to 75-week-old mice for 25 weeks improves metabolism and muscle function, and reduces ageing biomarkers and frailty across sexes. In lifespan studies, genetic deletion of *Il11* extended the lives of mice of both sexes, by 24.9% on average. Treatment with anti-IL-11 from 75 weeks of age until death extends the median lifespan of male mice by 22.5% and of female mice by 25%. Together, these results demonstrate a role for the pro-inflammatory factor IL-11 in mammalian healthspan and lifespan. We suggest that anti-IL-11 therapy, which is currently in early-stage clinical trials for fibrotic lung disease, may provide a translational opportunity to determine the effects of IL-11 inhibition on ageing pathologies in older people.

Nature, Aug 1, 2024

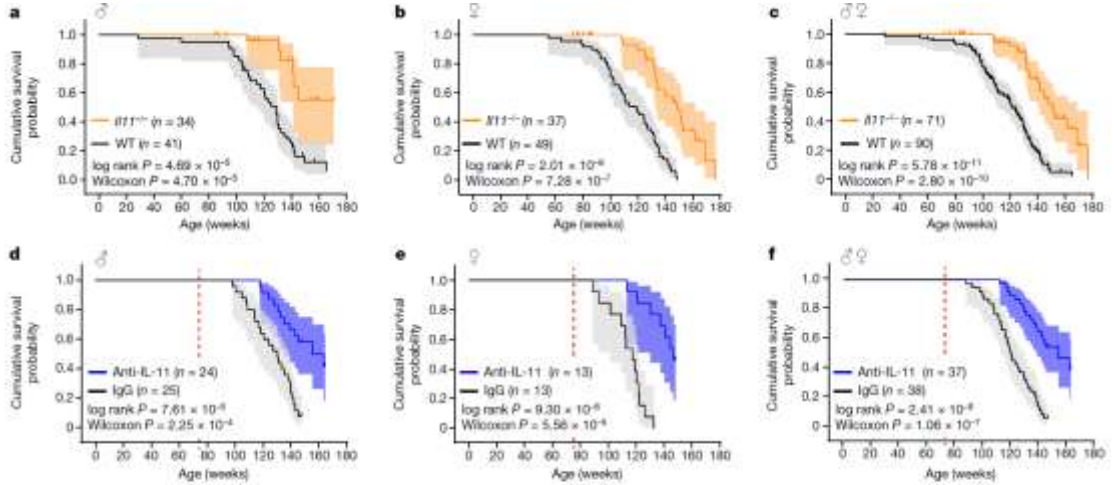


Fig. 5 | Genetic or pharmacologic inhibition of IL-11 extends life expectancy of male and female mice. a–c, Kaplan–Meier survival curves (shading represents 95% confidence interval) showing the cumulative survival probabilities for male (**a**), female (**b**) and sex-pooled (**c**) wild-type and *Il11*$^{-/-}$ mice. **d–f**, Kaplan–Meier survival curves showing the cumulative survival probabilities for male (**d**), female (**e**) and sex-pooled (**f**) mice, comparing those receiving monthly administration of IgG or X203 (40 mg kg^{-1}, intraperitoneal injection), starting from 75 weeks of age (red dotted line). Statistical significance (two-tailed *P* value) was assessed by means of the log-rank (Mantel–Cox) and Wilcoxon test for survival curve comparisons.

June 26, 2025

Mabwell Bioscience and Calico Life Sciences Announce Exclusive Licensing Agreement for Novel IL-11 Targeting Monoclonal Antibody

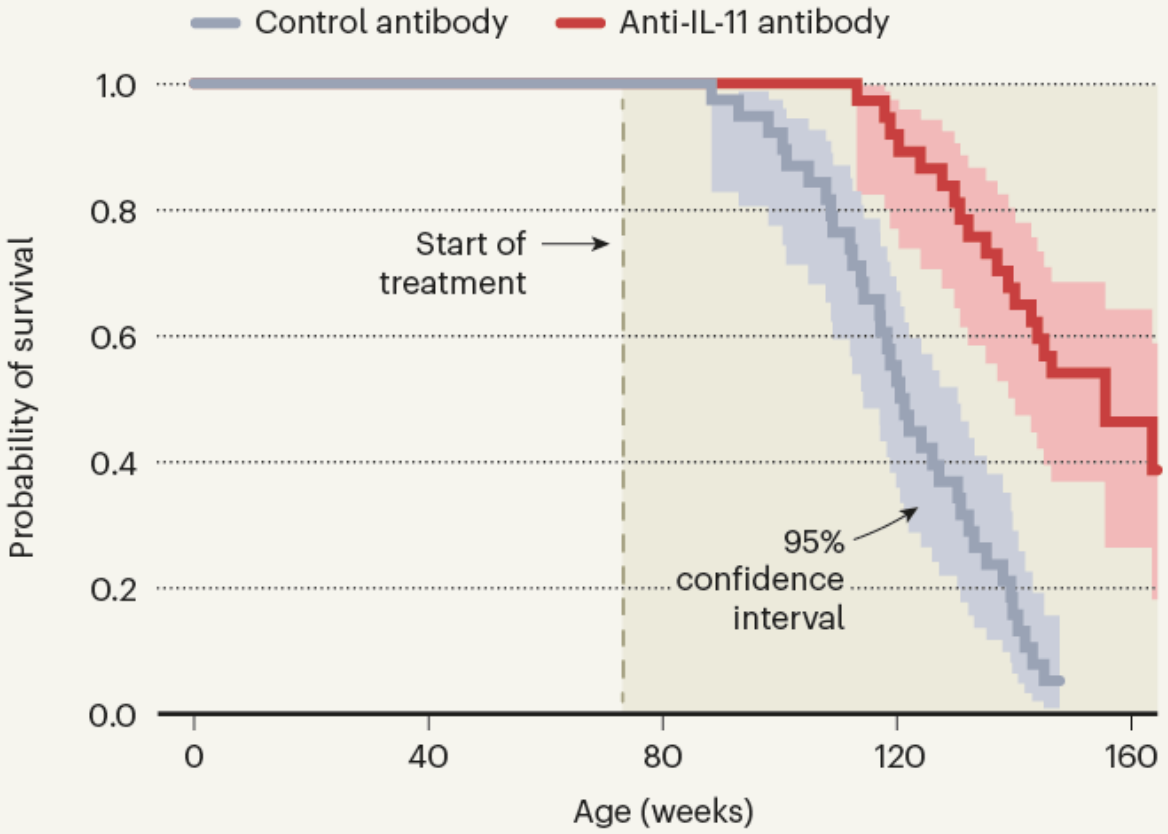
Source: https://www.nature.com/articles/s41586-024-07701-9

IL-11 Antibody Effect Size in Mice is Meaningful

Richard Miller, "Blocking an inflammatory protein slows the pace of ageing," *Nature*, July 29, 2025

Strikingly, mice in which *Il11* was deleted lived longer than did control mice, and administration of the anti-IL-11 antibody to genetically normal mice also extended their lifespan (Fig. 1). Because most deaths in laboratory mice are due to cancers, the lifespan results imply that IL-11 has a key role in the processes that lead to cancer at older ages in mice — and, by extension, potentially also in humans.

Source: https://www.nature.com/articles/d41586-024-02300-0



Biotechs Developing Anti IL-11 Antibodies*

Boehringer Ingelheim

Calico

Lassen THERAPEUTICS

VRG THERAPEUTICS

Note: Human IL-11 homozygous loss-of-function mutants suffer from craniofacial malformations.

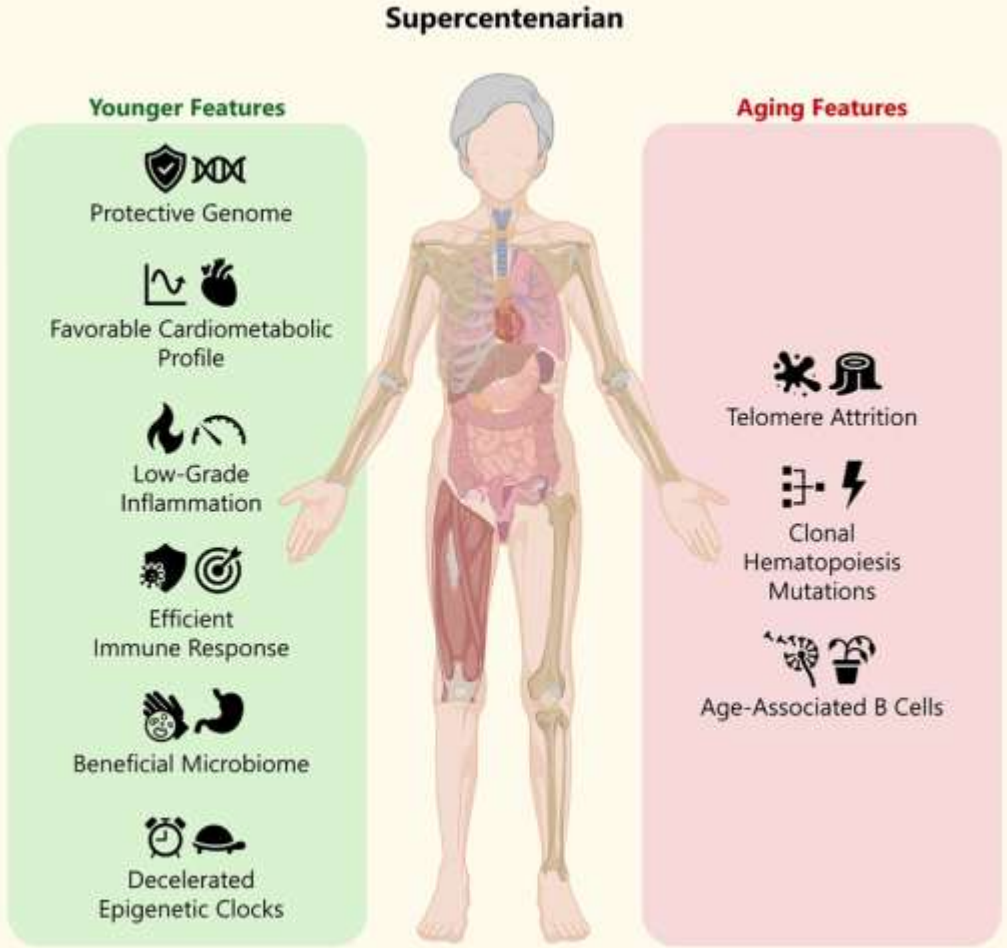
* Both Boehringer's and Calico's molecules are licensed in. Also, Huabo Biopharm of China is developing an anti IL-1 / TSLP bispecific antibody.

Analysis of The World's Oldest Person Points to Four Genetic Variants that Appear Protective

Santos-Pujol E et al., "The multiomics blueprint of the individual with the most extreme lifespan," *Cell Rep Med*. Oct 21, 2025; 6(10):102368.

Extreme human lifespan, exemplified by supercentenarians, presents a paradox in understanding aging: despite advanced age, they maintain relatively good health. To investigate this duality, we have performed a high-throughput multiomics study of the world's oldest living person, interrogating her genome, transcriptome, metabolome, proteome, microbiome, and epigenome, comparing the results with larger matched cohorts. The emerging picture highlights different pathways attributed to each process: the record-breaking advanced age is manifested by telomere attrition, abnormal B cell population, and clonal hematopoiesis, whereas absence of typical age-associated diseases is associated with rare European-population genetic variants, low inflammation levels, a rejuvenated bacteriome, and a younger epigenome.

The analysis focused on identifying functional variants that might impact genes or gene sets associated with longevity or disease resistance. The comparison was made between M116's genome and a control set of 75 Iberian women from the 1000 Genomes Project to identify "extreme" variants potentially linked to her longevity. We identified 7 homozygous variants in M116's genome, affecting 16 protein-coding and 3 non-coding genes. Remarkably, none of these rare homozygous variants were found in the control European populations, suggesting that these variants could contribute to her exceptional longevity. Examples include homozygous variants detected on *DSCAML1*, a gene associated with immune function and cognition retention; *MAP4K3*, linked to lifespan regulation of *Caenorhabditis elegans* and to autoimmune disease, cancer, and aging; *TSPYL4* and *NT5DC1*, linked to homeostatic pulmonary function[7] and the protocadherin alpha cluster (*PCDHA1-9*), related to aging brain health and heart disease.



Source: https://www.sciencedirect.com/science/article/pii/S2666379125004410

Genetic Mutational Data Point to Metabolic Pathways as Drivers of Aging – Particularly IGF-1 and AMPK Genes

Rare genetic coding variants associated with human longevity and protection against age-related diseases

Jhih-Rong Lin[1,16], Patrick Sin-Chan[2,16], Valerio Napolioni[3], Guillermo G. Torres[4], Joydeep Mitra[1], Quanwei Zhang[1], M. Reza Jabalameli[1], Zhen Wang[1], Nha Nguyen[1], Tina Gao[5], Regeneron Genetics Center*, Matthias Laudes[6], Siegfried Görg[7], Andre Franke[4], Almut Nebel[4], Michael D. Greicius[8], Gil Atzmon[5,9], Kenny Ye[10], Vera Gorbunova[11], Warren C. Ladiges[12], Alan R. Shuldiner[2], Laura J. Niedernhofer[13], Paul D. Robbins[13], Sofiya Milman[1,5], Yousin Suh[1,14,15], Jan Vijg[1], Nir Barzilai[1,5] and Zhengdong D. Zhang[1]✉

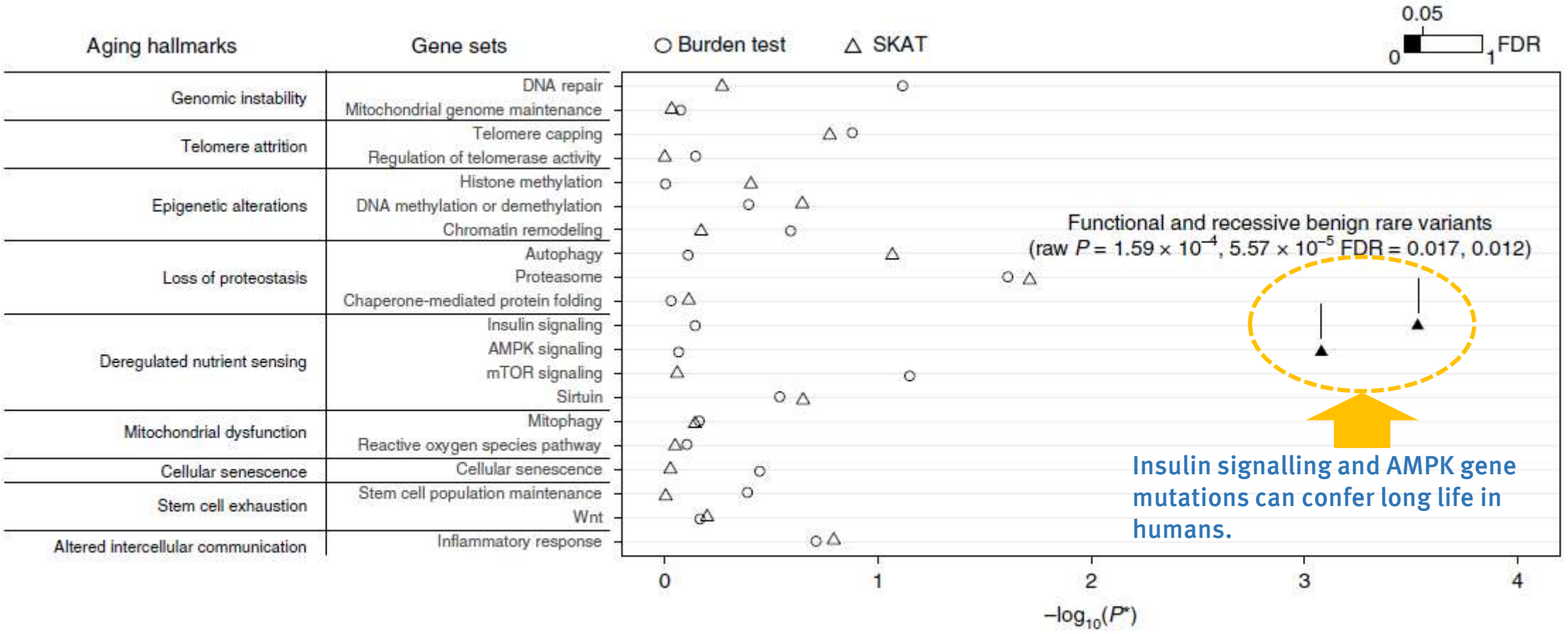
Extreme longevity in humans has a strong genetic component, but whether this involves genetic variation in the same longevity pathways as found in model organisms is unclear. Using whole-exome sequences of a large cohort of Ashkenazi Jewish centenarians to examine enrichment for rare coding variants, we found most longevity-associated rare coding variants converge upon conserved insulin/insulin-like growth factor 1 signaling and AMP-activating protein kinase signaling pathways. Centenarians have a number of pathogenic rare coding variants similar to control individuals, suggesting that rare variants detected in the conserved longevity pathways are protective against age-related pathology. Indeed, we detected a pro-longevity effect of rare coding variants in the Wnt signaling pathway on individuals harboring the known common risk allele APOE4. The genetic component of extreme human longevity constitutes, at least in part, rare coding variants in pathways that protect against aging, including those that control longevity in model organisms.

This 2021 paper carried out by researchers at Albert Einstein with Regeneron is quite interesting. The researchers show that protective mutations exist which confer long life in genes in the insulin signalling and AMPK area but not in mTOR, sirtuins or WNT pathways. This paper focused on the genetics of centenarians (a very good idea) and, indeed, genetic factors in humans become more important as we age ever longer.

Source: https://www.nature.com/articles/s43587-021-00108-5

Lin et al. Study (2021): Rare Variant Association of Genes with Longevity Among Aging-Related Pathways

Lin JR et.al, "Rare genetic coding variants associated with human longevity and protection against age-related diseases," *Nature Aging*, Sep 2021; 1(9):783-794.



Source: https://www.nature.com/articles/s43587-021-00108-5

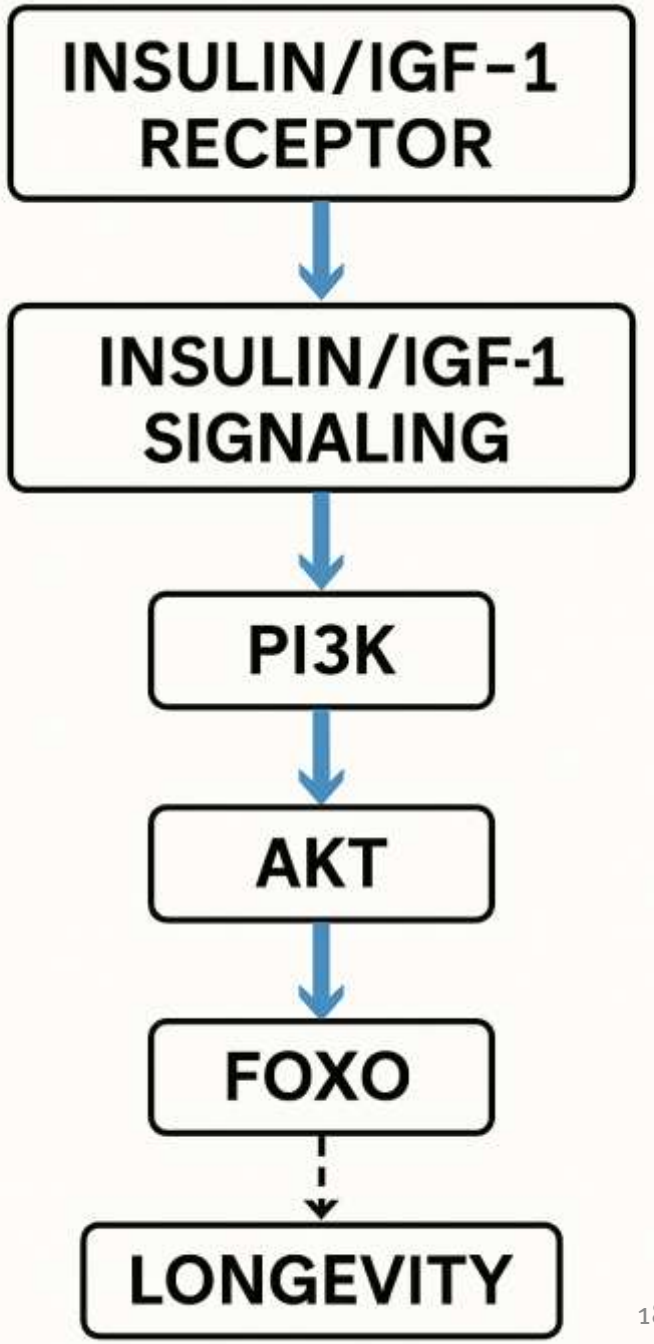
How IGF-1 and FOXO3 Genetics Impact Longevity

Insulin is a signaling hormone that tells cells to internalize glucose and burn it. If glucose burning is the main principal cause of human age limit, then reduction of the amount of insulin overall and improved insulin sensitivity is a good thing. It turns out that IGF-1R is an insulin-like hormone receptor that governs insulin sensitivity and is intricately linked to longevity across essentially all species (discussed in our first report).

The Lin et al. (2021) study shows that the most powerful known genetic mutation for impacting human longevity involves insulin signalling genes. Indeed, human longevity appears to be shaped by lifelong modulation of the insulin/IGF-1 signaling (IIS) pathway, with convergent evidence from genetics, physiology, and rare human "experiments of nature."

Centenarians across multiple populations are enriched for rare, partial loss-of-function variants in IGF1R, IGF1, and downstream IIS components like FOXO3, AKT1, and IRS1, all of which damp signaling intensity and shift cells toward stress resistance, improved metabolic efficiency, and reduced growth-driven aging pathways. In the same sense that smaller dogs live longer than larger dogs (largely associated with IIS), we humans can become more metabolically efficient and put less stress on our mitochondria by having less growth hormone, less insulin signaling and associated shorter stature. Knocking out both insulin receptor and IGF-1 receptor in mice leads to even greater longevity.

The strongest clinical proof of the IIS hypothesis comes from Ecuadorian individuals with GHR deficiency (Laron syndrome), who exhibit profound resistance to cancer and diabetes due to chronically low IGF-1 signaling, demonstrating how reducing IIS suppresses key age-related diseases even if it does not extend lifespan in challenging environments.



Multiple Studies: IGF-1, FOXO3 Genetics and Survival

Category	Cohort/Study	N	Gene / Variant	Main Finding	Interpretation	Reference
Centenarian genetics – IGF1R	Ashkenazi centenarians	384	IGF1R (A37T, R407H)	Reduced IGF1R signaling; enriched in centenarians	Partial IGF1R loss-of-function promotes longevity	Suh et al., PNAS 2008 (link)
Centenarian genetics – IGF1	Ashkenazi longevity cohort	2,487	IGF1 (I91L, A118T)	Functional variants reduce IGF1R activation	Mild IGF-1 signaling reduction supports longevity	Ali et al., Sci Rep 2025 (link)
FOXO3 longevity gene	Japanese, German, U.S. centenarians	Multiple cohorts › 10,000	FOXO3 (rs2802292 & others)	Strong, reproducible association with exceptional longevity	FOXO3 enhances stress resistance, autophagy, DNA repair	Flachsbart et al., Aging Cell 2009 (link)
Insulin signaling – IRS1	Iceland & European cohorts	~30,000	IRS1 (Gly972Arg)	Variant reduces insulin signaling; protective metabolic profile	Mild insulin resistance at receptor ⇢ improved longevity traits	Kilpeläinen Nat Genet 2011 (Link)
Growth hormone receptor	Multiple global cohorts	Small cohorts	GHR exon 3 deletion (d3-GHR)	Associated with male longevity and enhanced GH response	Modulates GH/IGF-1 amplitude over life	Ben-Avraham Sci Adv 2017 (Link)

Source: Stifel Investment Banking Department.

Does Caloric Restriction Impact Human Lifespan?

Caloric restriction (CR)—reducing calorie intake without malnutrition—has long been known to extend lifespan in short-lived species such as yeast, worms, flies, and mice. In these models, CR slows aging by lowering insulin and IGF-1 signaling, reducing oxidative damage, activating autophagy, and improving mitochondrial efficiency. Studies in primates have yielded mixed results: the Wisconsin rhesus-monkey trial showed longer lifespan and fewer age-related diseases, while the National Institute on Aging (NIA) study found no increase in lifespan, though both confirmed better metabolic and cardiovascular health. These findings suggest that while CR reliably enhances healthspan, its effect on lifespan may depend on diet composition, genetics, and species longevity.

In humans, the evidence remains indirect but promising. Observational studies in long-lived populations such as pre-industrial **Okinawans** indicate that modest, nutrient-dense caloric restriction correlates with reduced rates of chronic disease and exceptional longevity. Controlled trials such as the **CALERIE Phase 2 study**—where participants sustained about a 12% reduction in caloric intake for two years—showed clear metabolic benefits, including improved insulin sensitivity, lower blood pressure, and reduced inflammation.

However, because of the study's limited duration and the long human lifespan, it provided no proof of actual life extension. Mechanistically, CR in humans activates many of the same cellular pathways linked to longevity in animals—suppression of mTOR, activation of AMPK, and upregulation of sirtuins—implying that the molecular machinery for lifespan extension exists but may require decades to manifest.

The emerging consensus is that milder strategies such as intermittent fasting or pharmacologic CR mimetics (e.g., rapamycin, metformin, NAD^+ boosters) may achieve many of the same benefits more safely, harnessing the evolutionary pathways of CR without requiring chronic deprivation.

There is some evidence that caloric restriction improves the lifespan of humans.

Persuasive Evidence Links Diet Composition to Lifespan

Caloric deprivation seems less important for human longevity than the types of foods that humans eat.

The **Seventh-day Adventist Health Studies**, which have followed tens of thousands of participants, provide some of the strongest long-term human data linking dietary patterns to longevity. Adventists, many of whom follow vegetarian or semi-vegetarian diets exhibit markedly lower rates of cardiovascular disease, diabetes, and cancer compared to the general U.S. population.

Across decades of follow-up, **life expectancy** among Adventists has been roughly **7–10 years longer** than national averages.

The **Mediterranean diet** has been another cornerstone of dietary longevity research, most prominently demonstrated in the **PREDIMED** trial in Spain. In this large randomized study, participants assigned to a Mediterranean diet rich in olive oil, nuts, and vegetables—without intentional calorie restriction—experienced roughly a **30% reduction in major cardiovascular events** compared to those on a low-fat control diet. Other cohort studies such as the **EPIC** study across Europe show that a Mediterranean-style diet correlates with **lower all-cause mortality, slower telomere shortening and improved biological aging markers**.

More recent and emerging work has focused on **intermittent fasting (IF), time-restricted eating (TRE), and calorie-reduction mimetics** as practical alternatives to continuous restriction. Early clinical trials show that intermittent fasting and circadian-aligned eating improve **insulin sensitivity, lipid metabolism, and inflammatory profiles**, paralleling the molecular effects of CR in animal models.

Although no human studies have yet shown direct lifespan extension, several trials demonstrate modest **reductions in biological age**, as measured by epigenetic clocks, after months to years of dietary modulation.

Fast-Mimicking Diet is a Promising Approach

Biochemist Valter Longo has devoted decades to discovering connections between nutrition and successful aging. He runs the Longevity Institute at the USC Leonard Davis School of Gerontology, which aims to extend healthspan while finding ways to prevent and treat aging-related conditions. Longo is also a professor of biological science at the USC Dornsife College of Letters, Arts and Sciences.

Armed with results from the lab — including clinical trials showing that cycles of a five-day fasting-mimicking diet can reduce risk factors for many life-threatening diseases — Longo calls for change in the kitchen. He founded L-Nutra, a rapidly growing aging company, which offers a fast-mimicking diet to consumers and institutions.

Longo: We've known for a long time that reducing calories without malnutrition can extend healthy lifespans in animal models. In fact, cancer in calorie-restricted monkeys is about 50 percent reduced. Cardiovascular disease is about 50 percent reduced as well. If we were able to do what we already know how to do in monkeys in people, it would be revolutionary and would eliminate the need for many drugs. But we also know that caloric restriction can be harmful. Ultimately, the monkeys didn't live much longer because they had as many problems as solutions — and it can be difficult to maintain over time. Periodic diets that mimic fasting offer a circumscribed way to deliver caloric restriction. Lab and clinical studies show that it is perhaps the most potent way to activate protection, repair and rejuvenation processes in the body. Current research on fasting, including a fasting-mimicking diet, represents attempts to understand and leverage the benefits of caloric restriction in a safe and manageable way.

Valter Longo, USC

Adapted from: https://keck.usc.edu/news/what-to-know-about-fasting-aging-the-longevity-diet-and-when-you-should-eat/

Are GLP-1's the First Longevity Drugs?

Editorial, *Nature*, November 12, 2025 (excerpt)

At the August meeting of Aging Research and Drug Discovery in Copenhagen, two speakers from Novo Nordisk and Eli Lilly electrified the audience by proposing that GLP-1 receptor agonists (GLP-1s) — the blockbuster obesity and diabetes therapies — may be the first longevity drugs. Beyond the unprecedented efficacy of GLP-1s in obesity and type 2 diabetes, evidence that they improve comorbidities has been accumulating at an impressive pace in recent years. From heart attack, stroke, heart failure and peripheral artery disease, to kidney and liver disease, to knee osteoarthritis and obstructive sleep apnea, the cascade of news about approved indications and major clinical studies has sparked media talk of a wonder drug that should be added to the water supply.

Clinical elucidation of all that these drugs can and cannot do will take careful study over many years, but early signs of their benefits for several chronic diseases of aging are already unmistakable — in some people with metabolic disease. For everyone else, clinical data are lacking. Yet the rapprochement between the two big GLP-1 drugmakers and the longevity field signals a shift toward drugs that have broad impact on multiple pathological processes and, eventually, a future of preventive medicine in which early screening and long-acting therapies ward off chronic diseases before they start.

The Copenhagen aging conference was not the first time that GLP-1s and aging had been discussed or that pharma had ventured into the longevity space. But the appearance of the two distinguished scientific leaders, Lotte Bjerre Knudsen from Novo Nordisk and Andrew Adams from Eli Lilly, discussing the longevity potential of these medicines before the aging research community was seen by many in attendance as momentous. The talks described emerging capabilities for preventive medicine and the benefits of GLP-1s for different conditions and organs, including pancreas, intestine, heart, blood vessels, brain, kidney and liver, and for all-cause mortality in some trials.

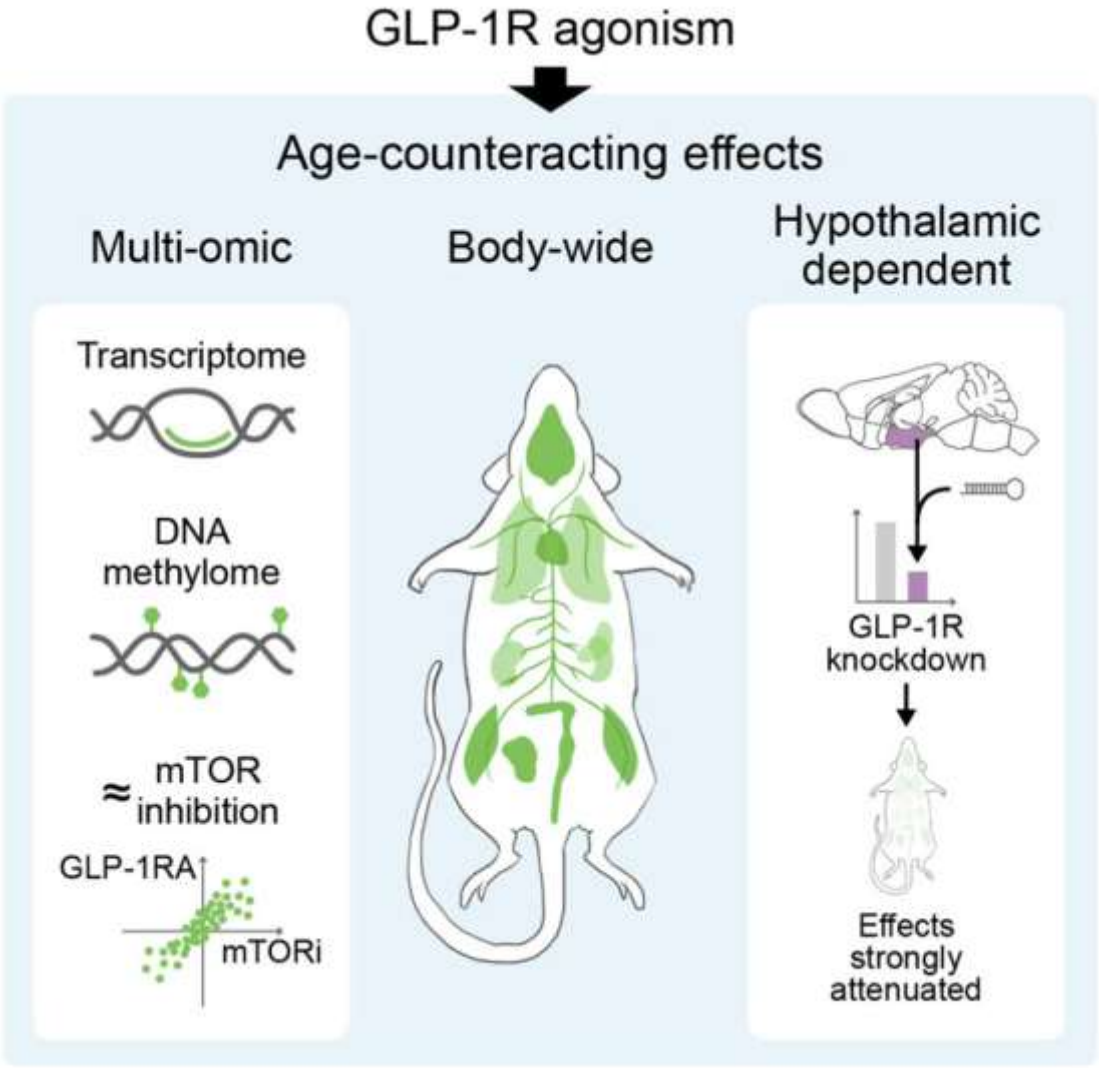
For people with obesity or type 2 diabetes, clinical trial data and real-world evidence have shown clearly that GLP-1s ameliorate some age-related comorbidities in those who are at high risk of them to start with. Improvements in cardiovascular outcomes and all-cause mortality were seen both in type 2 diabetes6 and in obesity without diabetes.

Source: https://www.nature.com/articles/s41587-025-02932-1. Also see: https://x.com/InSilicoMeds/status/1969132636292727156?s=20, https://www.forever.ai/p/glp-1s-the-worlds-first-longevity

Mouse Evidence Shows That GLP-1 Drugs Have mTOR Like Effects on Aging

J. Huang et al., "Body-wide multi-omic counteraction of aging with GLP-1R agonism," *Cell Metabolism*, Nov 19, 2025.

Identifying practical ways to counteract aging and associated degenerative disorders is urgently needed. We performed deep molecular profiling and functional assessments in aging male mice to show that glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment broadly counteracts age-related changes. In mice treated with a GLP-1RA from 11 months for 30 weeks, we observed strong body-wide multi-omic age-counteracting effects and improved selected physical functions. Importantly, the effects were specific to aged mice, not young adults, and were attained with a relatively low dose that minimally affected food intake or body weight. With GLP-1RA treatment beginning at 18 months for 13 weeks, the molecular age-counteracting effects were even stronger and largely dependent on hypothalamic GLP-1R, pointing to a brain-body axis of aging modulation. Comparison with mammalian target of rapamycin (mTOR) inhibition, a proven anti-aging strategy, revealed strong multi-omic similarities. Our findings have broad implications for the mechanisms behind GLP-1RAs' pleiotropic benefits, guiding clinical trials, and informing development of anti-aging-based therapeutics.



Source: https://www.cell.com/cell-metabolism/fulltext/S1550-4131(25)00474-7

Calico: Dietary Restriction / Intermittent Fasting Both Extend Lifespan in Mice

Dietary restriction impacts health and lifespan of genetically diverse mice

Nature, Oct 17, 2024

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Caloric restriction extends healthy lifespan in multiple species[1]. Intermittent fasting, an alternative form of dietary restriction, is potentially more sustainable in humans, but its effectiveness remains largely unexplored[2–8]. Identifying the most efficacious forms of dietary restriction is key for developing interventions to improve human health and longevity[9]. Here we performed an extensive assessment of graded levels of caloric restriction (20% and 40%) and intermittent fasting (1 and 2 days fasting per week) on the health and survival of 960 genetically diverse female mice. We show that caloric restriction and intermittent fasting both resulted in lifespan extension in proportion to the degree of restriction. Lifespan was heritable and genetics had a larger influence on lifespan than dietary restriction. The strongest trait associations with lifespan included retention of body weight through periods of handling—an indicator of stress resilience, high lymphocyte proportion, low red blood cell distribution width and high adiposity in late life. Health effects differed between interventions and exhibited inconsistent relationships with lifespan extension. 40% caloric restriction had the strongest lifespan extension effect but led to a loss of lean mass and changes in the immune repertoire that could confer susceptibility to infections. Intermittent fasting did not extend the lifespan of mice with high pre-intervention body weight, and two-day intermittent fasting was associated with disruption of erythroid cell populations. Metabolic responses to dietary restriction, including reduced adiposity and lower fasting glucose, were not associated with increased lifespan, suggesting that dietary restriction does more than just counteract the negative effects of obesity. Our findings indicate that improving health and extending lifespan are not synonymous and raise questions about which end points are the most relevant for evaluating aging interventions in preclinical models and clinical trials.

This study sponsored by Calico is quite interesting in that it looked at a lot of mice and found quite strong effects of dietary restriction (DR) on mouse lifespan. Whether you got there through intermittent fasting or just eating less didn't matter much.

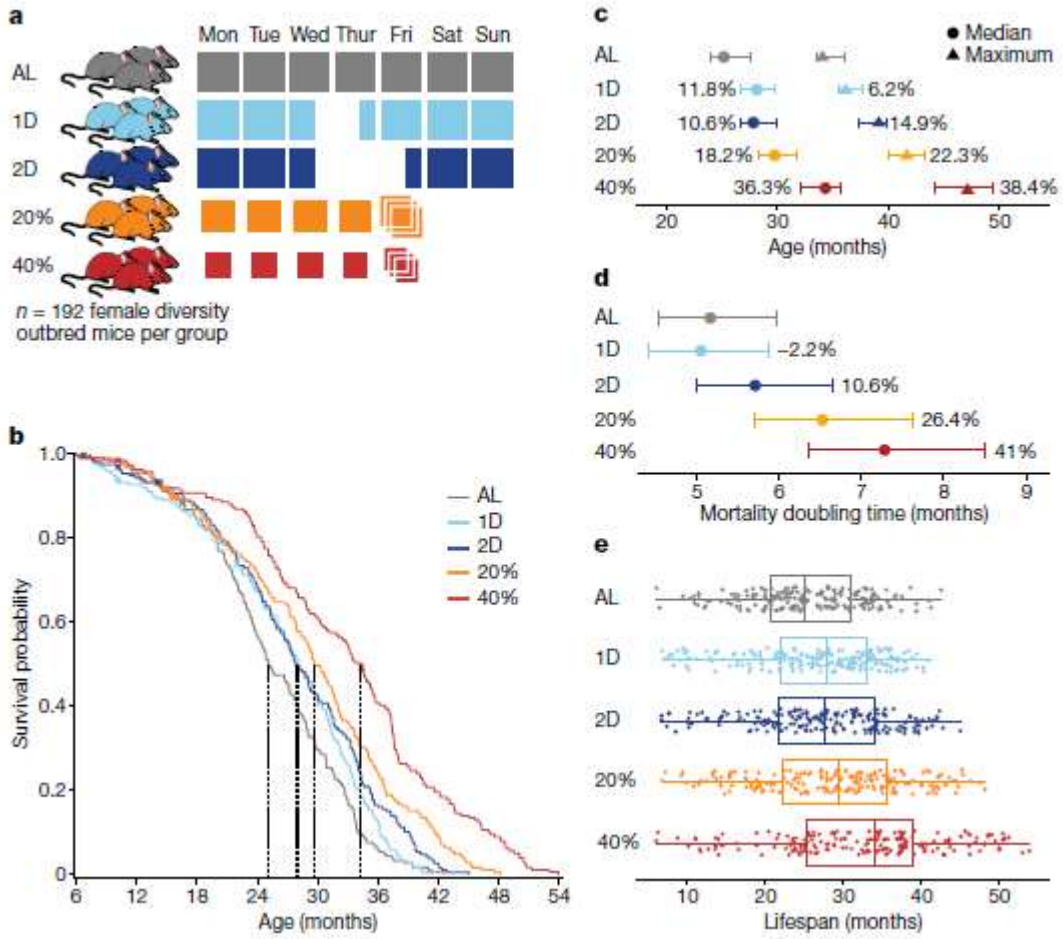


Fig. 1 | DR extends lifespan in DO mice. a, The study design: 960 female DO mice were randomized to one of five diet intervention groups: ad libitum (AL); one day (1D) or two consecutive days (2D) per week fasting; or CR at 20% (20%) or 40% (40%) of estimated adult food intake. b, Kaplan–Meier survival curves by diet group. The dashed lines indicate the median lifespan. Censoring events are indicated by an 'X'. c, Kaplan–Meier estimates of median (50% mortality) and maximum (90% mortality) lifespan by diet group, showing the percentage change relative to AL and the 95% confidence intervals (computed using R/survfit). n = 937 mice. d, Mortality doubling times estimated from a Gompertz log-linear hazard model, showing the percentage change relative to AL and the 95% confidence intervals (computed using R/flexsurvreg). n = 937 mice. e, Individual mouse lifespans (points) within diet groups. n = 188 (AL), n = 188 (1D), n = 190 (2D), n = 189 (20%) and n = 182 (40%). The box plots show the median lifespan (centre line), quartiles (box limits) and range (whiskers).

Source: https://www.nature.com/articles/s41586-021-03781-z

Calico Study Finds Some Important “Buts” in the Dietary Restriction Literature (at Least in Mice)

Di Francesco et al. (2024):

1 Metabolic Markers Do Not Capture the Benefits of DR

Our results have several important implications. First, they suggest a divergence of the health and longevity effects of DR. Several well-described impacts of DR on metabolic health, such as improved fasting blood glucose, energy expenditure and oscillations in respiratory quotient, did not predict lifespan within diet groups. This means that, although DR-induced changes in metabolic traits can be beneficial for health, they may not necessarily translate into a substantial extension of lifespan. This insight has important implications for the choice of biomarkers in human dietary intervention studies, which frequently focus on metabolic health

2 Extreme DR is Not Necessarily Lifespan Extending

Second, our findings more generally imply that the effects of DR on health and lifespan may be partially non-overlapping, and certain lifespan-extending properties of DR may in fact be detrimental to other aspects of physiological health. For example, although mice on 40% CR are healthy by most measures, we saw indications of adverse effects including life-long loss of lean mass, lower body temperature, food-seeking behaviour (an indication of hunger) and changes in immune repertoire that could potentially confer susceptibility to infection. These effects in mice may raise concerns regarding the potential risks of extreme DR for humans.

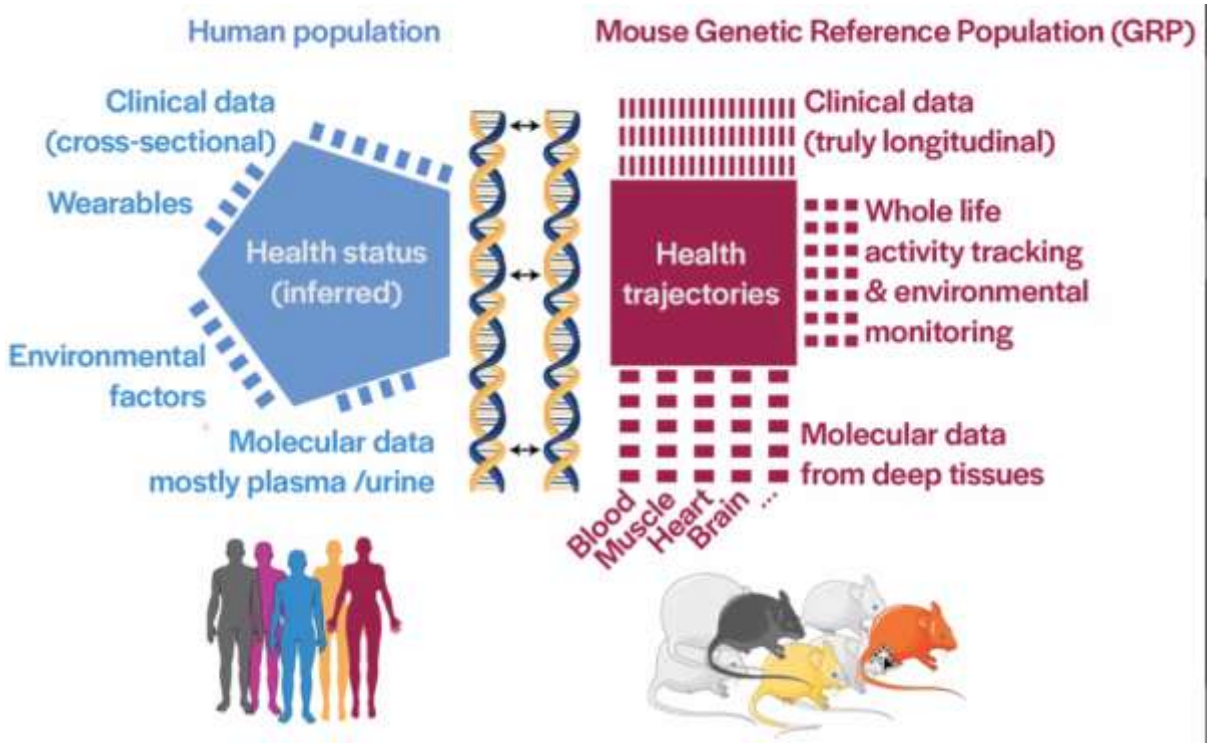
3 Genetic Factors More Important than DR

We obtained whole-genome genotyping data for 929 (out of 937) mice and looked at the combined effects of diet and genetics on lifespan. For mice that lived to at least 6 months of age, genetic background explained 23.6% of variation in lifespan ($h2 = 0.236$, 95% bootstrap confidence interval 0.106–0.360), while diet explained only 7.4% of variation. As mice aged, heritability declined to 17.1% for mice surviving past 12 months and to 15.9% for mice surviving past 18 months. In parallel, the contribution of diet to lifespan increased with age to 8.4% at 12 months and to 11.4% at 18 months. Similar trends of decreasing genetic effect and increasing effects of DR were previously reported for body weight

Source: https://www.nature.com/articles/s41586-021-03781-z

Advancing Translational Work on Oxidative Stress at EPFL

It is quite impressive to see how much mileage that Calico was able to get out of a large study of mice aging in the context of dietary restriction. Mice don't live that long, and we are highly knowledgeable about how to learn from gene alterations in mice. In our view, there is substantial room for additional translational work of this type. Johan Auwerx of EPFL is doing particularly interesting work in this area with the Healthspan Diversity Project which involves analyzing over 100,000 samples from 82 mouse strains to associate genotype, phenotype and behavior in the context of age. The idea is to create a mouse biobank dataset that should yield many insights (see image).



EPFL, "Aged but Not Old, August 6, 2023 (link)

Another way to intercept diseases is to adopt a healthy lifestyle, such as by eating right and getting regular exercise. These kinds of lifestyle factors play a crucial role in extending our healthspan. Data clearly show that for most people, their health tends to decline rapidly after retirement. Auwerx explains: "The key is staying active. We also have systems now that can combine genetic data with real-time health parameters measured by smart watches and other connected devices. This is a booming field, and it means we'll soon be able to intercept more and more diseases before patients start needing treatment."

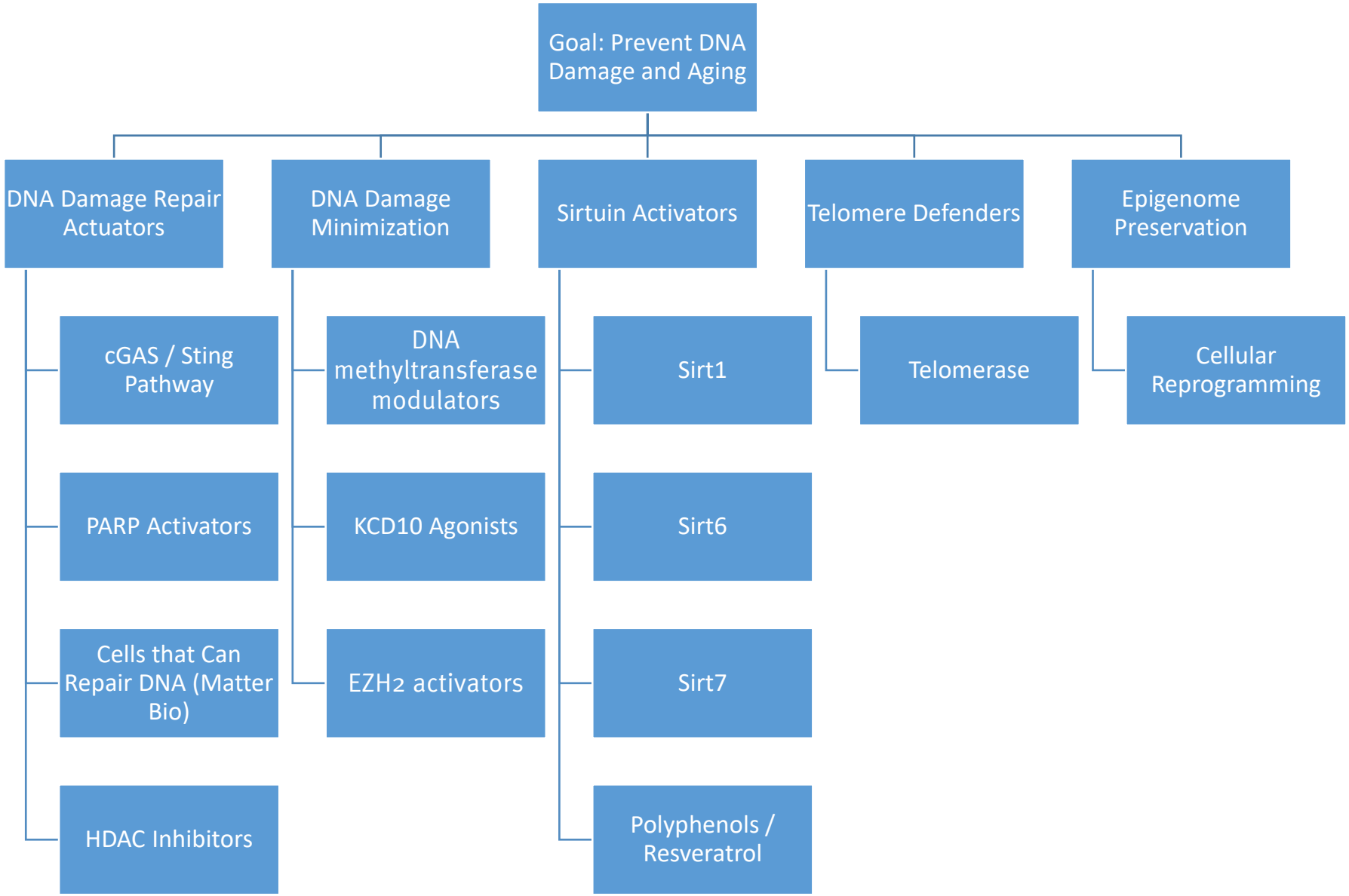
That's the idea behind the Healthspan Diversity Project, which Auwerx and his research group launched in 2018. They're studying the factors that influence longevity in mice and comparing this information with clinical data on cohorts of human patients. The goal is to be able to apply their findings on mice to humans.

Source: Image from Johan Auwerx.

Second Area:

DNA Damage

Dendrogram of Therapeutic Options for DNA Damage



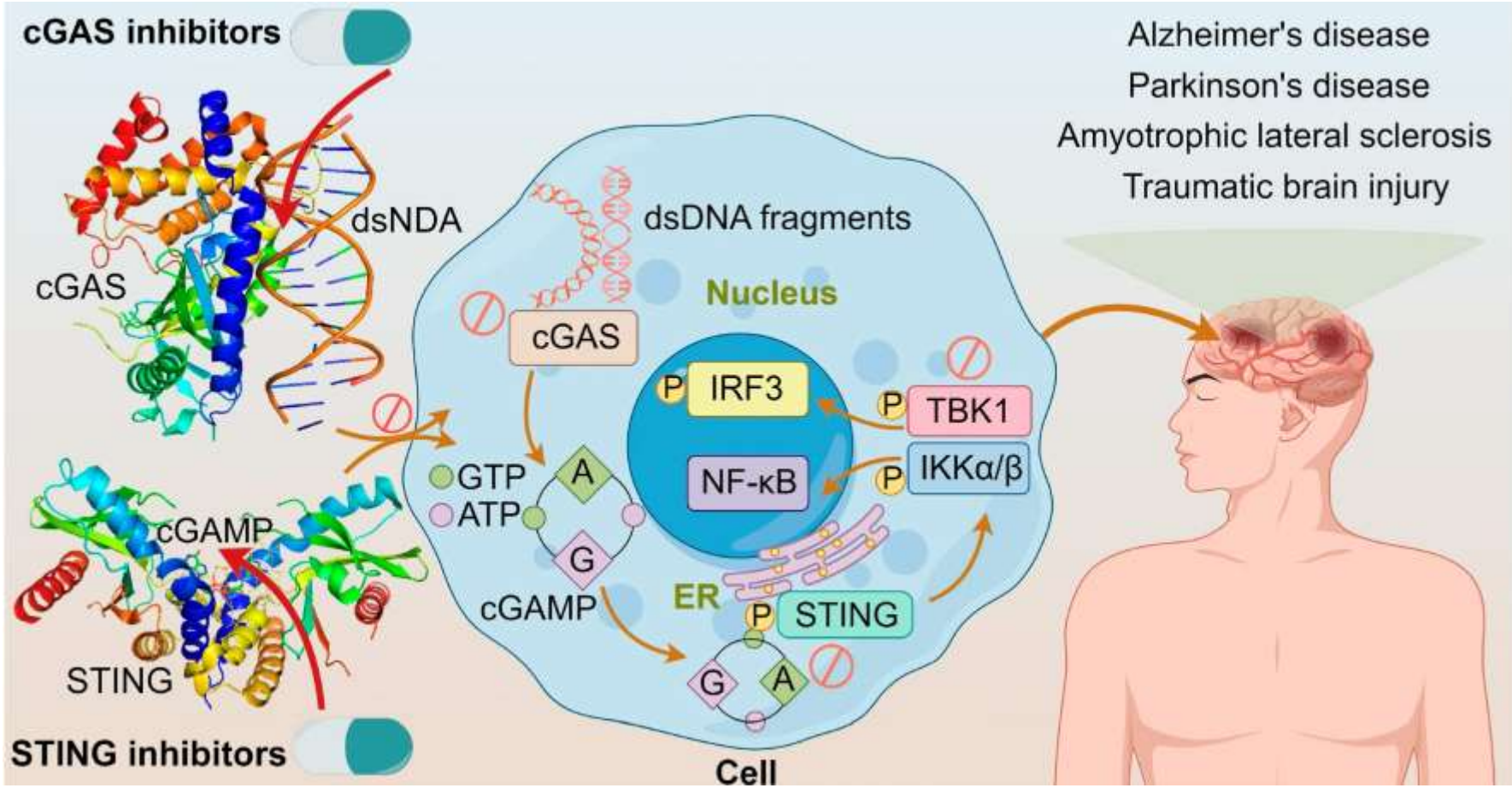
Multiple Options Available for Managing DNA Damage and Its Effect on Aging

Therapeutic Approach	Mechanism	Longevity Evidence in Humans?	Evidence Supporting	Evidence Against/Limitations
Telomerase Activators	Extends telomeres and enhances repair	No	In mice, telomerase activation (including TA-65 derivatives) lengthens short telomeres and can improve some healthspan measures without a large spike in cancer in certain models. A randomized, placebo-controlled trial of TA-65 in humans showed increased telomere length in lymphocytes at low dose vs. telomere loss in placebo.	Telomere lengthening is a proxy, not direct proof of reduced DNA damage or improved survival. Telomerase is also a classic cancer-enabling factor; long-term safety, especially in people with latent malignancies, is not well defined. No trials show reduced mortality or cancer incidence.
Epigenetic Therapies	New class of DNA-protective or repair-supporting drugs, because the epigenome regulates genome stability itself—controlling chromatin compaction, DNA accessibility, and transcriptional silencing of damaged regions.	No	When epigenetic control erodes with age, heterochromatin relaxes, DNA repair becomes inefficient, and transposable elements activate, causing secondary DNA damage. The therapeutic rationale, therefore, is that restoring youthful chromatin structure and DNA methylation patterns could indirectly limit new DNA damage and improve repair fidelity.	We are not aware of human data. There are issues here with specificity of the therapies.
CIRBP injections or agonists	CIRBP protein binds both RNA and PARP polymers and directly promotes DNA end protection	No	CIRBP overexpression in human cells increased repair accuracy and reduced mutation rates, while its depletion in whale cells impaired these functions. In Drosophila, CIRBP overexpression even extended lifespan.	CIRBP has been described as a novel oncogene in bladder cancer, where its overexpression promotes proliferation and tumor progression via MAPK/ERK and p38 signaling. CIRBP doesn't just stay inside cells.
cGAS / STING inhibitors	Mimics DNA damage repair mechanism in the naked mole rat.	No	The case of the naked mole rat is dramatic, showing that control of cGAS can limit DNA damage of aging.	Weakening of the cGAS / STING system may increase vulnerability to disease and infection.
PARP Activators	Pharmacologic activation of PARP1, other repair factors could boost repair of single- and double-strand breaks and maintain genome integrity.	No	We currently use PARP inhibitors in cancer (to increase unrepaired damage in tumor cells), not activators. Systemic "repair-boosting drugs" aren't in widespread clinical use. There is a theoretical concern that hyper-active repair in pre-malignant cells could allow survival of clones that should have been eliminated.	Human effect not well-established. Very early concept.
Sirtuin activators (e.g., SIRT1, SIRT6, SIRT7 agonists)	NAD^+-dependent histone deacetylases maintain chromatin stability and coordinate DNA double-strand break repair; SIRT6 also promotes base-excision repair.	No	SIRT6 overexpression extends lifespan in mice and delays genomic instability; SIRT1 activation (e.g., by resveratrol) improves DNA repair efficiency in vitro. Human trials with resveratrol/NR/NMN show activation of sirtuin signaling and reduced oxidative stress.	Direct lifespan or DNA-damage data in humans are lacking; high-dose activators have mixed bioavailability and off-target effects. GSK bought Sirtris and failed with a sirtuin activator.
HDAC inhibitors (e.g., butyrate, valproate, vorinostat)	Temporarily open chromatin and promote transcriptional rebalancing and DNA repair gene expression.	No	In cell and mouse models, HDAC inhibition improves DNA damage response and neuroprotection after stress; some cancer data show enhanced repair.	Chronic HDAC inhibition can paradoxically cause genomic instability or tumorigenesis; requires precise timing/dosing.
DNMT (DNA methyltransferase) modulators	Normalize aberrant DNA methylation that accumulates with aging, especially loss of methylation at repetitive regions and gain at promoter CpG islands.	No	Restoring DNMT1/3A/3B balance in aged mice prevents LINE-1 activation and genome instability; hypomethylation correlates with double-strand breaks in senescent cells.	Pharmacologic DNMT inhibitors (used in leukemia) actually *reduce* methylation and can worsen instability; precise upregulation is not yet clinically feasible.
Histone methylation modifiers (e.g., EZH2 activators)	Reinforce heterochromatin ($H3K9me3$, $H3K27me3$), preventing DNA double-strand break accumulation in repetitive DNA.	No	$H3K9me3$ restoration in aged stem cells or premature-aging models improves genomic stability and stem-cell renewal.	Still preclinical; EZH2 inhibitors are oncologic drugs that *reduce* methylation; context-specific activation needed for aging prevention.
Polyphenols / dietary epigenetic modulators (e.g., resveratrol)	Activate sirtuins and AMPK, modulate histone acetylation and DNA methylation, and reduce ROS that indirectly damages DNA.	No	Human and animal studies show lower oxidative damage markers and improved epigenetic stability; lifespan extension in rodents fed polyphenols.	Effects modest and pleiotropic; unclear if epigenetic modulation is the main driver of benefit.

Source: Stifel Investment Banking Department.

cGAS Inhibitors for Aging

We have seen the example of cGAS inhibition in the naked mole rat. Ideally, one would do some type of gene edit to the four amino acids that are changed in the mole rat to put the human cGAS machinery to work for the prevention of DNA damage – which is a critical aspect of aging. One could imagine doing this as a germline edit at conception to ensure that a human (or dog) could live much longer. Another approach would be to simply inhibit the cGAS / STING system entirely. Eric Topol notes that this might be a little harder than it looks. He notes:



"While this pathway is implicated in age-related diseases, the problem here is the duality of the therapeutic challenge. On one hand, the cGAS sensor to detect DNA damage would seem vital for mounting defense against invading pathogens but also amping up anti-tumor immunity, which is why cGAS agonists are being developed vs cancer. On the other hand, blocking untoward self-directed immunity and chronic inflammation would be achieved by inhibitors of cGAS-STING."

Pipeline of cGAS Inhibitors / STING Antagonists in Development

Company	Program / ID	Target	Modality	Stage	Indications	Notes
Ventus Therapeutics	VENT-03	cGAS inhibitor	Oral small molecule	Entering Phase 2	Systemic lupus erythematosus (initial), broader I&I	Ventus positions VENT-03 as first-in-class cGAS inhibitor; Ph2 plan publicly stated.
ImmuneSensor Therapeutics	IMSB301	cGAS inhibitor	Oral small molecule	Phase 1	Inflammatory/autoimmune diseases	Company's platform centers on cGAS–STING; IMSB301 described as potent, selective cGAS inhibitor.
Novartis (via IFM Due acquisition)	IFM-32531	STING inhibitor (antagonist)	Oral small molecule (covalent, brain-penetrant)	Phase 1	Immunology / neuro-inflammation areas (not yet publicly narrowed)	Novartis acquired IFM Due's STING antagonist portfolio; latest pipeline deck lists IFM-32531 in Ph1.
Novartis (IFM Due)	(undisclosed)	cGAS inhibitor	Small molecule	Preclinical	Auto-inflammatory/autoimmune	IFM Due's second program targets cGAS upstream of STING.
Bayer + Curadev	(undisclosed)	STING antagonists	Small molecules	Preclinical	Inflammation, fibrosis, auto-immune (broadly stated)	Long-running collaboration to develop STING antagonists.
Merck & Co. (historical / IP)	(undisclosed)	STING antagonist(s)	Small molecules	Discovery Stage	Not disclosed	Not clear where this program is in development.

Source: Stifel Investment Banking Department.

STING Antagonists and Disruption of YAP/TAZ Pathway Also Interesting to Prevent Cell Senescence

Sladitschek-Martens HL et al., "YAP/TAZ activity in stromal cells prevents ageing by controlling cGAS-STING," *Nature, July* 2022; 607(7920):790-798.

Ageing is intimately connected to the induction of cell senescence, but why this is so remains poorly understood. A key challenge is the identification of pathways that normally suppress senescence, are lost during ageing and are functionally relevant to oppose ageing. Here we connected the structural and functional decline of ageing tissues to attenuated function of the master effectors of cellular mechanosignalling YAP and TAZ. YAP/TAZ activity declines during physiological ageing in stromal cells, and mimicking such decline through genetic inactivation of YAP/TAZ in these cells leads to accelerated ageing. Conversely, sustaining YAP function rejuvenates old cells and opposes the emergence of ageing-related traits associated with either physiological ageing or accelerated ageing triggered by a mechano-defective extracellular matrix. Ageing traits induced by inactivation of YAP/TAZ are preceded by induction of tissue senescence. This occurs because YAP/TAZ mechanotransduction suppresses cGAS-STING signalling, to the extent that inhibition of STING prevents tissue senescence and premature ageing-related tissue degeneration after YAP/TAZ inactivation. Mechanistically, YAP/TAZ-mediated control of cGAS-STING signalling relies on the unexpected role of YAP/TAZ in preserving nuclear envelope integrity, at least in part through direct transcriptional regulation of lamin B1 and ACTR2, the latter of which is involved in building the peri-nuclear actin cap. The findings demonstrate that declining YAP/TAZ mechanotransduction drives ageing by unleashing cGAS-STING signalling, a pillar of innate immunity. Thus, sustaining YAP/TAZ mechanosignalling or inhibiting STING may represent promising approaches for limiting senescence-associated inflammation and improving healthy ageing.

Source: https://www.nature.com/articles/s41586-022-04924-6

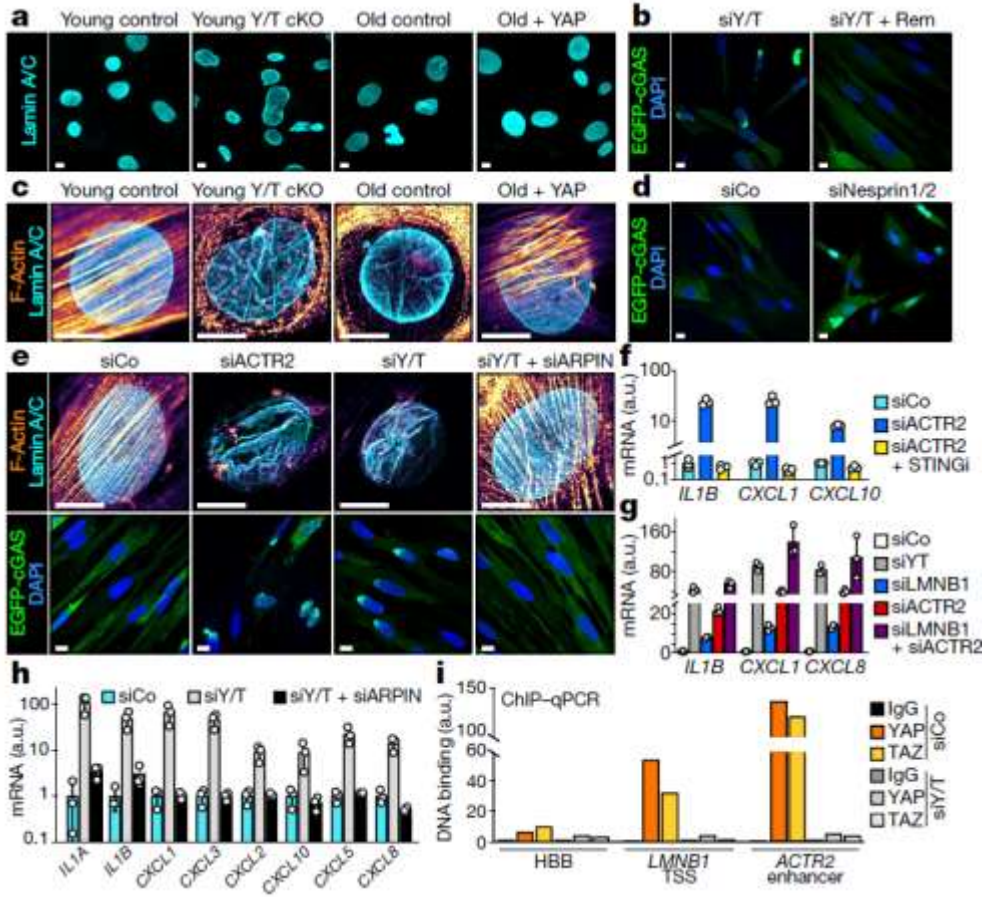


Fig. 5 | YAP/TAZ protect the NE through lamin B1 and the actin cap. a, Nuclear morphology in primary MAFs (scale bar, 10 µm) under the indicated conditions. Quantifications in Extended Data Fig. 9a. **b**, EGFP–cGAS reporter signal in YAP/TAZ-depleted WI-38 cells with or without Remodelin treatment (Rem). Scale bar, 10 µm. Quantifications in Extended Data Fig. 9h. **c**, Superresolution microscopy analysis of actin cap integrity in MAFs under the indicated conditions. Scale bar, 10 µm. **d**, EGFP–cGAS reporter signal in control (siCo) and nesprin1/2-depleted (siNesprin1/2) WI-38 cells. Scale bar, 10 µm. **e**, Super-resolution microscopy analysis of actin cap integrity (top) and confocal images of EGFP–cGAS reporter signal (bottom) in WI-38 cells under the indicated conditions. Scale bar, 10 µm. Quantifications in Extended Data Fig. 10l,r. **f**, SASP marker gene expression is induced by ACTR2 depletion (siACTR2) in a STING-dependent manner in WI-38 fibroblasts, as assessed by RT–qPCR. Data ($n = 3$ independent experiments) are shown as mean ± s.d. **g**, RT–qPCR for SASP markers showing synergistic effects of combined ACTR2 and lamin B1 (siACTR2 + siLMNB1) depletion, resembling YAP/TAZ depletion (siY/T) in WI-38 fibroblasts. Data are shown as mean ± s.d. ($n = 3$ independent experiments). **h**, Expression of SASP markers in YAP/TAZ depleted WI-38 cells is prevented by concomitant depletion of the endogenous ARP2/3 inhibitor ARPIN. Data are shown as mean ± s.d. ($n = 3$ independent experiments). **i**, Representative ChIP–qPCR experiment in WI-38 cells: YAP / TAZ bind to cognate regulatory promoter and enhancer elements of *LMNB1* and *ACTR2*. Relative DNA binding was calculated as fraction of input, and normalized to IgG. Enrichment relative to siY/T: 30-fold for TAZ-IP on *LMNB1* promoter, 13.7-fold for IP-YAP on *LMNB1* promoter; 32.7-fold for IP-TAZ on *ACTR2* enhancer and 26.6-fold for IP-YAP on *ACTR2* enhancer.

KCD10 Agonism May be Helpful in Minimizing DNA Damage

Alison Satake, Mayo Clinic, Oct 8, 2025

ROCHESTER, Minn. — Mayo Clinic researchers have identified a protein that acts like a traffic controller for DNA, preventing damage during cell division — a discovery that could lead to new cancer therapies, according to a study published in Nature.

"DNA is the code of life. It's critical for how a cell functions, but it's also critical for our own being and defines what we are," says Zhenkun Lou, Ph.D., the Swanson/Schmucker Endowed Professor to Support Health and Cancer Research at Mayo Clinic and the senior author of the new study.

Zhenkun Lou, Ph.D.

When cells divide, DNA must be copied from one cell to the next — a process called replication. Dr. Lou's research team discovered that a protein called KCTD10 plays a surprising role in protecting DNA during this critical stage. Acting like a built-in sensor, KCTD10 helps shield the DNA replication machinery from damage.

Cells also depend on another key process called transcription, where the cell decodes the DNA to create RNA. That RNA then can be translated into proteins, which are essential for healthy tissues and the body's everyday functions.

Nature, Oct 8, 2025

KCTD10 is a sensor for co-directional transcription–replication conflicts

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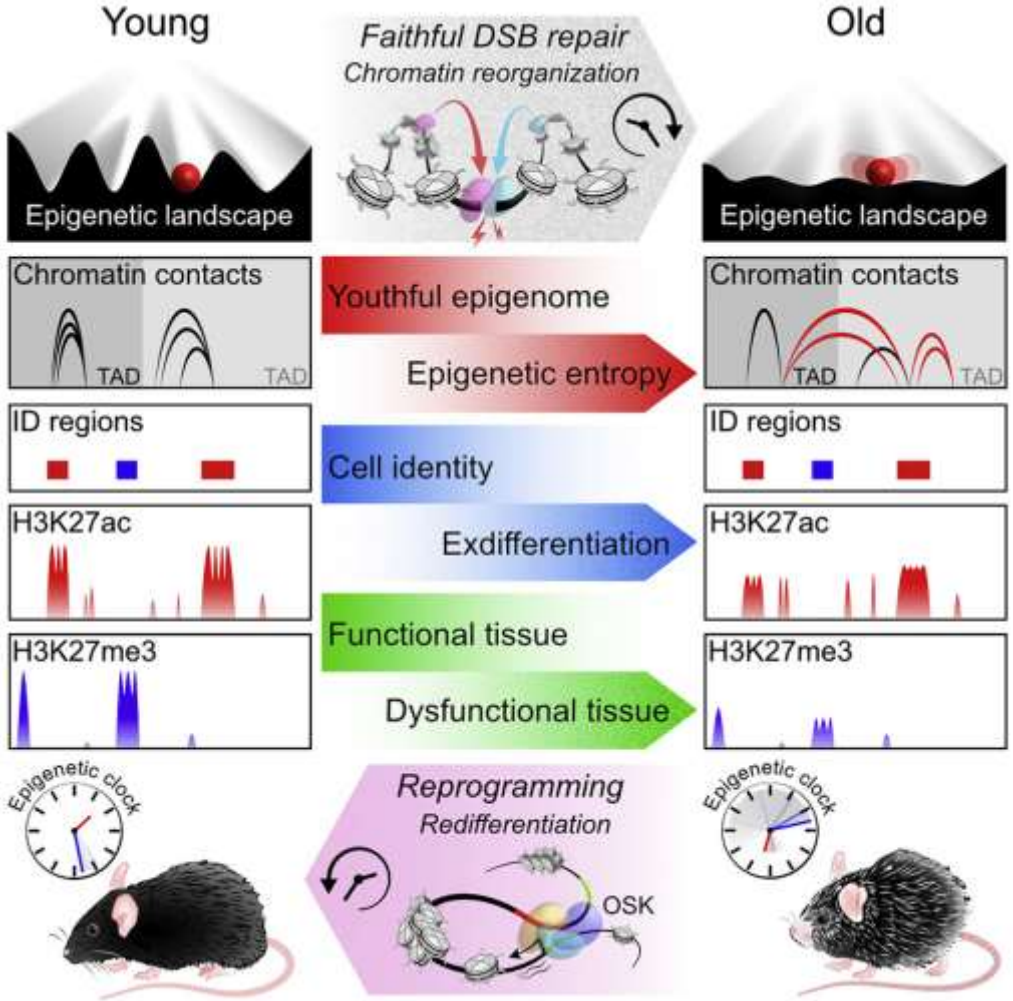
During DNA replication, the replisome must remove barriers and roadblocks including the transcription machinery[1,2]. Transcription–replication conflicts (TRCs) occur when there are collisions between the replisome and transcription machinery, and are increasingly recognized as an important source of mammalian genome instability[3]. How cells facilitate replisome bypass at sites of TRCs is incompletely understood. Here we show that the CUL3–KCTD10 E3 ligase senses TRCs and promotes remodelling of the RNA polymerase complex to allow replisome bypass. We found that the substrate adaptor KCTD10 interacts with the replisome and the transcription machinery and regulates both in unstressed conditions. These bivalent interactions allow KCTD10 to detect co-directional TRCs and facilitate higher-order assembly of KCTD10 complexes that recruit CUL3 to induce the ubiquitination and removal of the RNA polymerase factor TCEA2. In the absence of KCTD10, there is increased retention of TCEA2 and the RNA polymerase complex, causing an accumulation of TRCs and increased DNA damage. Our results demonstrate how replication can proceed through transcriptionally active regions, utilizing a unique bridging function of the CUL3–KCTD10 complex. These findings provide a framework for how the coordination between transcription and replication may contribute to the maintenance of genome stability.

Sources: https://newsnetwork.mayoclinic.org/discussion/mayo-clinic-researchers-discover-traffic-controller-protein-that-protects-dna-and-may-help-kill-cancer-cells/, https://www.nature.com/articles/s41586-025-09585-9

Epigenetic Reprogramming is a Promising Way to Overcome the Effects of DNA Damage

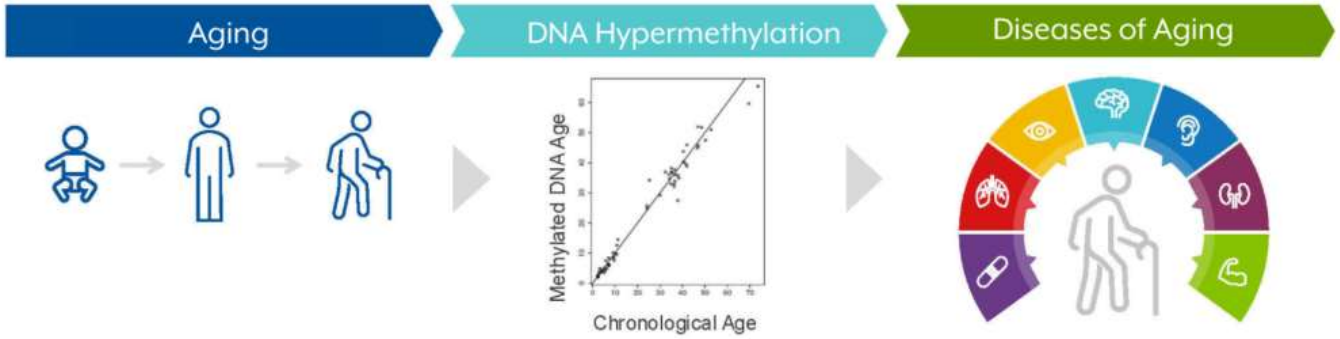
J.H. Yang et al., "Loss of epigenetic information as a cause of mammalian aging," *Cell*, Feb 29, 2024;187(5):1312-1313.

All living things experience an increase in entropy, manifested as a loss of genetic and epigenetic information. In yeast, epigenetic information is lost over time due to the relocalization of chromatin-modifying proteins to DNA breaks, causing cells to lose their identity, a hallmark of yeast aging. Using a system called "ICE" (inducible changes to the epigenome), we find that the act of faithful DNA repair advances aging at physiological, cognitive, and molecular levels, including erosion of the epigenetic landscape, cellular exdifferentiation, senescence, and advancement of the DNA methylation clock, which can be reversed by OSK-mediated rejuvenation. These data are consistent with the information theory of aging, which states that a loss of epigenetic information is a reversible cause of aging. Epigenetic changes linked to aging, including changes in DNA methylation (DNAme) patterns, H3K4me3, H3K9me3 and H3K27me3 (Benayoun et al., 2015; Pal and Tyler, 2016; Sen et al., 2016), are also seen in multicellular organisms. Examples include lifespan extension in worms deficient in the H3K4 trimethylation complex (Greer et al., 2010, 2011) or in flies overexpressing the Sir2 gene (Jiang et al., 2013; Rogina and Helfand, 2004; Wood et al., 2016), and the relatively stable epigenome of long-lived naked mole rats (Tan et al., 2017). Many epigenetic changes follow a specific pattern, including methylation of specific CpGs of the epigenetic clock (Hannum et al., 2013; Horvath, 2013; Lu et al., 2021; Petkovich et al., 2017; Weidner et al., 2014). To test whether epigenetic changes are a cause of mammalian aging, we developed systems to degrade and reset epigenetic information in cells and mice. Our data are consistent with aging in mammals being the equivalent of a software problem, the result of corrupted epigenetic information that can be restored from an existing back-up copy.



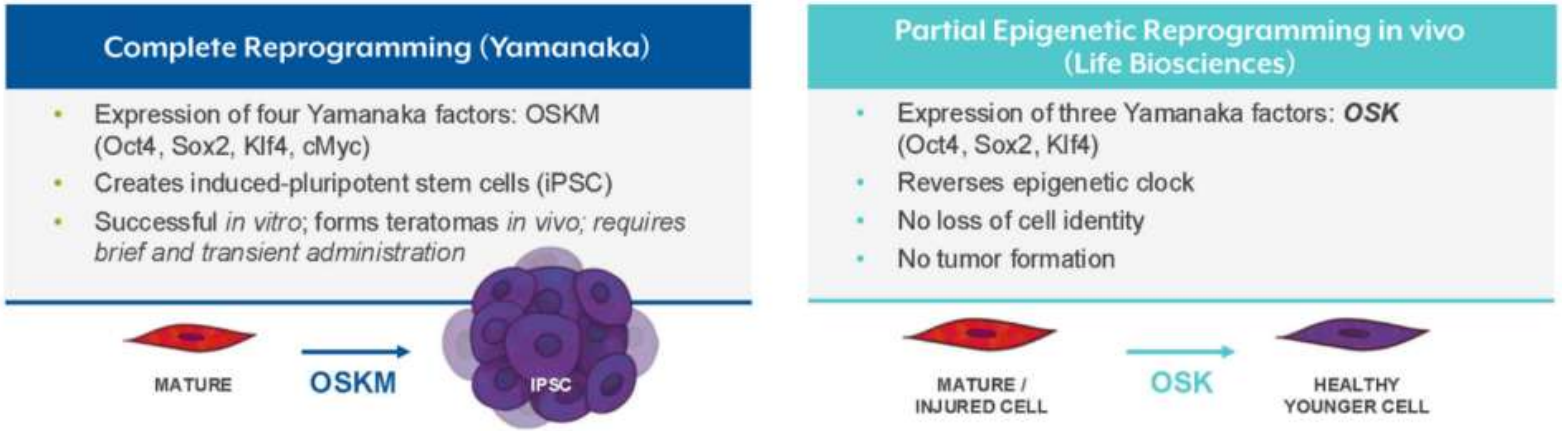
Source: https://www.cell.com/cell/fulltext/S0092-8674(22)01570-7

Life Biosciences Focuses on Epigenome Reprogramming to Overcome Aging



As we age, epigenetic markers called methyl groups accumulate on DNA and contribute to gene expression changes that may lead to disease. These epigenetic changes may result from lifestyle factors (e.g., smoking, drinking, etc.), aging, disease, and injury. Life Bio's therapeutic approach targets the epigenetic alterations that contribute to multiple age-related diseases.

Life Bio's therapies utilize three transcription factors – Oct-4, Sox-2, and Klf-4 (referred to as "OSK") – that aim to reprogram the epigenome and thereby restore aged cells to a younger state, enabling more effective cell function.



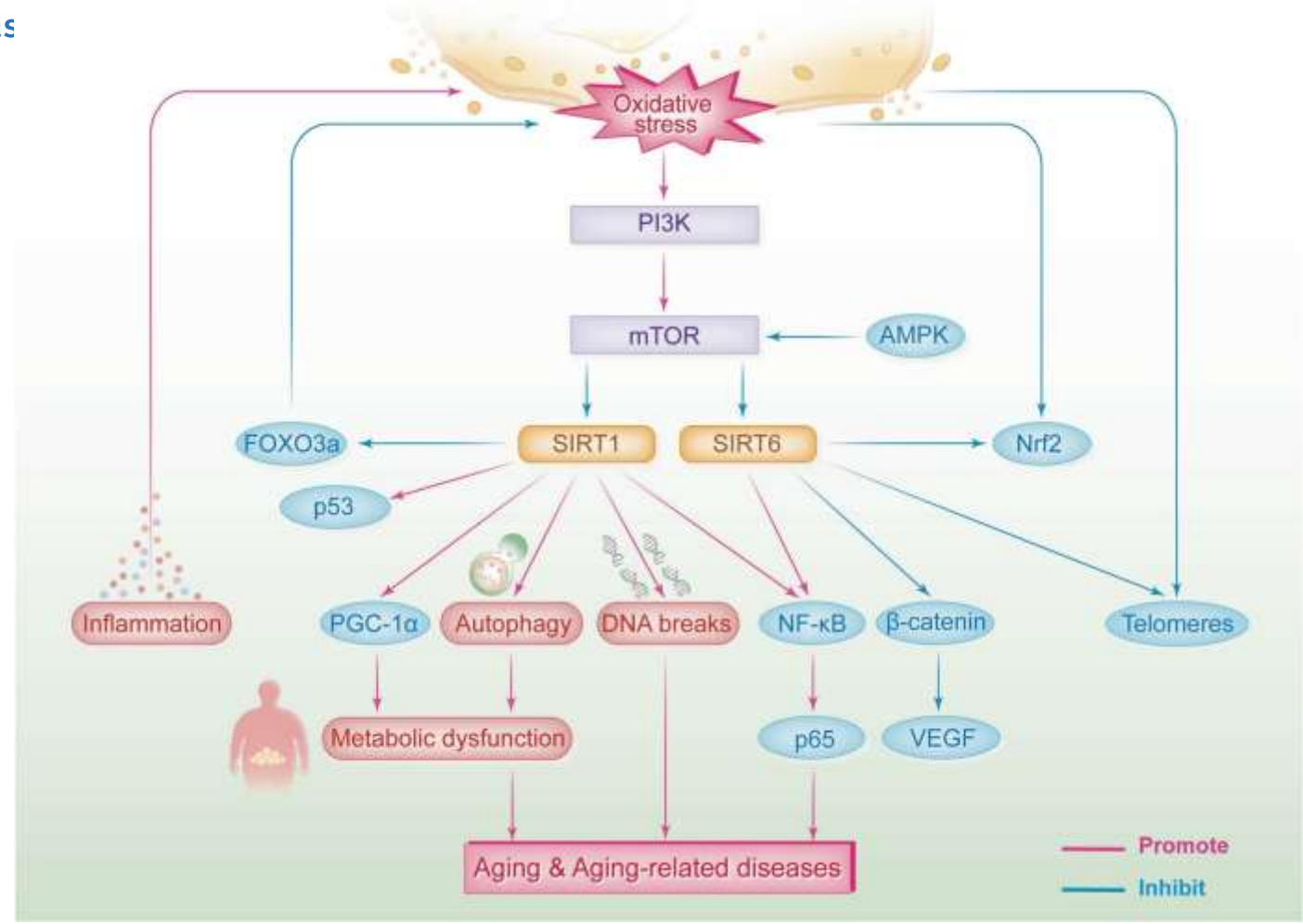
Life Bio's lead gene therapy candidate, ER-100 (AAV2-OSK), has demonstrated safety and efficacy in multiple pre-clinical animal models by local injection into the eye (intravitreally).

Source: https://www.lifebiosciences.com/

SIRT1/6 Agonists Can Potentiate the DNA Damage Response and Counteract Other Aging-Related Factors

You Y, Liang W. SIRT1 and SIRT6: The role in aging-related diseas
***Biophys Acta Mol Basis Dis.* 2023 Oct;1869(7):166815.**

Aging is associated with an accumulation of genomic mutations and rearrangements, which lead to gradually increased organ dysfunctions. These genomic alterations arise from aberrant repair of DNA breaks. SIRT1 deacetylates various DNA repair factors such as NBS1 and SUV39H1 to facilitate DNA repair through chromatin remodeling and transcriptional silencing. SIRT1 also regulates signaling molecules associated with DNA damage and stress response, such as p53, BRCA1, FOXO3a, Ku70, and TGF-β, to promote DNA repair. SIRT1−/− mice exhibit impaired DNA damage repair, genome instability, and tumorigenesis. SIRT6 has been shown to deacetylate histone H3 at lysine 9 in response to DNA damage to promote DNA double-strand break (DSB) repair. SIRT6−/− mice exhibit a premature aging phenotype with genome instability. Overexpression of SIRT6 in mammalian cells under oxidative stress strongly boosts DSB repair by activating poly (ADP-ribose) polymerase (PARP1). SIRT6 can also directly bind to SUV39H1 to help restore the original heterochromatin structure following DNA damage. Moreover, recent studies have revealed that SIRT6 can directly bind to and recognize DSBs and that SIRT1 can interact with and deacetylate SIRT6 to promote its recognition of DSBs to facilitate DNA repair in humans and mice.

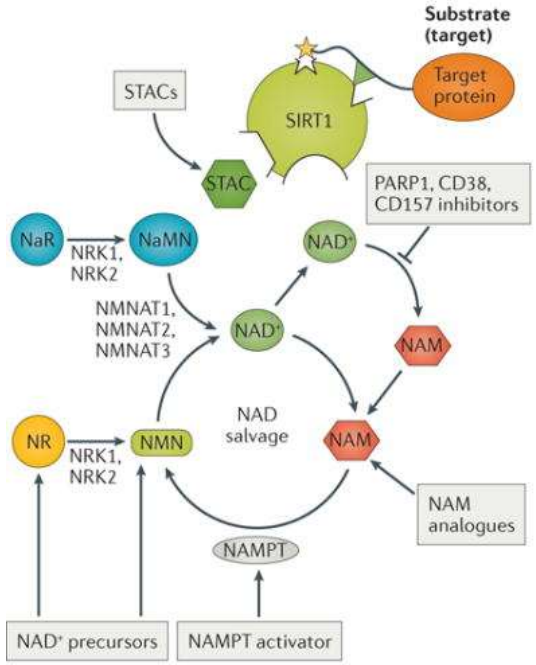


Source: https://www.sciencedirect.com/science/article/pii/S0925443923001813

Multiple Therapeutic Strategies Can be Used to Agonize Sirtuin Activity

Bonkowski MS, Sinclair DA. Slowing aging by design: the rise of NAD+ and sirtuin-activating compounds. *Nat Rev Mol Cell Biol*. 2016 Nov;17(11):679-690.

Sirtuin activity can be stimulated through various mechanisms: allosterically by sirtuin-activating compounds (STACs), such as resveratrol, SRT1720 and SRT2104, which lower the Km for the target proteins; increasing nicotinamide adenine dinucleotide (NAD+) levels by providing its precursors nicotinamide riboside (NR) or nicotinamide mononucleotide (NMN); inhibiting the glycohydrolases CD38 or CD157 (with apigenin, quercetin, GSK 897-78c)142,143; inhibiting poly(ADP-ribose) polymerases (PARPs); activating nicotinamide phosphoribosyltransferase (NAMPT) with P7C3; or by providing nicotinamide (NAM) analogues, such as methyl-NAM. Nicotinamide riboside kinase 1 (NRK1) and NRK2 convert NR and nicotinic acid riboside (NaR) is to NMN and nicotinic acid mononucleotide (NaMN), respectively. NaMN and NMN are converted to NAD+ by nicotinamide mononucleotide adenylyltransferase 1 (NMNAT1), NMNAT2 and NMNAT3. Sirtuins directly or indirectly target more than 100 signalling proteins with relevance to human disease in a variety of tissues ranging from brain to blood. Although STACs have therapeutic potential, certain diseases, such as cancer in certain contexts and Parkinson disease, may benefit from sirtuin inhibition. EF2, elongation factor 2; FOXO, forkhead box O; HNGB1, high-mobility group box 1; IL, interleukin; LXR, liver X receptor; MMP9, matrix metalloproteinase 9; NF-κB, nuclear factor-κB; NLRP3, NOD-, LRR- and pyrin domain-containing 3; PGC1α, peroxisome proliferator-activated receptor-γ co-activator 1α; PPAR, peroxisome proliferator-activated receptor; STAT5, signal transducer and activator of transcription; TGFβ, transforming growth factor-β; UCP2, mitochondrial uncoupling protein 2.



Target proteins	Tissues and pathologies
FOXO NF-κB	**Brain** • Alzheimer disease • Neurodegenerative disease
STAT5 EF2	**Eye** • Macular degeneration • Keratoconjunctivitis sicca
AKT TGFβ	**Skin** • Psoriasis • Severe plaque-type psoriasis
FOXO UCP2	**Pancreas** • Glucose sensing • Hyperinsulinaemia • Metabolic syndrome
PGC1α FOXO	**Muscle** • Type 2 diabetes • Sarcopaenia • Cardiovascular disease
LXR PPARα	**Liver** • Metabolic syndrome • Hepatic steatosis
PPARγ MYC	**Fat** • Inflammatory cytokines • Metabolic syndrome
IL-8 MMP9	**Lung** • Chronic obstructive pulmonary disease
HNGB1 NLRP3	**Blood** • Sepsis • Endotoxin-induced inflammation

Source: https://www.nature.com/articles/nrm.2016.93

The Telomere / Telomerase Story Has Substantial Weaknesses

The greatest weakness of the story is that it ignores the fact that cells can replicate. The idea of limited telomere length, as spelled out by Hayflick, is that a cell can only replicate so many times, but daughter cells can start all over with a fresh replication limit. Cell senescence, in a way, is a far greater danger because senescent cells can no longer replicate, limiting the organism's ability to regenerate itself.

Telomere length correlates with chronological and biological age, but the relationship is inconsistent across tissues and individuals. For example, leukocyte telomere length (commonly used as a biomarker) varies widely within age-matched populations and is influenced by genetics, stress, inflammation, and lifestyle. Some shorter-lived species (like mice) have much longer telomeres than humans yet far shorter lifespans—showing that **telomere length alone does not dictate lifespan**. In humans, many tissues retain proliferative capacity well into old age despite substantial telomere attrition, suggesting compensatory mechanisms.

If telomere shortening limits cell proliferation, then enhancing telomerase to "reverse aging" should extend life. In mice, telomerase reactivation can rejuvenate some tissues, but in humans, it risks **oncogenesis**. Telomere shortening is also a **tumor-suppressive mechanism**—cells with critically short telomeres undergo senescence or apoptosis, preventing malignant transformation. Stimulating telomerase systemically could allow precancerous cells to evade this checkpoint. Hence, while telomere attrition contributes to aging phenotypes, it also serves as an evolutionary trade-off balancing regeneration and cancer prevention.

Third Area:

Senescent Cells

Strategies for Managing the Effects of Cell Senescence on Aging

Cells that cease replicating are said to have entered **senescence**. Some dysfunctional senescent cells persist in tissues, secreting inflammatory molecules, which contribute to chronic diseases and aging—a phenomenon known as the **senescence-associated secretory phenotype** (SASP).

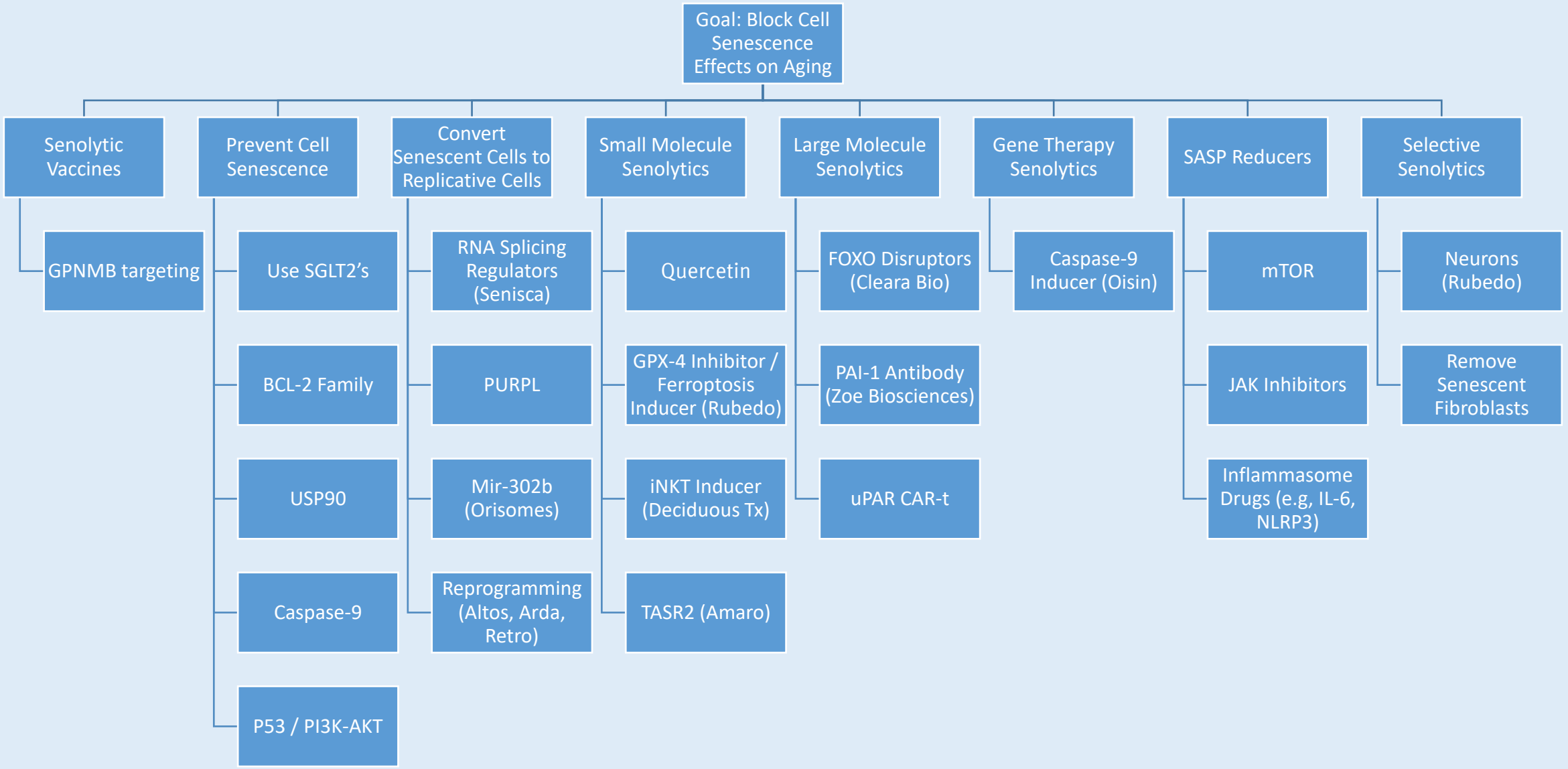
The concept of SASP was formally introduced by Coppé et al. (2008), who established it as a hallmark of cellular senescence. This work detailed how senescent cells secrete pro-inflammatory cytokines, growth factors, and proteases, linking SASP to both tumor promotion and age-related diseases.

The potential for senescence-targeting interventions was initiated by Jim Kirkland's group in Boston in 2004 and continued at Mayo. The work relied on Dr. Ned Sharpless' finding at the time that senescent cell abundance is inversely related to use of caloric restriction and other interventions that can delay aging phenotypes in mice under certain conditions. By 2015 this group had shown that **senolytic drugs**, which removed senescent cells, could alleviate age-related impairments in aged mice.

These findings supported the idea that senescent cells contribute directly to aging and that their selective elimination could offer therapeutic benefits.

More recently, Sadelain and Lowe (2020, 2024) explored the use of Chimeric Antigen Receptor T-cell (CAR-T) therapy to target and eliminate senescent cells. Their studies demonstrated that CAR-T cell therapy could reverse age-related pathologies and was both safe and effective in mice. This approach represents a promising avenue for translating senescence-targeting therapies into clinical applications.

Dendrogram of Therapeutic Options for Cell Senescence



Multiple Features of Senescent Cells Create Targeting Opportunities

Gasek NS, Kuchel GA, Kirkland JL, Xu M. Strategies for Targeting Senescent Cells in Human Disease. *Nat Aging*. 2021 Oct;1(10):870-879.

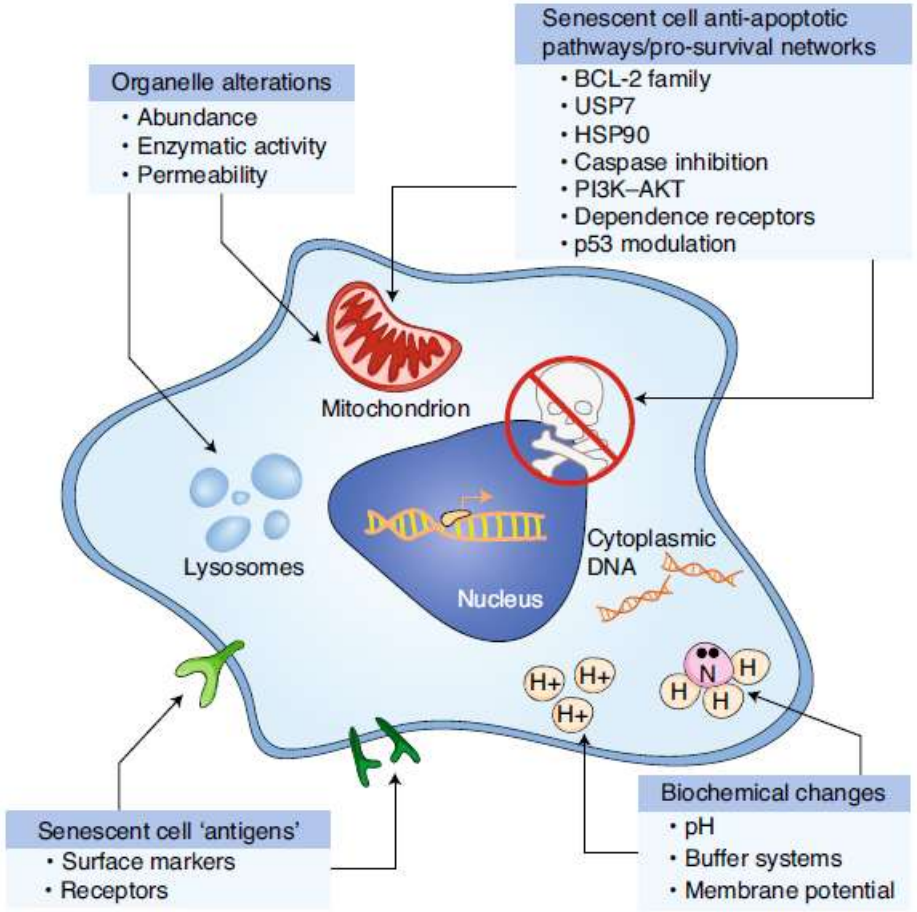


Fig. 2 | Senescent cell features targeted by senolytics. Select features of senescent cells have been leveraged to specifically reduce their abundance. Broadly, these targets include unique surface markers, SCAP and other survival networks, biochemical adaptations and changes in organelle characteristics.

Table 1 | Select features of senescent cells

Morphologic features	Increased size[56]
	Increased granularity[56,57]
Cell cycle blockade	p21–p53 (ref. [52])
	p16–RB (ref. [52])
Mitochondrial changes	Increased size/number[9]
	Increased ROS production[62]
	Decreased membrane integrity[62]
Lysosomal changes	Increased size/number[58]
	Increased SA-β-gal activity[59]
	Lipofuscin accumulation[61]
Nuclear changes	Telomere shortening[6,52,63]
	DDR (telomere-associated foci, γ-H2AX)[8,63]
	Lamin B1 loss[65]
	Senescence-associated heterochromatin foci[66]
	Decreased DNA replication[6]
Additional selected features	Cytosolic DNA/cGAS–STING activation[79–81]
	LINE-1 retrotransposon de-repression[67]
	Remodeling of SASP-associated super-enhancers[84]
	Other senescence transcriptional changes[55,69,70]

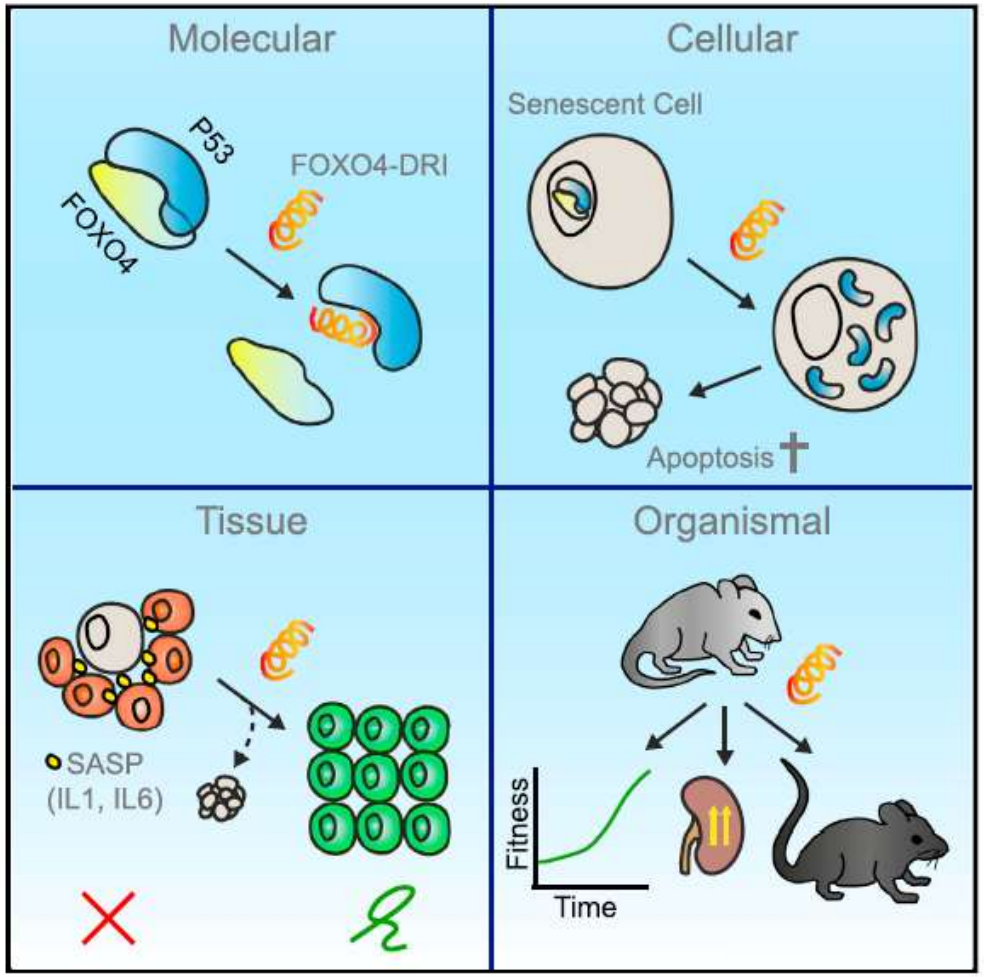
Source: https://www.nature.com/articles/s43587-021-00121-8

FOXO Peptides Promising as Senolytics

Baar MP, et al., *Cell*. 2017 Mar 23;169(1):132-147.

The accumulation of irreparable cellular damage restricts healthspan after acute stress or natural aging. Senescent cells are thought to impair tissue function, and their genetic clearance can delay features of aging. Identifying how senescent cells avoid apoptosis allows for the prospective design of anti-senescence compounds to address whether homeostasis can also be restored. Here, we identify FOXO4 as a pivot in senescent cell viability. We designed a FOXO4 peptide that perturbs the FOXO4 interaction with p53. In senescent cells, this selectively causes p53 nuclear exclusion and cell-intrinsic apoptosis. Under conditions where it was well tolerated in vivo, this FOXO4 peptide neutralized doxorubicin-induced chemotoxicity. Moreover, it restored fitness, fur density, and renal function in both fast aging $Xpd^{TTD/TTD}$ and naturally aged mice. Thus, therapeutic targeting of senescent cells is feasible under conditions where loss of health has already occurred, and in doing so tissue homeostasis can effectively be restored.

Targeted Apoptosis of Senescent Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging



Source: https://linkinghub.elsevier.com/retrieve/pii/S0092-8674(17)30246-5

SGLT2's as Senolytics

SGLT2 inhibition eliminates senescent cells and alleviates pathological aging

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Accepted: 2 May 2024

Published online: 30 May 2024

Check for updates

Goro Katsuumi[1,2,12], Ippei Shimizu[3,4,12], Masayoshi Suda[1,5,12], Yohko Yoshida[1,6], Takaaki Furihata[1], Yusuke Joki[1], Chieh-Lun Hsiao[1], Liang Jiaqi[1], Shinya Fujiki[2], Manabu Abe[7], Masataka Sugimoto[8], Tomoyoshi Soga[9,10] & Tohru Minamino[1,11]

Nature Aging, July 2024

It has been reported that accumulation of senescent cells in various tissues contributes to pathological aging and that elimination of senescent cells (senolysis) improves age-associated pathologies. Here, we demonstrate that inhibition of sodium–glucose co-transporter 2 (SGLT2) enhances clearance of senescent cells, thereby ameliorating age-associated phenotypic changes. In a mouse model of dietary obesity, short-term treatment with the SGLT2 inhibitor canagliflozin reduced the senescence load in visceral adipose tissue and improved adipose tissue inflammation and metabolic dysfunction, but normalization of plasma glucose by insulin treatment had no effect on senescent cells. Canagliflozin extended the lifespan of mice with premature aging even when treatment was started in middle age. Metabolomic analyses revealed that short-term treatment with canagliflozin upregulated 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside, enhancing immune-mediated clearance of senescent cells by downregulating expression of programmed cell death-ligand 1. These findings suggest that inhibition of SGLT2 has an indirect senolytic effect by enhancing endogenous immunosurveillance of senescent cells.

Source: https://www.nature.com/articles/s43587-024-00642-y

BCL2 PROTAC Showing Promise as a Senolytic

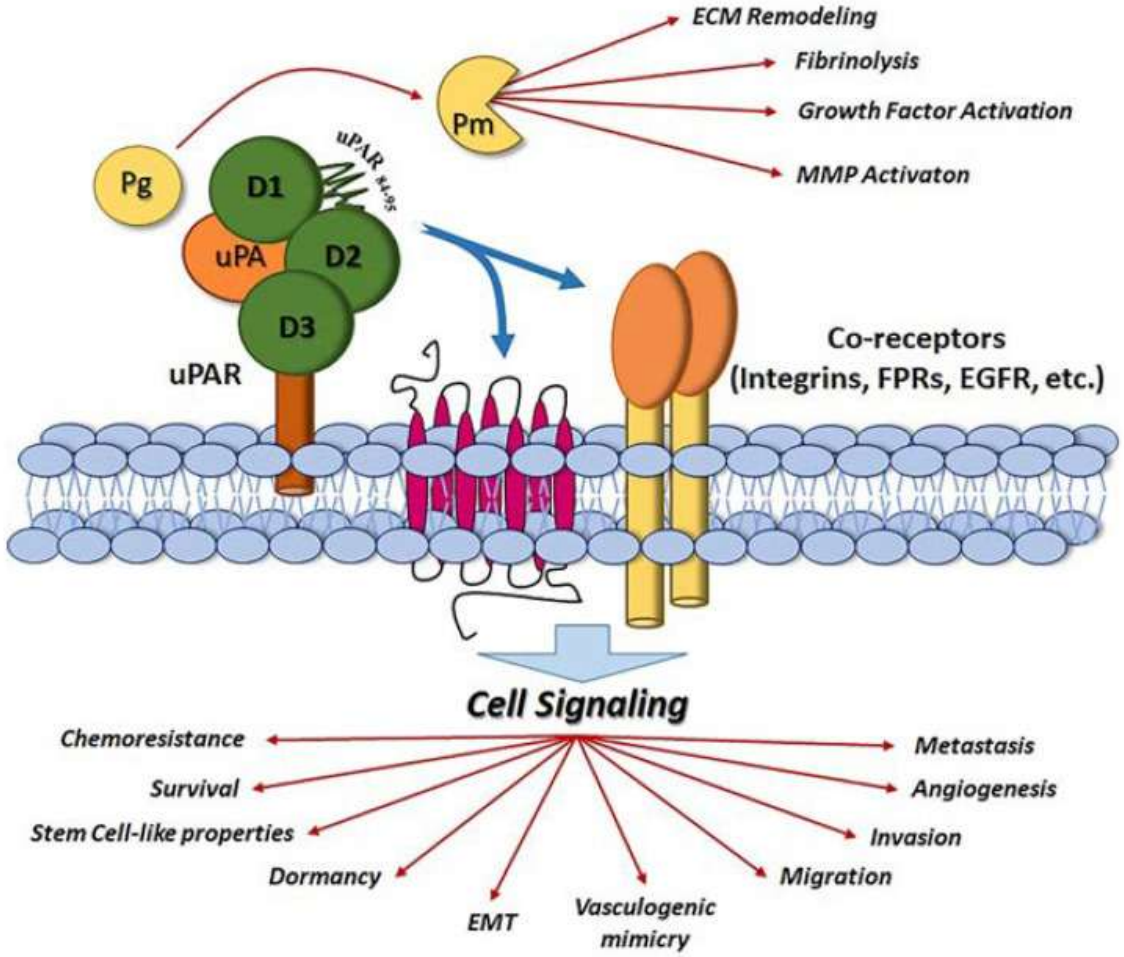
Yang Y, "A BCL-xL/BCL-2 PROTAC effectively clears senescent cells in the liver and reduces MASH-driven hepatocellular carcinoma in mice," *Nat Aging*. 2025 Mar;5(3):386-400.

Accumulation of senescent cells (SnCs) plays a causative role in many age-related diseases and has also been implicated in the pathogenesis and progression of metabolic dysfunction-associated steatotic liver disease (MASLD). Senolytics that can selectively kill SnCs have the potential to be developed as therapeutics for these diseases. Here we report the finding that 753b, a dual BCL-xL/BCL-2 proteolysis-targeting chimera (PROTAC), acts as a potent and liver-tropic senolytic. We found that treatment with 753b selectively reduced SnCs in the liver in aged mice and STAM mice in part due to its sequestration in the liver. Moreover, 753b treatment could effectively reduce the progression of MASLD and the development of hepatocellular carcinoma (HCC) in STAM mice even after the mice developed substantial metabolic dysfunction-associated steatohepatitis (MASH) and hepatic fibrosis. These findings suggest that BCL-xL/BCL-2 PROTACs have the potential to be developed as therapeutics for MASLD to reduce MASH-driven HCC.

Source: https://www.nature.com/articles/s43587-025-00811-7

uPAR Signaling Pathway

- **Focal Adhesion Kinase (FAK) and Src Kinases**: uPAR interacts with integrins (e.g., αvβ3, α5β1) and EGFR, leading to the activation of FAK and Src kinases.
- **PI3K/AKT Pathway**: uPAR engagement activates PI3K, leading to AKT phosphorylation.
- **MAPK Pathway**: Interaction with integrins and EGFR transactivates the MAPK pathway.
- **Chemotaxis and Migration**:
  - **Chemotactic Activity**: The uPAR84-95 sequence interacts with formyl-peptide receptors (FPR1, FPR2), promoting cell migration and angiogenesis.
  - **Cytoskeletal Rearrangements**: uPAR binding to vitronectin (Vn) and integrins facilitates cytoskeletal changes necessary for cell movement.
- **Angiogenesis**: uPAR regulates angiogenesis through proteolytic activity and direct interactions with VEGFR2 via LRP-1.



Sources: https://pubmed.ncbi.nlm.nih.gov/24138928/, https://www.nature.com/articles/s41576-018-0004-3

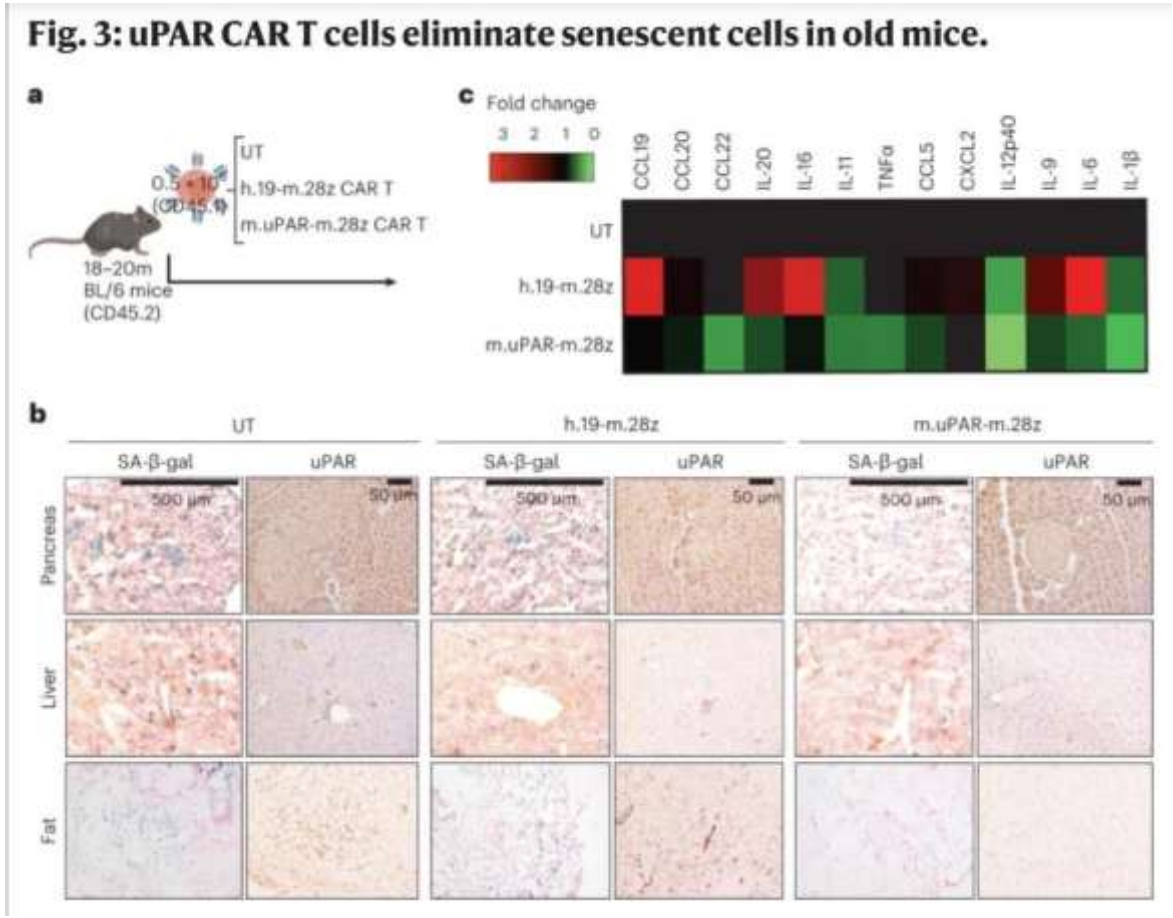
Senolytic CAR-T Cell Therapy

Mechanism of Action:

- **Engineering**: CAR-T cells are engineered to express receptors that recognize specific antigens on the surface of target cells.
- **Recognition and Binding**: The CAR on the T cell surface binds to uPAR on senescent cells
- **Activation and Killing**: Once bound, the CAR-T cells become activated, releasing cytotoxic granules that induce apoptosis in the senescent cells, effectively reducing the senescent cell burden.

Research:

- A study led by Scott Lowe of MSKCC and Michel Sadelein of Columbia demonstrated that CAR-T cells targeting uPAR effectively cleared senescent cells in mouse models, improving metabolic function and physical performance.



Sources: Amor et al. Nature Aging (2024)

uPAR Peptide (Alternative to CAR-t) Also Works Well in Targeting Senescent Cells

A chimeric peptide promotes immune surveillance of senescent cells in injury, fibrosis, tumorigenesis and aging

Received: 9 August 2023

Accepted: 15 October 2024

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Check for updates

Xinliang Ming[1,2,3,12], Ze Yang[1,2,12], Yuqiao Huang[1,2,12], Zhiguo Wang[4], Qingyan Zhang[1,2], Changchang Lu[1,2], Yandi Sun[1,2], Yuanhao Chen[1,2], Liang Zhang[5], Jicheng Wu[1,2,6], Hao Shou[1,2], Zhimin Lu[2,7,8,9,10] & Ben Wang[1,2,7,8,9,11]

The accumulation of senescent cells can lead to tissue degeneration, chronic inflammatory disease and age-related tumorigenesis. Interventions such as senolytics are currently limited by off-target toxicity, which could be circumvented by instead enhancing immune-mediated senescent cell clearance; however, immune surveillance of senescent cells is often impeded by immunosuppressive factors in the inflammatory microenvironment. Here, we employ a chimeric peptide as a 'matchmaker' to bind to the urokinase-type plasminogen activator receptor, a cell surface marker of senescent cells. This peptide modifies the cell surface with polyglutamic acid, promoting immune cell-mediated responses through glutamate recognition. By enhancing the recruitment of immune cells and directly coupling senescent cells and immune cells, we show that this chimeric peptide induces immune clearance of senescent cells and restores tissue homeostasis in conditions such as liver fibrosis, lung injury, cancer and natural aging in mice. This chimeric peptide introduces an immunological conversion strategy that rebalances the senescent immune microenvironment, offering a promising direction for aging immunotherapy.

Nature Aging
Jan 2025

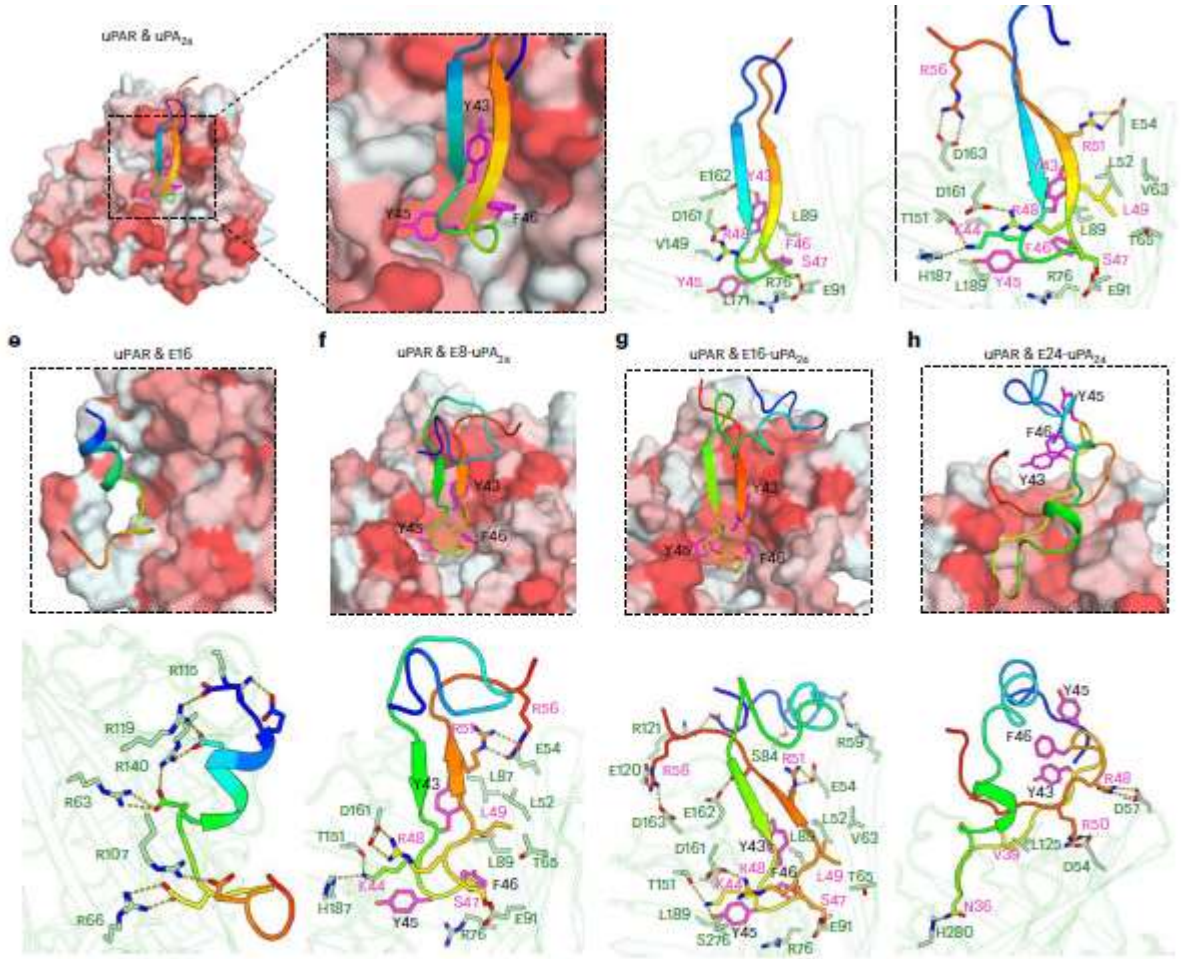


Fig. 1 | Design and targeting validation of the chimeric peptide. a, Sketch of the mouse uPAR and uPA structural domains. **b**, The sequence of uPA_{24} ranged from amino acids 34 to 57 in the amino-terminal sequence of mouse uPA, the ligand for uPAR. E16-uPA_{24} consists of 16 glutamates added to the amino terminus of the target peptide uPA_{24}. **c**, The location of the peptide uPA_{24} on the hydrophobic surface of uPAR, with red and white representing hydrophobic and hydrophilic features, respectively. **d**, Intermolecular interactions in the crystal (left) and MD-equilibrated (right) structures. Both the hydrogen bonding and electrostatic interactions are indicated by yellow dotted lines. **e**–**h**, MD-equilibrated binding conformations and interactions of uPAR and peptides (E16, E8-uPA_{24}, E16-uPA_{24}, and E24-uPA_{24}). The hydrophobic surface of uPAR is illustrated with the red and white regions exhibiting hydrophobic and hydrophilic features, respectively. The secondary structures of uPAR and the peptides are shown in pale green and rainbow cartoons (blue for the amino terminus and orange for the carbonyl terminus), respectively. The residues involved in hydrophobic contacts, hydrogen bonds and electrostatic interactions are shown as sticks (magenta for the Y43–Y45–F46 triplet and rainbow for the other peptide residues, pale green for uPAR), with the hydrogen bonds and electrostatic interactions represented by yellow dotted lines.

Senolytic Vaccine Concept is Intriguing

Suda M, et al., "Senolytic vaccination improves normal and pathological age-related phenotypes and increases lifespan in progeroid mice," *Nature Aging*. Dec 2021; 1(12):1117-1126.

Elimination of senescent cells (senolysis) was recently reported to improve normal and pathological changes associated with aging in mice. However, most senolytic agents inhibit antiapoptotic pathways, raising the possibility of off-target effects in normal tissues. Identification of alternative senolytic approaches is therefore warranted. Here we identify glycoprotein nonmetastatic melanoma protein B (GPNMB) as a molecular target for senolytic therapy. Analysis of transcriptome data from senescent vascular endothelial cells revealed that GPNMB was a molecule with a transmembrane domain that was enriched in senescent cells (seno-antigen). GPNMB expression was upregulated in vascular endothelial cells and/or leukocytes of patients and mice with atherosclerosis. Genetic ablation of Gpnmb-positive cells attenuated senescence in adipose tissue and improved systemic metabolic abnormalities in mice fed a high-fat diet, and reduced atherosclerotic burden in apolipoprotein E knockout mice on a high-fat diet. We then immunized mice against Gpnmb and found a reduction in Gpnmb-positive cells. Senolytic vaccination also improved normal and pathological phenotypes associated with aging, and extended the male lifespan of progeroid mice. Our results suggest that vaccination targeting seno-antigens could be a potential strategy for new senolytic therapies.

Source: https://www.nature.com/articles/s43587-021-00151-2

Approaching Senescence Caused by Retrovirus is a Promising Area

X. Liu, "Resurrection of endogenous retroviruses during aging reinforces senescence," *Cell* Jan 19, 2023;186(2):287-304.e26.

Whether and how certain transposable elements with viral origins, such as endogenous retroviruses (ERVs) dormant in our genomes, can become awakened and contribute to the aging process is largely unknown. In human senescent cells, we found that HERVK (HML-2), the most recently integrated human ERVs, are unlocked to transcribe viral genes and produce retrovirus-like particles (RVLPs).

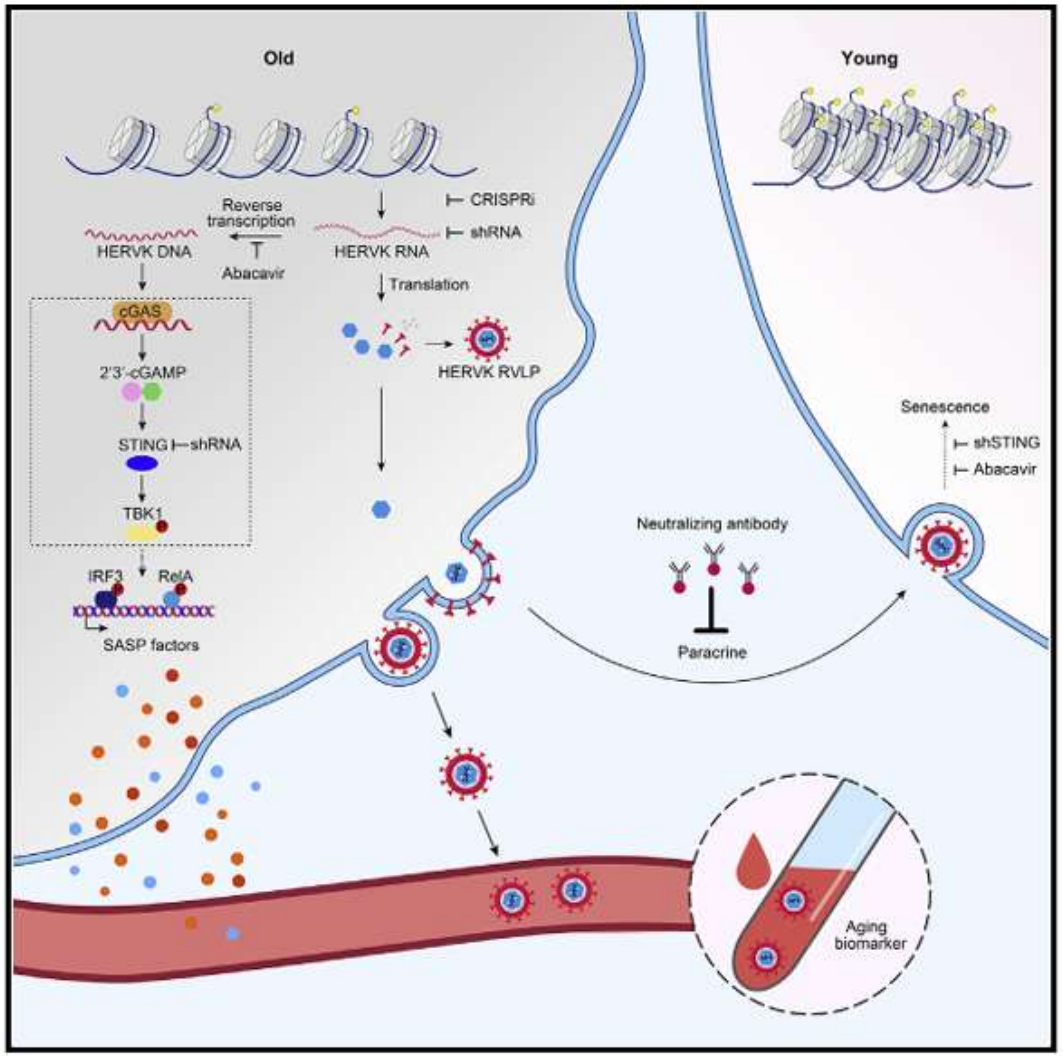
These HERVK RVLPs constitute a transmissible message to elicit senescence phenotypes in young cells, which can be blocked by neutralizing antibodies.

The activation of ERVs was also observed in organs of aged primates and mice as well as in human tissues and serum from the elderly.

Their repression alleviates cellular senescence and tissue degeneration and, to some extent, organismal aging. These findings indicate that the resurrection of ERVs is a hallmark and driving force of cellular senescence and tissue aging.

Source: https://www.cell.com/cell/fulltext/S0092-8674(22)01530-6. Also see https://www.science.org/content/article/blocking-jumping-genes-help-fight-disease-aging

Resurrection of endogenous retroviruses during aging reinforces senescence

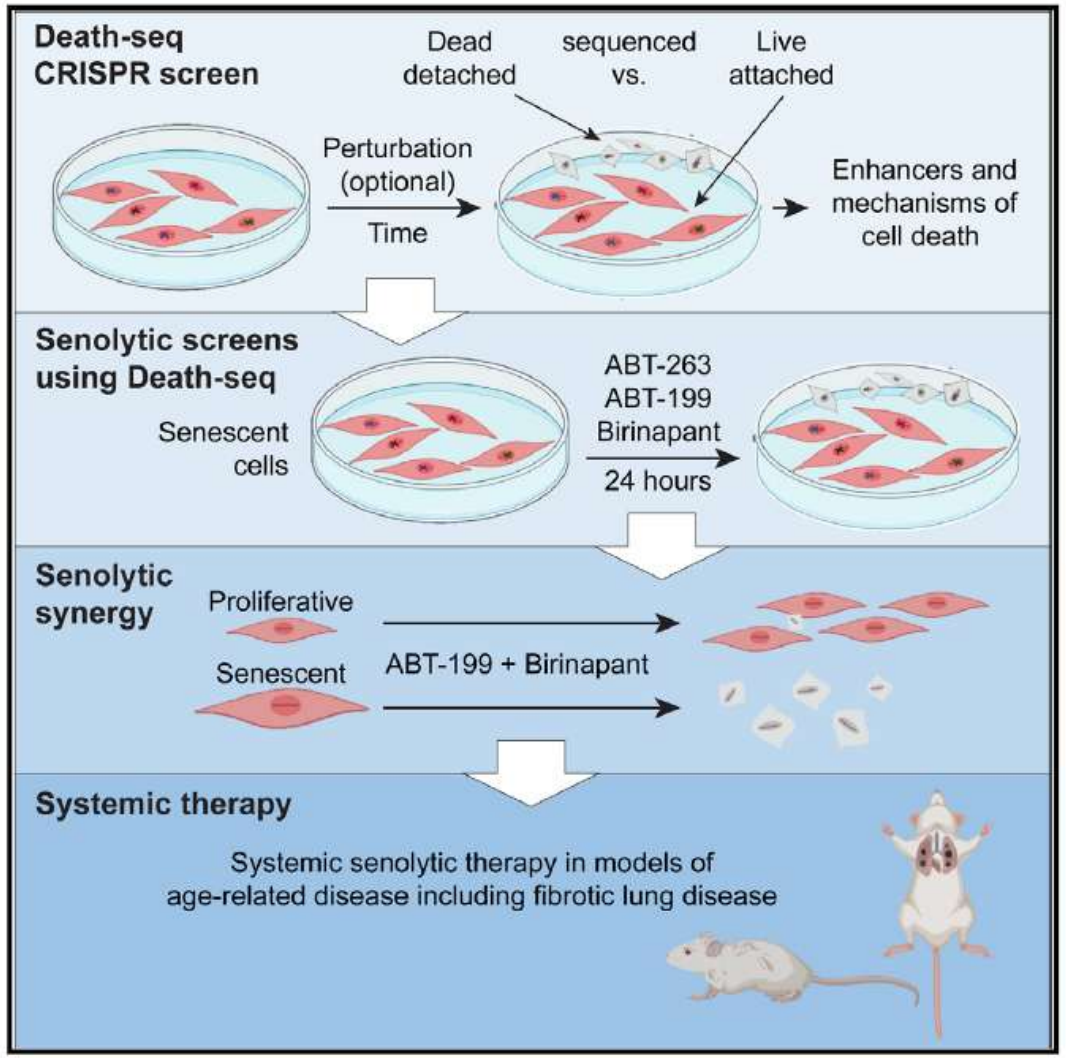


Methods to Screen for Senolytics Have Been Prioritized

Colville A. et al., "Death-seq identifies regulators of cell death and senolytic therapies," *Cell Metab*. Oct 3, 2023; 35(10):1814-1829.e6.

Current methods for genome-wide screens to identify genes whose deletion might promote the death of damaged or senescent cells are generally underpowered because of the short timescales of cell death as well as the difficulty of scaling non-dividing cells. Here, we establish "Death-seq," a positive-selection CRISPR screen optimized to identify enhancers and mechanisms of cell death. Our screens identified synergistic enhancers of cell death induced by the known senolytic ABT-263. The screen also identified inducers of cell death and senescent cell clearance in models of age-related diseases by a related compound, ABT-199, which alone is not senolytic but exhibits less toxicity than ABT-263.

Graphical abstract



Authors

Alex Colville, Jie-Yu Liu, Cristina Rodriguez-Mateo, ..., Joseph C. Wu, Michael C. Bassik, Thomas A. Rando

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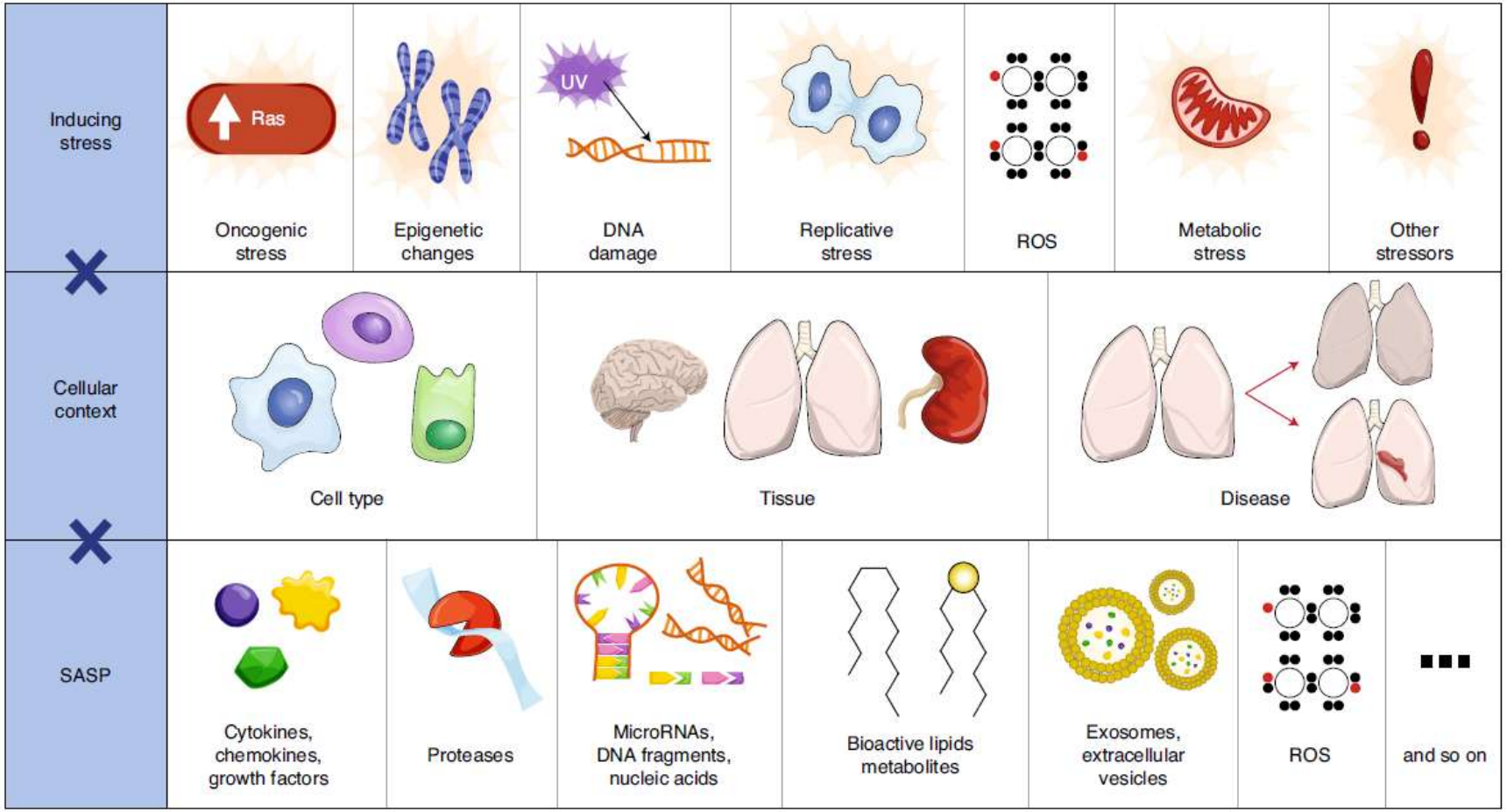
In brief

Colville et al. present a genetic screening method called Death-seq to compare positively selected dying cells directly against living cells to improve the ability to systematically identify enhancers and mechanisms of cell death. They then applied this method to identify enhancers of selective cell death in senescent cells in age-related disease.

Source: https://www.cell.com/cell-metabolism/fulltext/S1550-4131(23)00303-0

Multiple Layers of Heterogeneity in Senescent Cells Creates Complexity in Targeting Them

Gasek NS, Kuchel GA, Kirkland JL, Xu M. Strategies for Targeting Senescent Cells in Human Disease. *Nat Aging*. 2021 Oct;1(10):870-879.



Source: https://www.nature.com/articles/s43587-021-00121-8

Due to Diversity in Cell Types, It is Hard to Remove All Senescent Cells

Evans SA, Teo YV, Hinthorn SJ, Clark K, Ito T, Sedivy JM, Neretti N. Single-Cell Transcriptomics Reveals Global Markers of Transcriptional Diversity across Different Forms of Cellular Senescence. *Aging Biol.* 2023;1(1):e20230008.

Cellular senescence (CS) is a state of irreversible cell cycle arrest, and the accumulation of senescent cells contributes to age-associated organismal decline. The detrimental effects of CS are due to the senescence-associated secretory phenotype (SASP), an array of signaling molecules and growth factors secreted by senescent cells that contribute to the sterile inflammation associated with aging tissues. Recent studies, both in vivo and in vitro, have highlighted the heterogeneous nature of the senescence phenotype. Single-cell transcriptomics has revealed that oncogene-induced senescence (OIS) is characterized by the presence of subpopulations of cells expressing different SASP profiles. We have generated a comprehensive dataset via single-cell transcriptional profiling of genetically homogenous clonal cell lines from different forms of senescence, including OIS, replicative senescence, and DNA damage-induced senescence. We identified subpopulations of cells that are common to all three major forms of senescence and show that the expression profiles of these subpopulations are driven by markers formerly identified in individual forms of senescence. These common signatures are characterized by chromatin modifiers, inflammation, extracellular matrix remodeling, and ribosomal protein gene expression (measured at the RNA level). The expression patterns of these subpopulations recapitulate primary and juxtacrine secondary senescence, a phenomenon where a pre-existing (primary) senescent cell induces senescence in a neighboring (secondary) cell through cell-to-cell contact. Hence, our results demonstrate that the formation of juxtacrine secondary populations of cells is common to multiple types of senescence and occurs in competition with primary senescence. **Finally, we show that these subpopulations show differential susceptibility to the senolytic agent Navitoclax, suggesting that senolytic agents targeting the apoptotic pathways may be clearing only a subset of senescent cells based on their inflammatory profiles.**

Source: https://agingcelljournal.org/Archive/Volume3/single_cell_transcriptomics_reveals_global_markers/

IL-23R a Promising Biomarker to Track Efficacy of Senolytic Interventions

IL-23R is a senescence-linked circulating and tissue biomarker of aging

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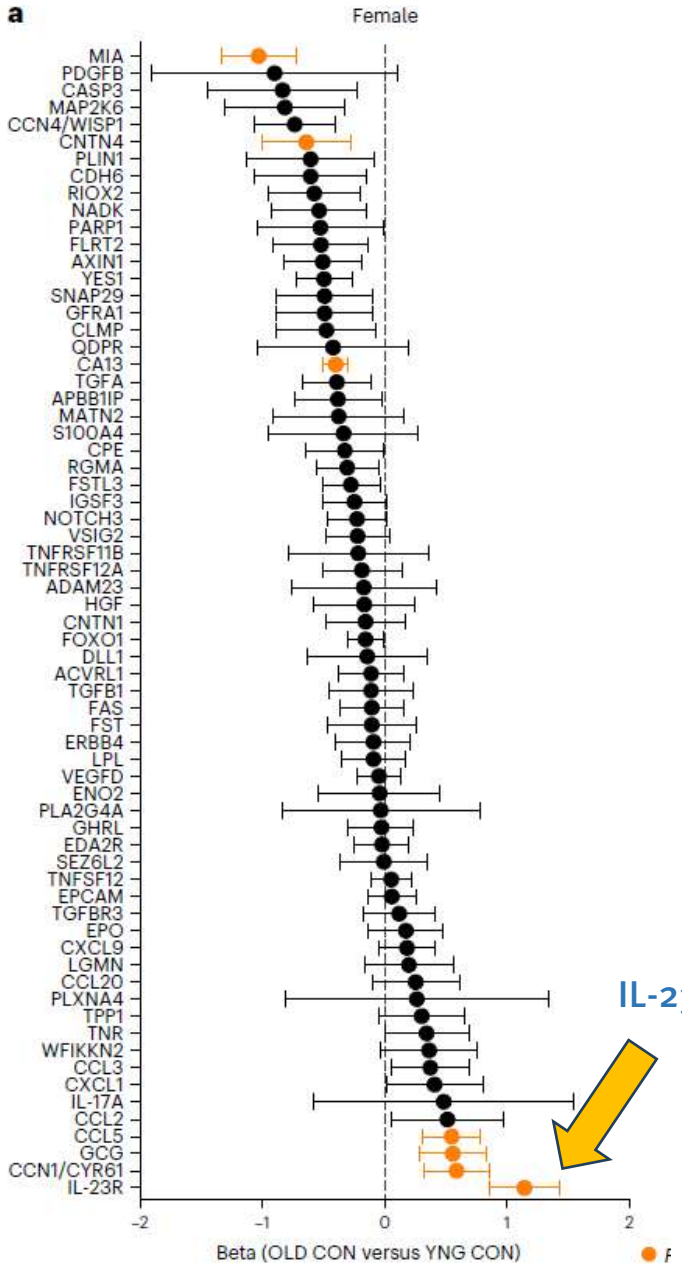
Check for updates

Chase M. Carver[1,2], Sonia L. Rodriguez[1,2], Elizabeth J. Atkinson[3], Andrew J. Dosch[1,2], Niels C. Asmussen[1,2], Paul T. Gomez[1], Ethan A. Leitschuh[1,2], Jair M. Espindola-Netto[1,2], Karthik B. Jeganathan[4], Madison G. Whaley[5], Theodore M. Kamenecka[6], Darren J. Baker[2,4,7], Andrew J. Haak[1,5], Nathan K. LeBrasseur[1,2] & Marissa J. Schafer[1,2,8,9]

Nature Aging

Cellular senescence is an aging mechanism characterized by cell cycle arrest and a senescence-associated secretory phenotype (SASP). Preclinical studies demonstrate that senolytic drugs, which target survival pathways in senescent cells, can counteract age-associated conditions that span several organs. The comparative efficacy of distinct senolytic drugs for modifying aging and senescence biomarkers in vivo has not been demonstrated. Here, we established aging- and senescence-related plasma proteins and tissue transcripts that changed in old versus young female and male mice. We investigated responsivity to acute treatment with venetoclax, navitoclax, fisetin or luteolin versus transgenic senescent cell clearance in aged *p16-InkAttac* mice. We discovered that age-dependent changes in plasma proteins, including IL-23R, CCL5 and CA13, were reversed by senotherapeutics, which corresponded to expression differences in tissues, particularly in the kidney. In plasma from humans across the lifespan, IL-23R increased with age. Our results reveal circulating factors as candidate mediators of senescence-associated interorgan signal transduction and translationally impactful biomarkers of systemic senescent cell burden.



IL-23R rates high

Source: https://www.nature.com/articles/s43587-024-00683-3

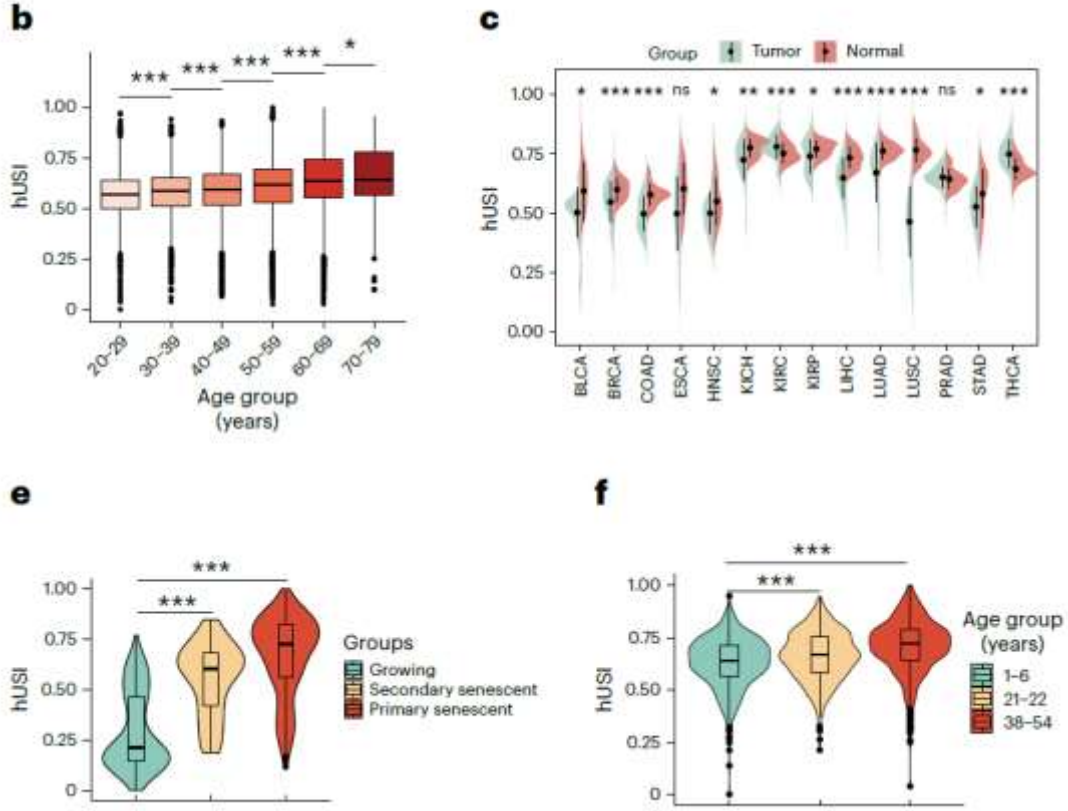
Conserved and distinct plasma proteins are altered by age in female and male mice. a,**b**, Beta estimates corresponding to comparison of old control (OLD CON) versus young control (YNG CON) protein abundance determined by Olink PEAs in female (**a**) and male (**b**) plasma samples.

Another Group Has Developed a Broad Anti-Senescence Biomarker Tracker Called hUSI

A transcriptome-based human universal senescence index (hUSI) robustly predicts cellular senescence under various conditions

Jing Wang et al, *Nature Aging*, June 2025

Despite the manifestation and contribution of cellular senescence to aging and various diseases, accurate identification of heterogeneous senescent cells remains challenging. Current senescence evaluation methods rely mainly on limited markers or homogeneous samples, which might fail to capture universal senescence features, limiting their generalizability. Here we developed the human universal senescence index (hUSI), an accurate and robust senescence evaluation method for diverse cells and samples. Based on features learned from the most comprehensive cellular senescence-associated transcriptome data so far, hUSI demonstrated its convincing connections with senescence phenotypes and superior robustness in predicting senescence state. Using hUSI, we discovered potential senescence regulators and mapped senescent cell accumulation across cell types in coronavirus disease 2019 (COVID-19). The method also facilitates decoding heterogeneous senescence states in melanoma tumors, identifying prognosis-associated signaling pathways. Overall, hUSI demonstrates its utility in characterizing cellular senescence across biological contexts, with broad applications in aging research and clinical practice.



Source: https://pubmed.ncbi.nlm.nih.gov/40442321/

An Alternative View of Senescence and Oxidative Stress: Pay Attention to Necrosis

We have argued in this report that senescence is largely a result of oxidative stress associated with mitochondrial respiration and that the negative feedback loops associated with cell senescence can lead to organismal mortality. A key idea then is to remove those senescent cells as quickly as possible to shut down the negative feedback loops. There is much to like about this point of view, including the fact that it offers an integrated theory, and that one that can explain the cascade of bad events that we have all seen in our aging cars and dying older relatives and friends.

Senescence theory is built around negative feedback loops and Passos' linkage of this theory to mitochondrial damage is particularly alluring to us.

Yet, when one reads through the many dozens of recently published papers on cell senescence, amidst the astonishing detail, there is an absolute paucity of attempt to sort out the mechanics of these feedback loops.

One effort that we find to be particularly interesting is that of Carina Kern and colleagues who argues that oxidative stress and senescence phenotypes can lead to a very specific pathological form of cell death: **necrosis**. She further argues that necrosis, which is unprogrammed cell death associated with stress, specifically involves the release of substantial hazardous intracellular contents including "DAMPS, oxidative agents, proteases, hydrolases and lipases".

What's nice about this particular theory is that explains *how* senescence releases all those unpleasant SASP factors that cascade to accelerate our demise. It's not at all clear whether necrosis is the sole intermediary of SASP release – or, perhaps, to what degree, might it be.

However, what is encouraging here is that Kern has identified another target for anti-aging drugs and the mitochondrial theory of aging. If the effect of mitochondrial damage is largely to cause senescence, which in turns leads to SASP release via necrosis, which in turn slowly kills us by turning off cell replication, then anti-necrosis drugs could be quite an interesting way to intervene in slowing aging.

Excerpts from a Recent Review Paper on Necrosis and Aging

Necrosis as a fundamental driver of loss of resilience and biological decline: what if we could intervene?

Oncogene, May 29, 2025

Carina Kern[1]✉, Joseph V. Bonventre[2,3,4], Alexander W. Justin[5], Kianoush Kashani[6], Elizabeth Reynolds[7,8], Keith Siew[9,10], Bill Davis[1], Halime Karakoy[1], Nikodem Grzesiak[1] and Damian Miles Bailey[11,12,13]

Necrosis Mediates Many Aging Feedback Loops

…necrosis is a central feature of chronic age-related diseases that triggers positive feedback loops. Once initiated, necrosis directly disrupts tissue integrity, leading to degeneration and loss of function. A key reason this degeneration is not adequately repaired is necrosis-driven positive feedback loops, resulting in cascading tissue damage.

These cycles overwhelm the body's wound-healing processes, leading to an inadequate repair response marked by patho-pathways that drive aberrant senescent cell accumulation, vascular disruption, and fibrosis. This results in persistent and difficult-to-treat conditions, while the overall loss of microarchitecture and function further predisposes tissues to necrosis, reinforcing an aging phenotype.

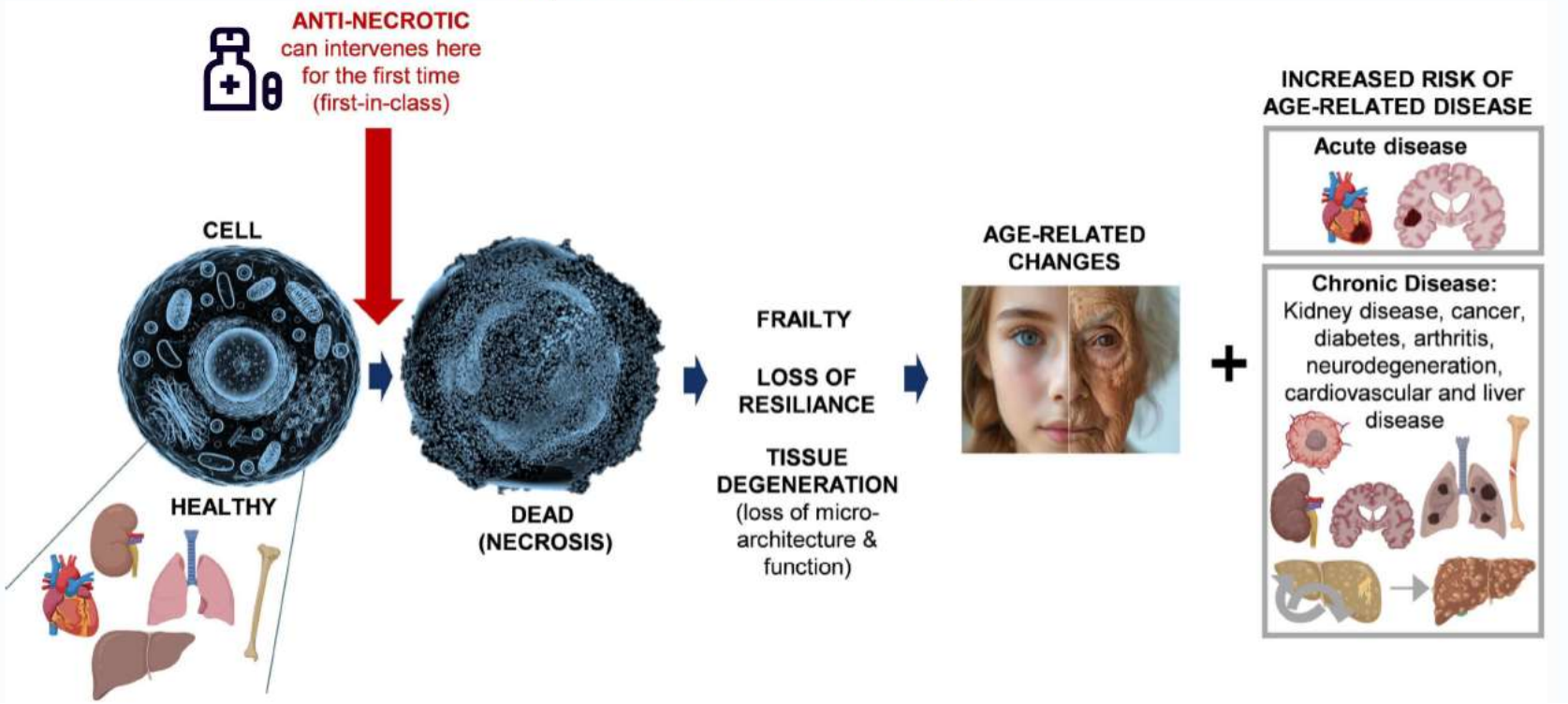
Direct Anti-Necrotics are Attractive Aging Interventions

Addressing the role of necrosis in aging could, therefore, extend healthspan. It is likely in large part due to such positive feedback loops that anti-inflammation therapies, including Interleukin-11 (IL-11), and senescent cell targeting senolytics and senomorphics show promise in alleviating aging phenotypes. By partially disrupting the cycle of necrosis and senescence, such treatments may preserve tissue function and delay the onset of age-related diseases. However, these are more limited and partial means to disrupt such cycles, **in contrast to a potential direct necrosis inhibitor that would switch off necrosis-induced damage feedback loops at their source, thereby preserving resilience and enhancing tissue regenerative capacity.**

Source: https://www.nature.com/articles/s41388-025-03431-y

Linkgevity is Preparing a Clinical Study of an Anti-Necrotic Drug that Works Through Calcium Channels

Notably, the mechanisms by which necrosis drives age-related degeneration are well-characterized; the key scientific gap has been the development of a successful means to block necrosis. LinkGevity has developed a first-in-class "Anti-Necrotic™", which can inhibit necrosis with an unprecedented 90% efficiency.



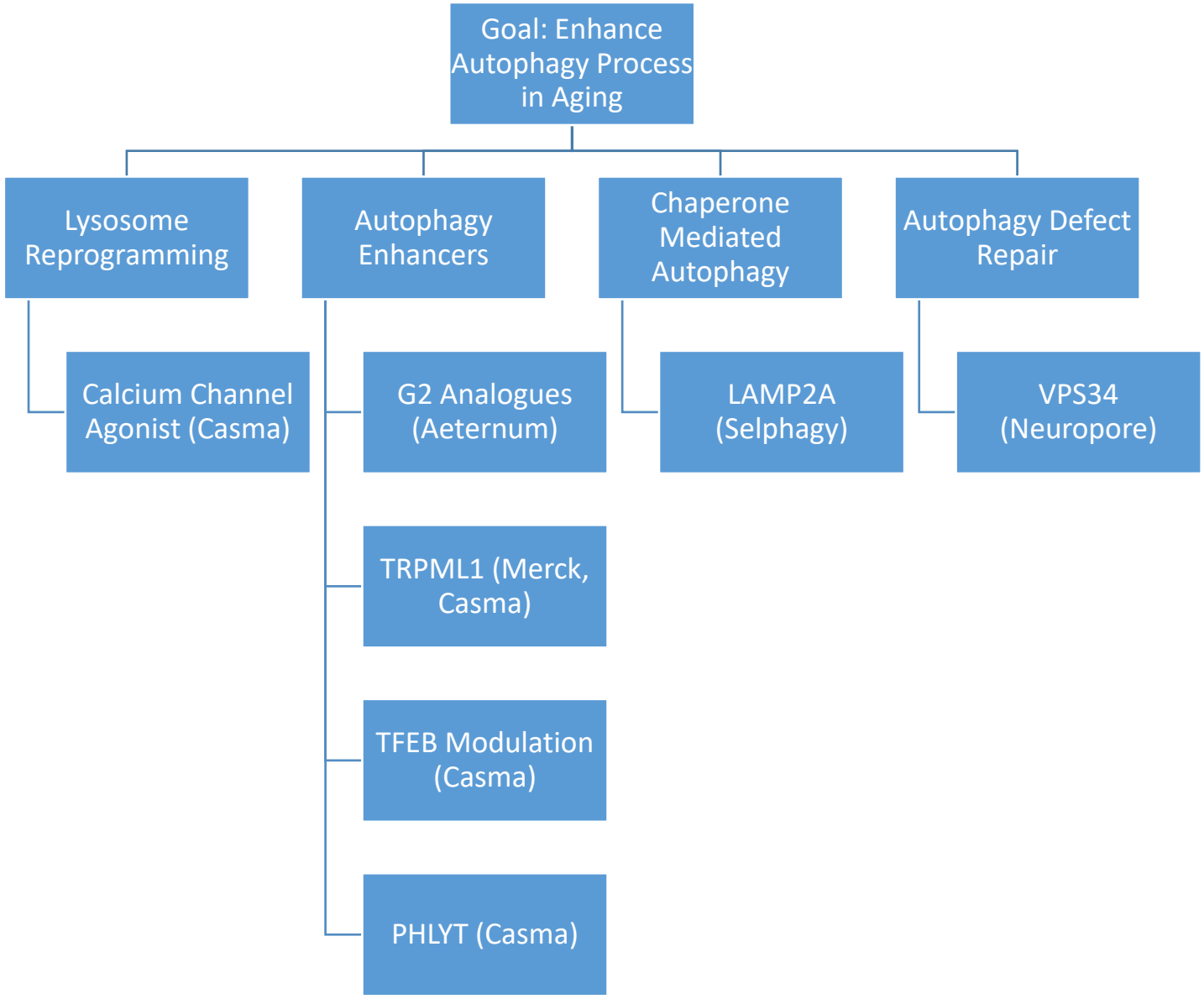
Having shown a strong ability to protect cells from necrosis caused by oxidative stress, Linkgevity is now working on going forward with a study to show that this drug works to protect humans from kidney damage.

Kidneys appear unusually vulnerable to the ravages of aging, particularly as a result of necrosis.

Fourth Area:

Autophagy Enhancement

Dendrogram of Therapeutic Options for Autophagy



Aeternum: G2 Analogs Effective in Enhancing Autophagy in a Huntington's Disease Model

Oh YM, Lee SW, Kim WK, Chen S, Church VA, Cates K, Li T, Zhang B, Dolle RE, Dahiya S, Pak SC, Silverman GA, Perlmutter DH, Yoo AS. Age-related Huntington's disease progression modeled in directly reprogrammed patient-derived striatal neurons highlights impaired autophagy. *Nat Neurosci*. 2022 Nov;25(11):1420-1433.

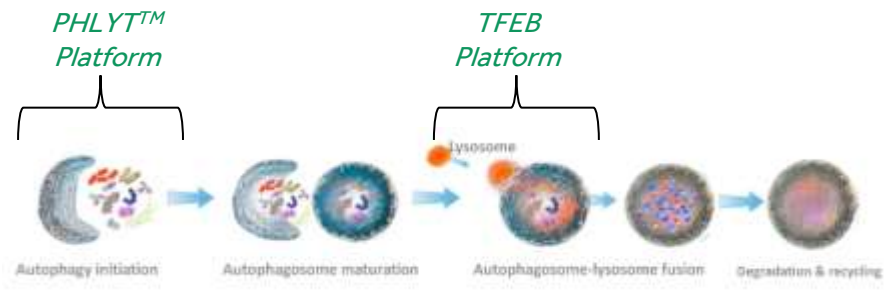
"In this study, we leveraged the conversion system to investigate how aging in Huntington's Disease may contribute to MSN degeneration by focusing on the finding that the degree of neuronal death in patient-derived MSNs corresponds to the stage of HD progression. MSNs converted from fibroblasts collected after the onset of clinical symptoms (HD-MSNs) display significantly higher levels of cell death than MSNs reprogrammed from patient fibroblasts collected at younger, pre-symptomatic stages (pre-HD-MSNs) or from age-matched healthy controls. We employed comparative transcriptomics, chromatin accessibility profiling and cellular phenotyping to reveal that HD-MSNs are characterized by marked downregulation of autophagy function compared to pre-HD-MSNs and control MSNs from both young and old age groups. We identify miR-29b-3p, whose marked upregulation in HD-MSNs over pre-HD-MSNs significantly limits autophagy in HD-MSNs via directly targeting STAT3 via human-specific binding sites in the 3′ untranslated region (UTR). The autophagy deficiency in HD-MSNs can be overcome chemically or genetically by a glibenclamide analog, G2, or by inhibiting miR-29b-3p, leading to the reduction of mutant HTT aggregation and protection of HD-MSNs from neuronal death. This study provides molecular insights into how aging in HD compromises autophagy in MSNs and its enhancement as a potent approach to increase MSN resilience against neurodegeneration in HD."

Huntington's Disease creates an accelerated aging phenotype. In this paper, a glibenclamide (G2) analog was effective in reversing neuronal death caused by Huntington's. The MOA was enhancement of autophagy. This approach is being pursued by the biotech Aeternum.

Source: https://pubmed.ncbi.nlm.nih.gov/36303071/

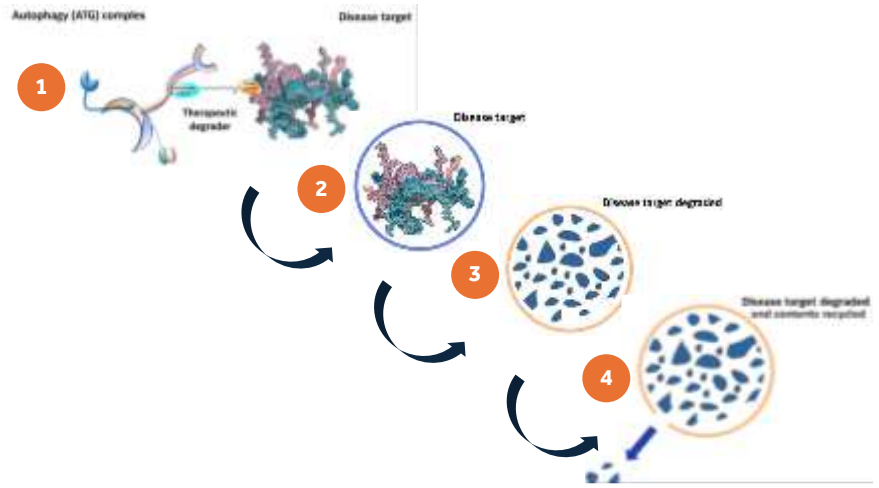
Casma Has Two Autophagy Enhancement Platforms

Platforms Overview



1. Autophagy pathway process shown, from start to end
2. PHLYT begins at the start of process with the selective targeting of specific disease targets and their subsequent degradation
3. TFEB focuses on lysosome and activation of lysosome where the degradative step of the autophagy-lysosomal pathway

PHLYT™ Platform

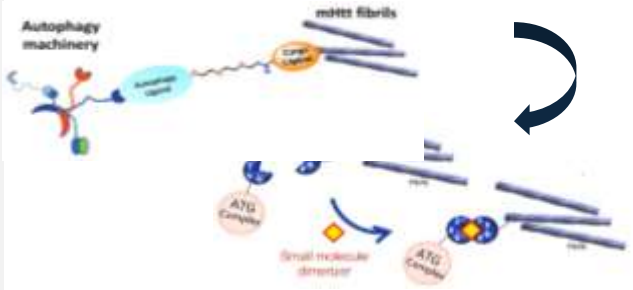


1. Degrader is a bifunctional molecule that recruits the ATG complex to the disease target using proprietary ligands
2. Proximity of ATG and disease target allows for an autophagosome to form around target
3. This merges with the lysosome and brings digestive enzymes to break down target into harmless amino and fatty acids
4. Degraded content is recycled into cell for other functions. This returns normal cell and tissue function

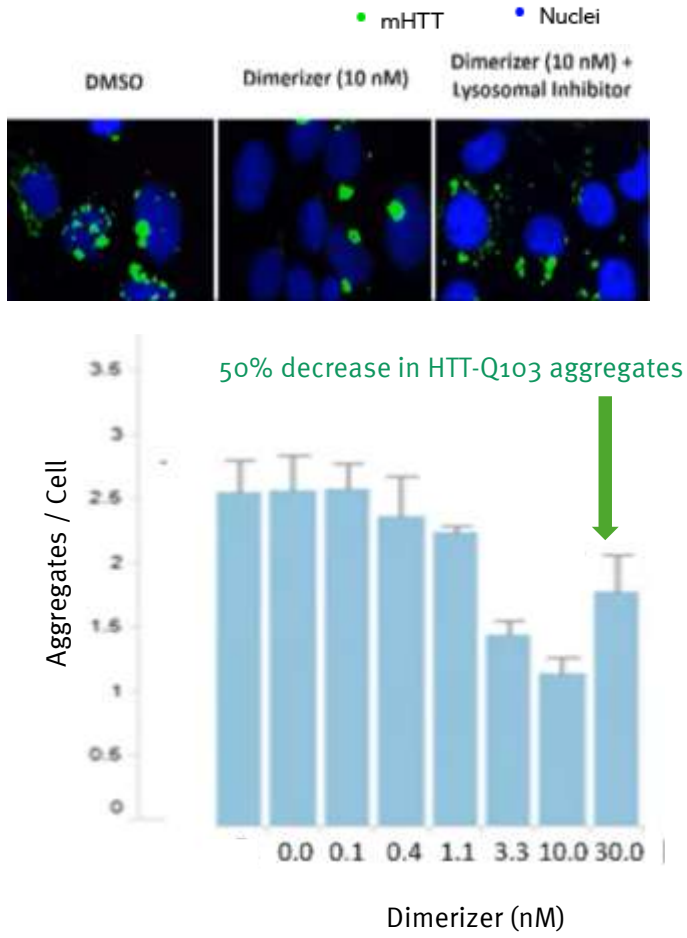
Source: Company Website, Company Presentation; Note: ATG = Autophagy Initiation Complex

Casma PHLYT™ Degraders Target PolyQ Repeat Disorders

Within CNS, the Company's primary PolyQ-based target is Huntington's Disease

Program Overview	
Targets	• Huntington's is caused by CAG expansions in the mHTT gene • Kennedy's is caused by a CAG/glutamine tract expansion in the androgen receptor • This leads to PolyQ expansion in both diseases
Mechanism of Action	
Clinical Development Plan	• Patients: n=30, 25 – 60 years old • Criteria: HD with ›= 36 CAG repeats • Primary Endpoint: Safety and MTD (maximum tolerable dose) • Secondary Endpoint: Pharmacokinetics (CSF and plasma), mHTTand Nfl levels (CSF and cognition)

mHTT[1] Aggregate Degradation



Source: Company Presentation

Fifth Area:

Cell Reprogramming

Cell Reprogramming

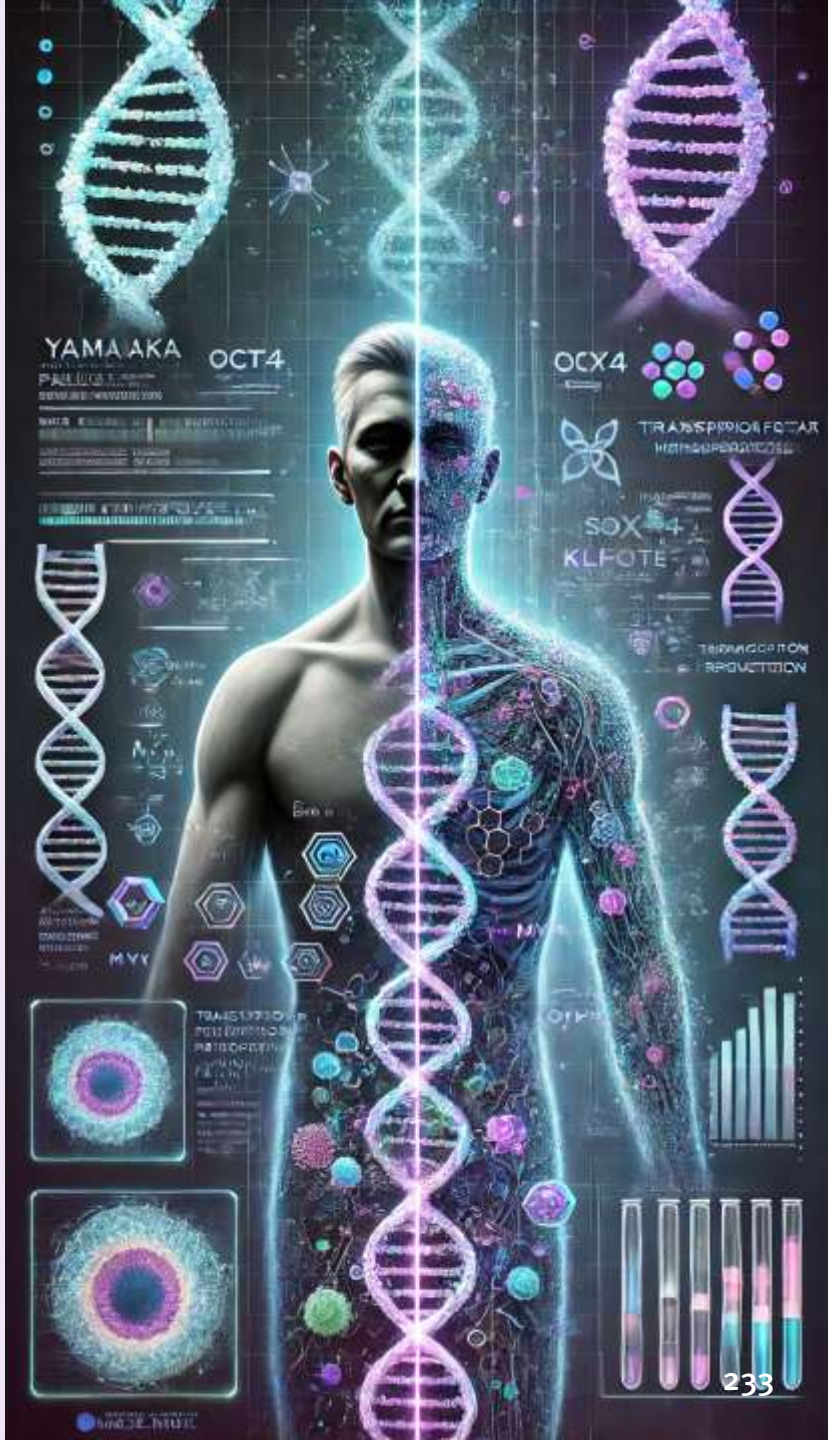
Vague concepts of rejuvenation have been around forever. Drink this magic potion and you will be young again etc. The 1990s version of this turned into stem cell injections.

But no one thought that there might be programmable transcription factors in the cell that could cause a cell to take on a younger phenotype.

Since Yamanaka's stunning 2006 paper showing that four transcription factors (called OKSM) control a cell's conversion back to a pluripotent type there has been an outpouring of research in this area.

Perhaps the two most notable contributions since then have come from Juan Belmonte. In a 2008 paper, Belmonte and colleagues showed that they could reprogram cells to a younger state *in vitro.*

Remarkably, in a 2016 paper Belmonte and colleagues showed that reprogramming of Yamanaka factors (OKSM) could reduce aging in a mouse. This raises the fascinating possibility of being able to reverse aging in humans. This stunning result was one of the main factors behind the largest venture fundraise in history. In 2019 Altos Labs hired Belmonte and raised $3 billion in order to develop anti-aging medicines based upon his partial reprogramming approach.



The Promise of the Cell Reprogramming Approach

“We now have pre-clinical data suggesting that the cellular dysfunction associated with ageing and disease can be reversible. This knowledge means that it may, one day, be possible to transform patients' lives by reversing disease, injury and the disabilities that can occur throughout life.”

Hal Barron

Chief Executive Officer

Altos Labs

Yamanaka Showed that Reprogramming Could Take a Mature Cell Back to a Pluripotent (Young) State

- Hypothesis: Select transcription genes induce pluripotency in somatic cells and maintain embryonic cell identity.
- Method:
  - A β*geo* cassette was inserted into the mouse gene Fbx15 through homologous recombination, and any resistance to the drug G418 in the assay was linked to induced pluripotency.
- Results:
  - When the 24 transcription factors from the somatic cell nucleus were introduced individually to the embryonic fibroblasts in mice, there were no drug resistant colonies.
  - However, when all 24 transcription factors were simultaneously introduced, the colonies were observed to be resistant to G418.
- Conclusions:
  - Particularly, the combination of Oct3/4, Sox2, Klf4, c-Myc proteins were significant in inducing pluripotency.
    - Their role were confirmed by gene expression analyses and teratoma formation assays.
    - The result of this combination is called an IPS (induced pluripotency stem) cell.

Recent Progress in Cell Reprogramming

The focus is on partial reprogramming and variations of OKSM in order to minimize the risk of cancer.

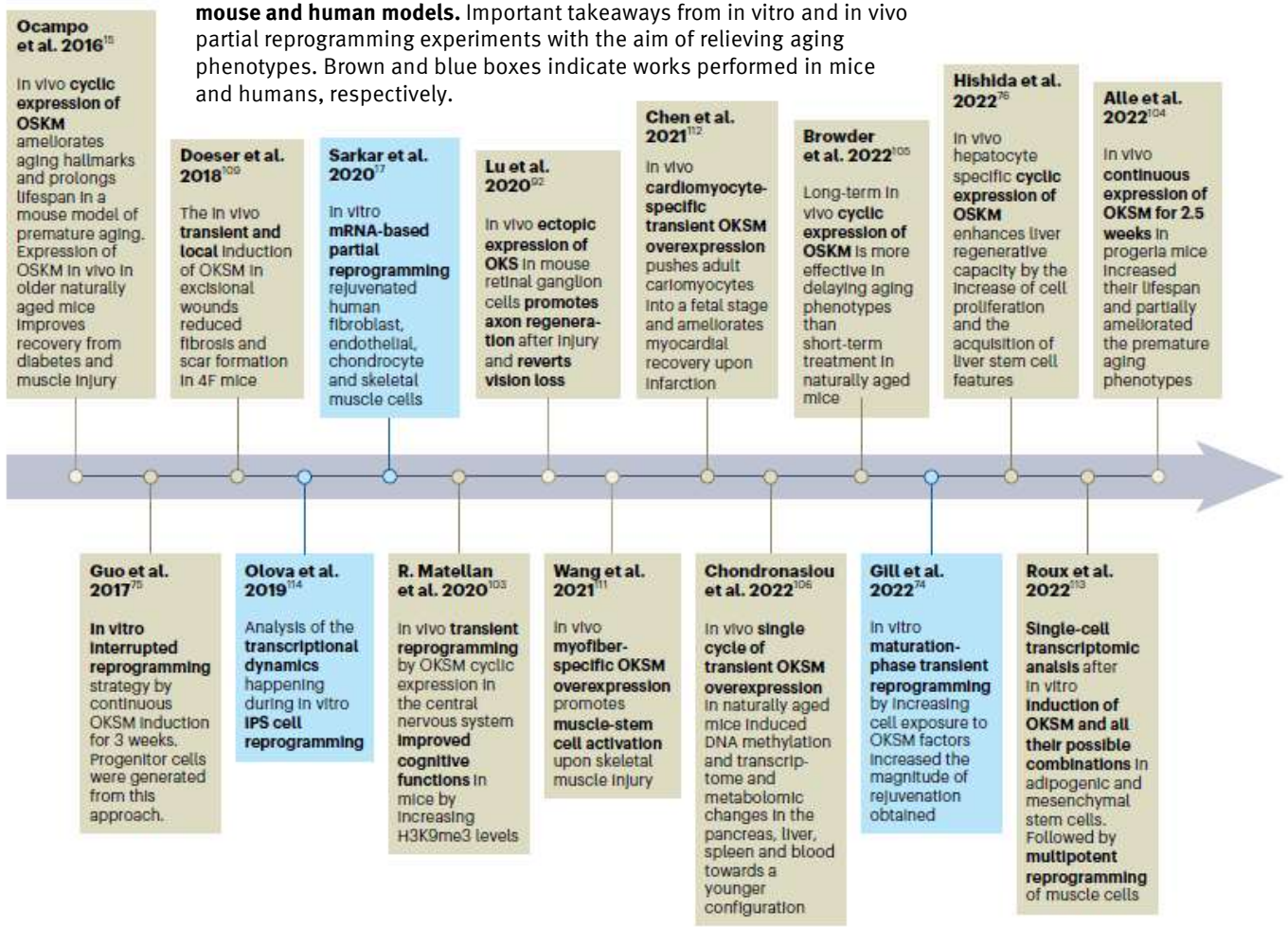


Fig 2. Timeline highlighting publications on partial reprogramming in mouse and human models. Important takeaways from in vitro and in vivo partial reprogramming experiments with the aim of relieving aging phenotypes. Brown and blue boxes indicate works performed in mice and humans, respectively.

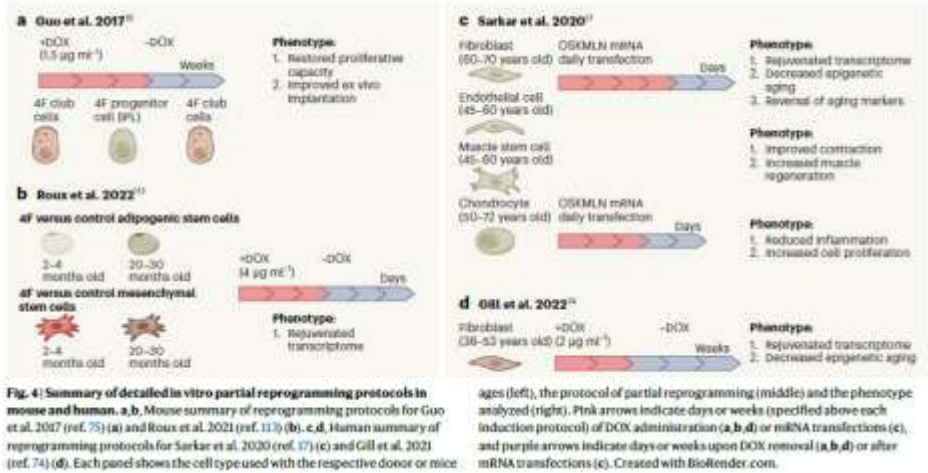


Fig. 4 | Summary of detailed in vitro partial reprogramming protocols in mouse and human. a,**b**, Mouse summary of reprogramming protocols for Guo et al. 2017 (ref. 75) (**a**) and Roux et al. 2021 (ref. 113) (**b**). **c**,**d**, Human summary of reprogramming protocols for Sarkar et al. 2020 (ref. 17) (**c**) and Gill et al. 2021 (ref. 74) (**d**). Each panel shows the cell type used with the respective donor or mice ages (left), the protocol of partial reprogramming (middle) and the phenotype analyzed (right). Pink arrows indicate days or weeks (specified above each induction protocol) of DOX administration (**a**,**b**,**d**) or mRNA transfections (**c**), and purple arrows indicate days or weeks upon DOX removal (**a**,**b**,**d**) or after mRNA transfections (**c**). Created with BioRender.com.

Source: Cipriano A, Moqri M, Maybury-Lewis SY, Rogers-Hammond R, de Jong TA, Parker A, Rasouli S, Schöler HR, Sinclair DA, Sebastiano V., "Mechanisms, pathways and strategies for rejuvenation through epigenetic reprogramming," *Nature Aging*, Jan 2024; 4(1):14-26.

Substantial Progress in the Last Three Years with Epigenetic Cell Reprogramming

This is really good progress for a technology that was discovered less than twenty years ago.

In Vivo Reprogramming Works in Primate Eye Disease

In Vivo Reprogramming Works in Primate Heart Disease (Mayo)

In Vivo Reprogramming is Now Being Tested in Humans for Heart Disease

In Vivo Reprogramming Definitely Extends Lifespan in Mice (but we haven't gotten further – yet)

We have learned to do reprogramming using mRNA (Sebastiano Lab)

Multiple Groups Around the World Have Mastered Epigenetic Reprogramming with Small Molecules (Gladyshev Lab, Ding Lab)

Note: Martin Borch Jenson, CSO of Gordian Technology, has delivered a nice lecture, available on Youtube on the progress that has been made with reprogramming and aging science but also the outstanding issues and potential avenues for future progress.

Our view is that the upcoming human trials of this technology in the eye at Life Technologies will be quite important.

In addition, it's worth noting that the original Yamanaka process of OKSM reprogramming has been successfully used to turn fibroblasts and other cells into pluripotent cells. These in turn have been used recently with great success in humans in treatment of Parkinson's disease. There are also programs underway for iPSC-based renewal in AMD, SCI and heart failure.

What we have not seen yet is progress beyond the mouse in life extension itself, even though that is a clear possibility. We know that there is huge investment in this area at companies like Altos. Perhaps, the dog is the next animal to work on. Let's see how progress unfolds in the years ahead.

Summary of Recent Research in Cellular Reprogramming Field

Study / PI / Date	Theme	Key Findings	Lifespan / Function Effects	Caveats / Risks	Representative Groups
Lu et al., David Sinclair 2020–2023	OSK restores vision in mice & primates	AAV-delivered OSK rejuvenates retinal ganglion cells, reverses methylation age, restores vision in aged/glaucomatous mice and non-human primates.	Functional reversal of blindness; durable neural repair.	Tissue-specific; not systemic; no lifespan data.	Life Biosciences, Harvard, Rejuvenate Bio
Ksander et al. David Sinclair 2023	OSK gene therapy restored vision in a non-human primate NAION model	the optic nerve one of the first tissues where partial reprogramming has advanced from mouse into primates.	First truly meaningful outcome from OSK gene therapy	Need to see long-term results and data in humans next	Life Biosciences
Macip Noah Davidson 2024	Systemic OSK extends lifespan in very old mice	Doxycycline-inducible AAV-OSK doubled remaining lifespan of 124-week-old mice; improved frailty and organ scores.	Reported ~109% remaining lifespan extension.	Low sample size; incomplete cause-of-death data; unreplicated.	Rejuvenate Bio
Sahu Juan Belmonte 2023	Targeted partial reprogramming in senescent cells	OSK expression tied to p16+ senescent cells improved wound healing and healthspan in aged mice.	Lifespan gain in progeroid mice; functional rejuvenation.	Requires precise promoter targeting; limited tissue scope.	Salk Institute, Altos
Browder Juan Belmonte 2022	Long-term partial reprogramming in normal aging	Cyclic OSKM expression rejuvenated molecular aging markers in multiple tissues.	Improved skin, kidney, metabolic profiles; no lifespan increase.	Some tumor risk; incomplete systemic benefit.	Sinclair Lab (Harvard)
Alle JM LeMaitre 2022	Early-life reprogramming pulses	Single early-life OSKM pulse shifted late-life epigenetic aging trajectory.	Possible 'set point' reset of aging signatures.	No direct lifespan data; developmental timing sensitive.	Stanford / Altos-linked
Mitchell etal. V. Gladyshef 2023	Chemical reprogramming cocktails	Small-molecule '7c/2c' cocktails rejuvenated mitochondria, splicing, and metabolism; extended lifespan in C. elegans.	Multi-omic rejuvenation without pluripotency.	No mammalian lifespan data yet.	Calico, Retro, academic consortia

Source: Stifel Investment Banking Department.

Progress Among Some Leading Reprogramming Biotechs

While the potential is huge, these companies are all early in the "reprogramming-for-rejuvenation" journey; many are still pre-clinical and have not yet registered large human trials.

	ALTOS	life BIOSCIENCES	NewLimit	REJUVENATE BIO	Retro
Approach	Cellular rejuvenation programming of aged/senescent cells; leveraging reprogramming technologies, high-end biology.	Partial epigenetic reprogramming platform (PER) using OSK (three factors) to rejuvenate aged/damaged cells (for e.g., optic neuropathies, liver disease).	Epigenetic reprogramming (youthful cell states) using AI, genomics, high-throughput screening; deliver mRNA etc. to rejuvenate cell/tissue function.	In vivo gene therapy using OSK (Oct4, Sox2, Klf4) via AAV to partially reprogram aged somatic cells and extend lifespan.	Multi-program: in vivo partial reprogramming, plasma/young-blood inspired therapeutics using HsC's, autophagy/aging-mechanism drivers; includes cell reprogramming of aged tissue.
Current Status & Funding	Founded in 2022; reported ~$3 billion in capital. Has been quiet about progress although published a nice white paper last year on cell reprogramming.	Founded circa 2017; has raised over $150 million.	Founded (Silicon Valley) with major funding; series B ~$130 m (2025), additional ~$45 m later, valuation ~US$1.6 b.	Private biotech; gene therapy focus on age-related disease. Published a landmark OSK AAV mouse study.	Founded ~2021; initial funding ~$180 m (from Sam Altman) with ambition to raise ~$1 billion.
Key Accomplishments	Built a "dream team" of scientists (including Yamanaka/Izpisúa-Belmonte) for reprogramming-based reversal of aging/disease.	Preclinical primate data: gene therapy with OSK restored visual function in non-human primate optic-nerve-stroke model (NAION).	Advancing lead program targeting the aging liver using mRNA to deliver transcription-factor modules; preparing for first clinical steps. Fierce Biotech	Reported that systemically delivered inducible OSK AAV in 124-week-old wild type mice extended remaining median lifespan by ~109%.	Developing three therapy modalities: reprogramming, autophagy, plasma stem-cell rejuvenation; plans first clinical trial (e.g., Alzheimer's) in Australia.
Trials / Next Steps	Work appears preclinical; many internal programs, but no widely reported human trials yet.	Plans human clinical trials: e.g., candidate ER-100 (OSK gene therapy) for optic neuropathies in 2026.	Next step: Push liver reprogramming medicine into clinic; timeline: "within a few years".	Preclinical stage; next steps likely toward translational large-animal or first-in-human safety studies (not yet publicly detailed).	Upcoming: First human trial expected imminently for Alzheimer's / brain aging; scaling stem-cell programs for blood/immune system which have high potential.

Source: Stifel Investment Banking Department.

Altos Labs Pursing Aging Through Cell Reprogramming

ALTOS

Greg Zuckerman, *Wall Street Journal*, August 20, 2023 (excerpt)

The investment firm Robert Nelsen co-founded in 1986, Arch Venture Partners, has racked up billions in profits from early stakes in companies developing methods to detect and treat cancer and other diseases.

Nelsen's latest and largest investment—several hundred million dollars, he says—is in a company attempting something even more ambitious than aiding health and longevity. Altos Labs, based in the San Francisco Bay Area, San Diego, and Cambridge, U.K., is working on ways to rejuvenate cells to eliminate disease—an approach called epigenetic reprogramming. Nelsen and Altos's founders believe they can turn the clock back on aging cells to restore functions characteristic of younger cells.

"Epigenetic reprogramming is the biggest thing in healthcare in 100 years. Or ever," he says. "We will clearly live much healthier and longer lives if this works." That's a huge if. Cellular rejuvenation has yet to be proven effective as a treatment. So far, the only data Altos and others in the field have produced is in mice, suggesting they are a long way from rolling out any products. Skeptics doubt cells can be reprogrammed to ward off age-related illnesses. Taking cells back to their youthful, healthier state long captured the imagination of scientists but seemed unlikely. Then a breakthrough paper published in 2006 by Japanese scientist Shinya Yamanaka and a colleague showed mature skin cells of mice could be reprogrammed into primordial, immature stem cells—called induced pluripotent stem cells—in effect resetting their molecular clocks. Yamanaka, who later shared a Nobel Prize for work in this area, is an adviser to Altos. In 2016, Spanish biochemist Juan Carlos Izpisua Belmonte, Altos's founding scientist, showed how the age of cells could be reverted without changing their genome and identity. His work demonstrated the potential for toggling between the 'old' and 'young' states of cells—the basis for Altos's effort to rejuvenate cells. "If we can turn the clock back so cells are healthy and resilient, you can reverse disease," Klausner says.

Source: https://www.wsj.com/health/wellness/for-this-venture-capitalist-research-on-aging-is-personal-bob-has-a-big-fear-of-death-519a091

There are Some Limitations and Persistent Worries with Cell Reprogramming for Aging

Efficiency and Consistency

- The reprogramming process is often inefficient and inconsistent, with only a small fraction of cells successfully reprogramming.

Tumorigenicity

- The potential for reprogrammed cells to form tumors, particularly when using factors like c-Myc, poses a significant safety concern.

Application

- It's interesting that we are seeing application of reprogramming mainly in mice and application to very limited organ systems (like the eye) in higher species. Many believe that the real potential of reprogramming will involve limited rather than broad applications.

Unclear How to Get to the Broad Promise

- No one has really shown that this technology might be applied to improve human lifespan overall – which would presumably require broad cell reconditioning

Genomic Instability

- Reprogramming can introduce genetic and epigenetic abnormalities, such as mutations and chromosomal aberrations.

Epigenetic Memory

- Reprogrammed cells often retain epigenetic memory of their tissue of origin, which can influence their behavior and differentiation potential.

Scalability and Cost

- Scaling up reprogramming protocols for clinical and industrial applications while keeping costs manageable is another major challenge.

Irv Weissman Lab & NIH: Knock Out of Myeloid HSC Restores Younger Immune Phenotype

Depleting myeloid-biased haematopoietic stem cells rejuvenates aged immunity

https://doi.org/10.1038/s41586-024-07238-x

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Check for updates

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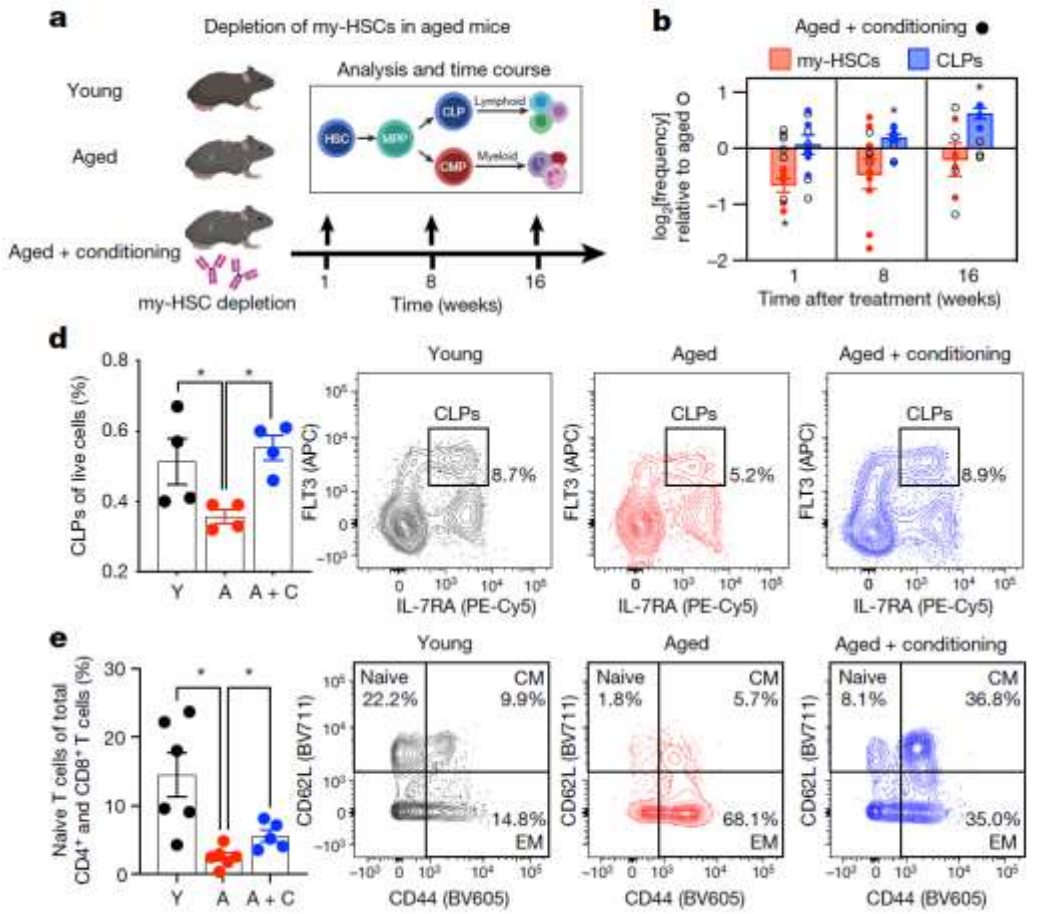
Ageing of the immune system is characterized by decreased lymphopoiesis and adaptive immunity, and increased inflammation and myeloid pathologies[1,2]. Age-related changes in populations of self-renewing haematopoietic stem cells (HSCs) are thought to underlie these phenomena[3]. During youth, HSCs with balanced output of lymphoid and myeloid cells (bal-HSCs) predominate over HSCs with myeloid-biased output (my-HSCs), thereby promoting the lymphopoiesis required for initiating adaptive immune responses, while limiting the production of myeloid cells, which can be pro-inflammatory[4]. Ageing is associated with increased proportions of my-HSCs, resulting in decreased lymphopoiesis and increased myelopoiesis[3,5,6]. Transfer of bal-HSCs results in abundant lymphoid and myeloid cells, a stable phenotype that is retained after secondary transfer; my-HSCs also retain their patterns of production after secondary transfer[5]. The origin and potential interconversion of these two subsets is still unclear. If they are separate subsets postnatally, it might be possible to reverse the ageing phenotype by eliminating my-HSCs in aged mice. Here we demonstrate that antibody-mediated depletion of my-HSCs in aged mice restores characteristic features of a more youthful immune system, including increasing common lymphocyte progenitors, naive T cells and B cells, while decreasing age-related markers of immune decline. Depletion of my-HSCs in aged mice improves primary and secondary adaptive immune responses to viral infection. These findings may have relevance to the understanding and intervention of diseases exacerbated or caused by dominance of the haematopoietic system by my-HSCs.

Nature, Apr 4, 2025



Note: Retro Bio (profiled later) is developing a cell therapy to remove myeloid HSC's.

Source: https://www.nature.com/articles/s41586-024-07238-x

Getting More Stem Cells into the Brain in Aging Could Slow Aging – While Excluding T-Cells Might Help

Spatial transcriptomic clocks reveal cell proximity effects in brain ageing

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Check for updates

Eric D. Sun[1,2,3], Olivia Y. Zhou[3,4,5], Max Hauptschein[3], Nimrod Rappoport[3], Lucy Xu[3,6], Paloma Navarro Negredo[3], Ling Liu[7,8,9], Thomas A. Rando[7,8,9], James Zou[2,13] ✉ & Anne Brunet[3,10,11,12,13] ✉

Old age is associated with a decline in cognitive function and an increase in neurodegenerative disease risk[1]. Brain ageing is complex and is accompanied by many cellular changes[2]. Furthermore, the influence that aged cells have on neighbouring cells and how this contributes to tissue decline is unknown. More generally, the tools to systematically address this question in ageing tissues have not yet been developed. Here we generate a spatially resolved single-cell transcriptomics brain atlas of 4.2 million cells from 20 distinct ages across the adult lifespan and across two rejuvenating interventions—exercise and partial reprogramming. We build spatial ageing clocks, machine learning models trained on this spatial transcriptomics atlas, to identify spatial and cell-type-specific transcriptomic fingerprints of ageing, rejuvenation and disease, including for rare cell types. Using spatial ageing clocks and deep learning, we find that T cells, which increasingly infiltrate the brain with age, have a marked pro-ageing proximity effect on neighbouring cells. Surprisingly, neural stem cells have a strong pro-rejuvenating proximity effect on neighbouring cells. We also identify potential mediators of the pro-ageing effect of T cells and the pro-rejuvenating effect of neural stem cells on their neighbours. These results suggest that rare cell types can have a potent influence on their neighbours and could be targeted to counter tissue ageing. Spatial ageing clocks represent a useful tool for studying cell–cell interactions in spatial contexts and should allow scalable assessment of the efficacy of interventions for ageing and disease.

Nature, Feb 6, 2025

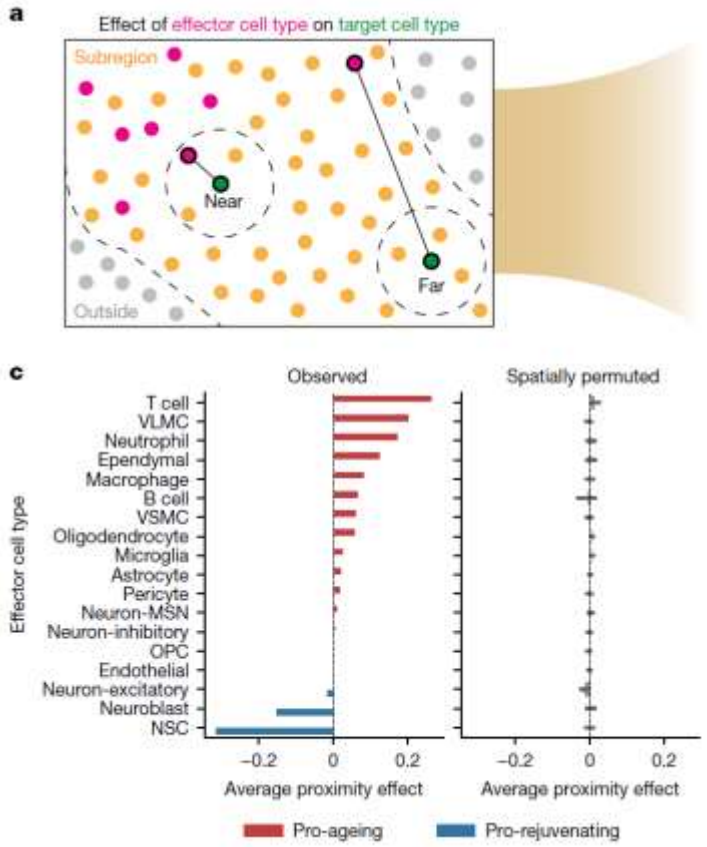


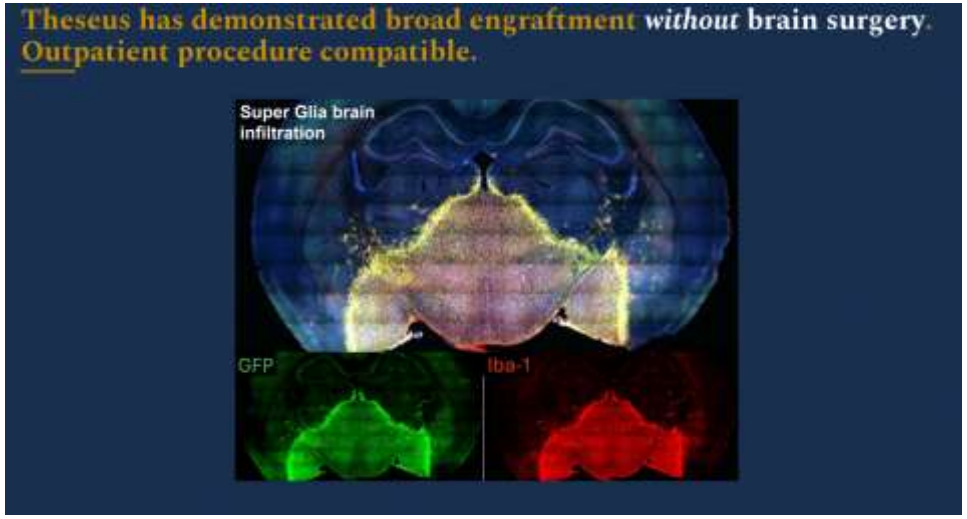
Fig. 4 | Proximity effects of cells on neighbouring cells during ageing and rejuvenation. a, Matching procedure for determining 'near' and 'far' target cells to compute the proximity effect of effector cells on the age acceleration of target cells. **b,** Heat map showing the proximity effect for different cell-type proximity relationships. Columns show the 14 target cell types with high performing spatial ageing clocks. Proximity relationships for which there are insufficient cell pairings (<50) to compute a proximity effect are denoted by 'X'. Colour bar is trimmed at top 2% absolute proximity effect values.

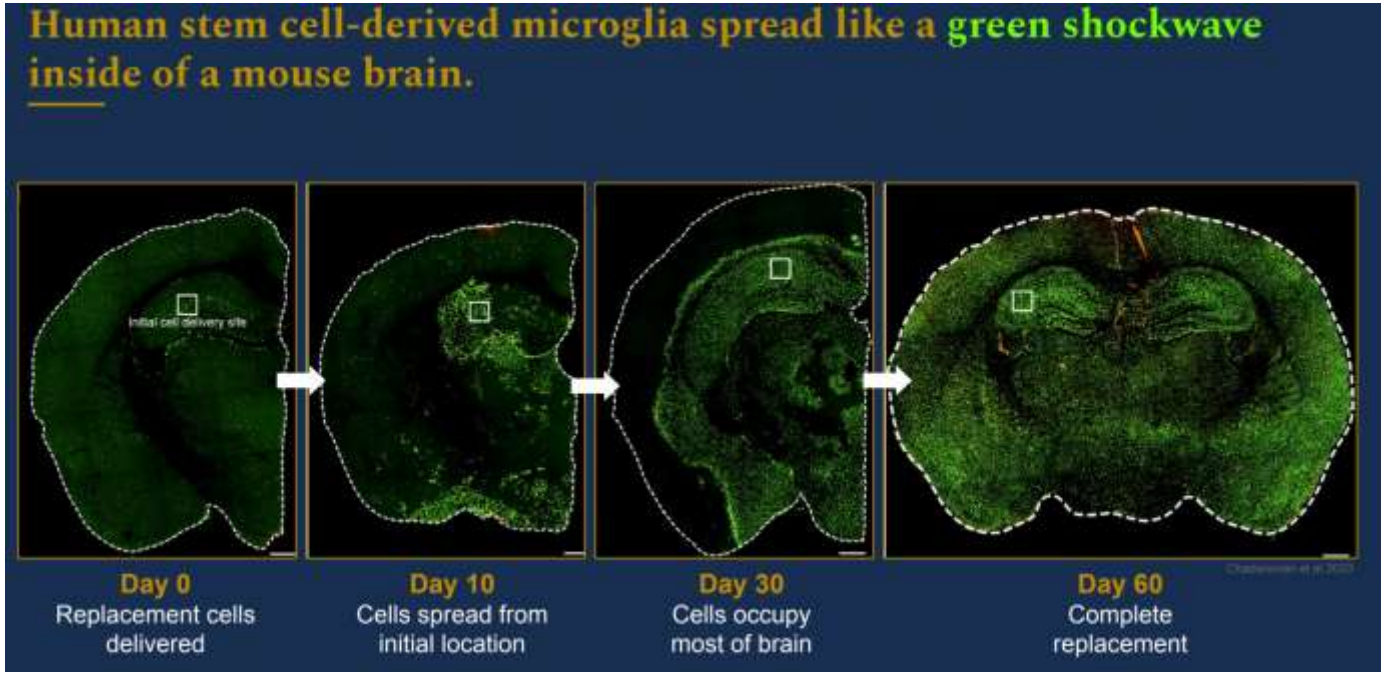
Source: https://www.nature.com/articles/s41586-024-08334-8

Theseus Therapies is Delivering Microglial Stem Cell Transplants

Theseus Therapies is a spinout from the lab of Marius Wernig of Stanford. The company's therapy involves a transfusion of 10 billion cells across the brain. These cells are microglial cells. Microglial cells are garbage collectors and drive long-term brain maintenance. Wernig's lab has done this in mice with very strong positive results on neurologic conditions (2022 Science Translational Medicine). The Theseus cells are gene edited to enhance their selective advantage in the brain.

Note: Other groups are also exploring strategies for restoring microglial health, including Calico and Altos. Some relevant seminars were at the June 2026 Keystone Symposium on Neural-Immunity and Neurodegeneration (link)





Source: Theseus Therapies Corporate Presentation, 2025

Chinese Group Has Achieved Impressive Anti-Aging Results with Mesenchymal Progenitor Cells in Primates

Senescence-resistant human mesenchymal progenitor cells counter aging in primates

Cell, Sep 4, 2025

Jinghui Lei,[1,23] Zijuan Xin,[1,2,3,23] Ning Liu,[4,8,23] Taixin Ning,[1,23] Ying Jing,[1,23] Yicheng Qiao,[4,8,23] Zan He,[1] Mengmeng Jiang,[2,3] Yuanhan Yang,[2,9] Zhiyi Zhang,[4] Liyun Zhao,[1] Jingyi Li,[2,3,9,22] Dongliang Lv,[2,9] Yupeng Yan,[2,3] Hui Zhang,[5] Lingling Xiao,[1] Baohu Zhang,[2,9] Haoyan Huang,[1] Shuhui Sun,[5] Fangshuo Zheng,[11] Xiaoyu Jiang,[2,9] Huifen Lu,[1] Xueda Dong,[4,10] Shasha Yue,[4] Chencan Ma,[4,8] Jichen Shuai,[1] Zhejun Ji,[2,3] Feifei Liu,[5] Yanxia Ye,[2,3] Kaowen Yan,[2,3] Qinchao Hu,[2,12] Gang Xu,[16,17] Qian Zhao,[1] Ruochen Wu,[2,9] Yusheng Cai,[2,3] Yanling Fan,[6]

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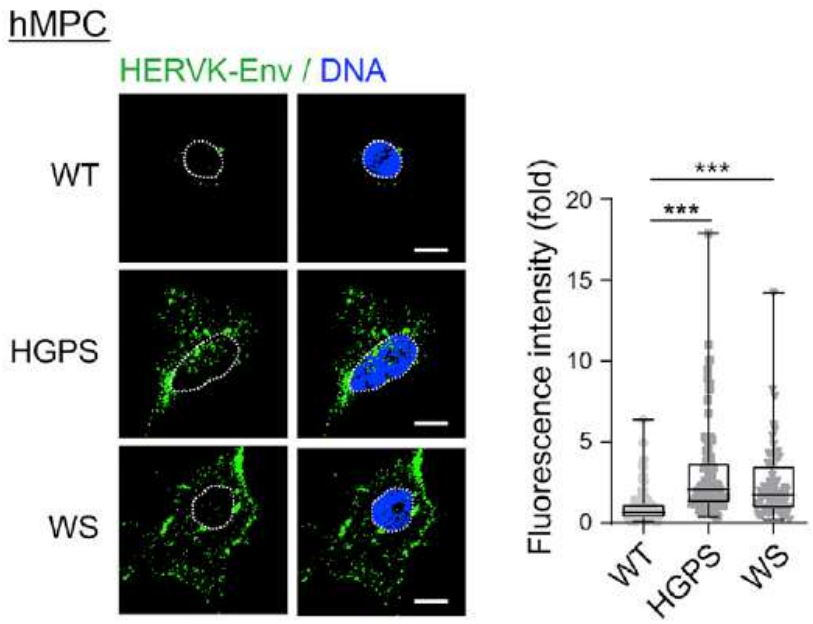
Aging is characterized by a deterioration of stem cell function, but the feasibility of replenishing these cells to counteract aging remains poorly defined. Our study addresses this gap by developing senescence (seno)-resistant human mesenchymal progenitor cells (SRCs), genetically fortified to enhance cellular resilience. In a 44-week trial, we intravenously delivered SRCs to aged macaques, noting a systemic reduction in aging indicators, such as cellular senescence, chronic inflammation, and tissue degeneration, without any detected adverse effects. Notably, SRC treatment enhanced brain architecture and cognitive function and alleviated the reproductive system decline. The restorative effects of SRCs are partly attributed to their exosomes, which combat cellular senescence. This study provides initial evidence that genetically modified human mesenchymal progenitors can slow primate aging, highlighting the therapeutic potential of regenerative approaches in combating age-related health decline.



HERVK viral proteins and RVLPs are increased in senescent cells.
Immunofluorescence staining of HERVK-Env in WT, HGPS, and WS hMPCs.

Source: https://www.cell.com/cell/abstract/S0092-8674(25)00571-9

Also Possible to Partly Reverse Immune Aging with Mesenchymal Cell Transplant

Mesenchymal thymic niche cells enable regeneration of the adult thymus and T cell immunity

Nature Biotechnology, Oct 30, 2025

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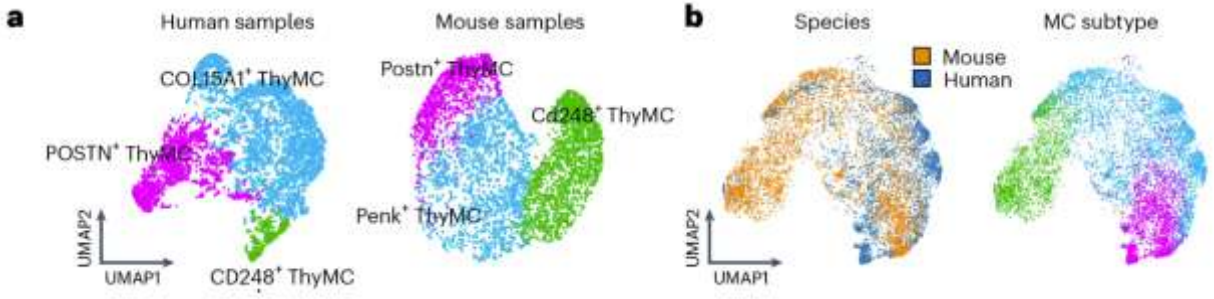
Accepted: 12 September 2025
Published online: 30 October 2025
Check for updates

Karin Gustafsson[1,2,3], Sergey Isaev[4,5], Kamdin Mirsanaye[6], Johanna Hofmann[7,8,9], Kameron A. Kooshesh[1,2,3], Ninib Baryawno[1,2,3,10], Anna Kiem[1,2,3], Nicolas Severe[1,2,3], Ting Zhao[1,2,3], Elizabeth W. Scadden[1,2,3], Joel A. Spencer[11], Christian Burns[11], Kumaran Akilan[11], Nikolaos Barkas[12], Hayalneh Gessessew[1,2,3], Konstantinos D. Kokkaliaris[1,2,3,7,8,13], Charles P. Lin[6], Peter V. Kharchenko[2,12,14] & David T. Scadden[1,2,3]

Fig. 2: Postn$^+$ ThyMCs preferentially express T cell regulators.

From: Mesenchymal thymic niche cells enable regeneration of the adult thymus and T cell immunity



Thymic atrophy and the progressive immune decline that accompanies it is a major health problem, chronically with age and acutely with immune injury. No definitive solution is available. Here we demonstrate that one of the three mesenchymal cell subsets identified by single-cell analysis of human and mouse thymic stroma is a critical niche component for T lymphopoiesis. The Postn$^+$ subset is perivascular, and its depletion abrogates T cell progenitor recruitment, likely through production of the chemokine Ccl19. It markedly declines with age and in the acute setting of hematopoietic stem cell transplant conditioning. When isolated and adoptively transferred, Postn$^+$ cells durably engraft the atrophic thymus, recruit early T progenitors, increase T cell neogenesis and enhance T cell response to vaccination. More readily available mesenchymal populations expressing Ccl19 provide similar effects. These data define a thymus lymphopoietic niche cell type that may be manipulated therapeutically to regenerate T lymphopoiesis.

Source: https://www.nature.com/articles/s41587-025-02864-w

Synthesis:

Approaches With High Promise to Extend Lifespan

Evidence to Date for Aging Interventions

	Persuasive Biological Rationale	Persuasive Genetic / Cross-Species Data	Persuasive Data in Non-Primate Animals	Persuasive Data in Primates / Humans
Healthspan Impacting (Diseases of Aging)	Diet and Exercise Metformin NAD+	Diet and Exercise mTOR / Rapamycin	Cardiolipin / Elamipretide Diet and Exercise DNMT Modulators mTOR / Rapamycin	Cardiolipin / Elamipretide Diet and Exercise Mesenchymal Cells NAD+
Longevity Impact (Live Within Normal Human Age Boundary)	Caloric Restriction Diet and Exercise DNMT / EZH2 IGF-1/IIS IL-11 Mitochondrial uncouplers NAD+ SIRT1 / SIRT6	Caloric Restriction IGF-1/IIS SIRT1 / SIRT6	Caloric Restriction Diet and Exercise IGF-1// IL-11 Masatinib + Quercetin Mitochondrial Uncouplers mTOR / Rapamycin SGLT2 SIRT6	AMPK Caloric Restriction Diet and Exercise IGF-1/IIS SGLT2
Lifespan Impact (Exceed Normal Human Age Boundary)	Cardiolipin / Elamipretide cGAS / STING D-PUFA's FOXO04 Peptides HSC Cell Reprogramming KCD10 Agonists Mesenchymal Cells Necrosis Inhibitors Partial Reprogramming	cGAS / STING CIRBP Agonism NAD+	BCL-2 inhibitors cGAS / STING CIRBP Agonism FOXO04 Peptides HSP90 Inhibitors NAD+ / SQ1 Heterochronic Parabiosis Partial Reprogramming uPAR CAR-t	

Summary of the Evidence

As is visible in the table on the previous page, there are a number of promising options for achieving a longer life. Also see Apollo's review of these options. If your goal is longevity extension – that is to die closer to your theoretical age limit – we have good news. There is plentiful evidence that caloric restriction, eating good food, exercise and avoiding toxins (e.g., smoking) can increase your longevity. If you are struggling to get there, a GLP-1 RA can help.

If you are looking for longevity in a pill, we are slowly getting there. The most promising candidates appear to be Longo's fast-mimicking diet which is on the market via L-Nutra, mitochondrial uncouplers, SGLT2's and mTORC1 drugs. SGLT2 inhibitors have the best broad evidence for life extension to date. Human mutational data shows quite persuasive evidence that modulation of the insulin-sensing pathway can extend longevity. Remarkably, Ecuadorans with homozygous GHR mutations are far less likely to get cancer and diabetes. Mutational data point to the reasonable likelihood that suppression of IGF-1R would cause humans to be more likely to live to their maximal lifespan. Loyal's drug for dogs works by suppressing IGF-1. A related drug is Paltusotine, in development by Crinetics. Paltusotine suppresses secretion of growth hormone (GH). That in turn leads to a decrease in IGF-1.

In contrast, things get a lot fuzzier if your goal is to exceed today's maximal lifespan. We think we have identified the right biology that would have to change: humans would need to have less damage from oxidative stress and less damage from double-strand DNA breaks.

No research has demonstrated yet that interventions of this type work in humans or primates (table on previous page).

But there are quite a few promising avenues from a biological perspective and ample data in mice are available. We are most persuaded by the mechanisms that certain species use to live longer. Both cGAS-STING antagonism and CIRBP agonism look promising. Further, there is some potential, albeit unproven, in FOXO4 peptides, HSP90 inhibitors and KCD10 agonists. Some of the mitochondrial drugs, like elamipretide, from Stealth BioTherapeutics, have high promise given their results in Barth Syndrome but we don't have aging data yet. By far, the most interesting approaches are partial cell reprogramming and targeted senolytics such as the uPAR CAR-T. Each strategy has a lot to work through. While partial reprogramming approaches have extended lifespan in mice it wasn't by that much and there are obvious questions about how this therapy is going to work in practice. Are we going to rejuvenate some of our "old" cells with infusions or is this going to be organ specific? Others advocate parabiosis but the effect sizes from this approach in mice have not been impressive.

Perhaps the most promising approach is the field of senolytics. If one could figure out how to target senescent cells well there is a good case for extending lifespan in this way. There are a number of fairly obvious directions in which to take this literature – which looks and feels similar to that for cancer ADCs. We are hopeful that progress in all of these areas will accelerate in the next decade.

Point 4: Anti-Aging Drugs Can be Tested

We are Seeing Multiple Proposed Credible Interventions Proposed for Aging

Alpha-Ketoglutarate	Autophagy enhancers	FOXO modulators	mTORC1 Inhibitors
Dasatinib	Fisetin	Mitochondrial enhancers	Metformin
NAD+	HSC Cell Therapies	Quercetin	Rapamycin
SGLT2 Inhibitor	Sirtuin activators	uPAR senolytic	Yamanaka reprogrammers

Let’s Suppose Some of These Interventions These Actually Worked

How would you ever know?

- We humans live too long
- Trials would take decades to test for real
- Very hard to finance a trial like this

Some Ideas For How to Proceed

1. 85-year-olds
2. Focus on surrogate biomarkers of aging
3. Hutchinson-Gilford Progeria Syndrome (15-year life expectancy)
4. Dogs – short lives (6 to 15 years)
5. Biomarker enhanced approach
6. Organ Reconditioning

Idea One

Run Trials on Very Old People

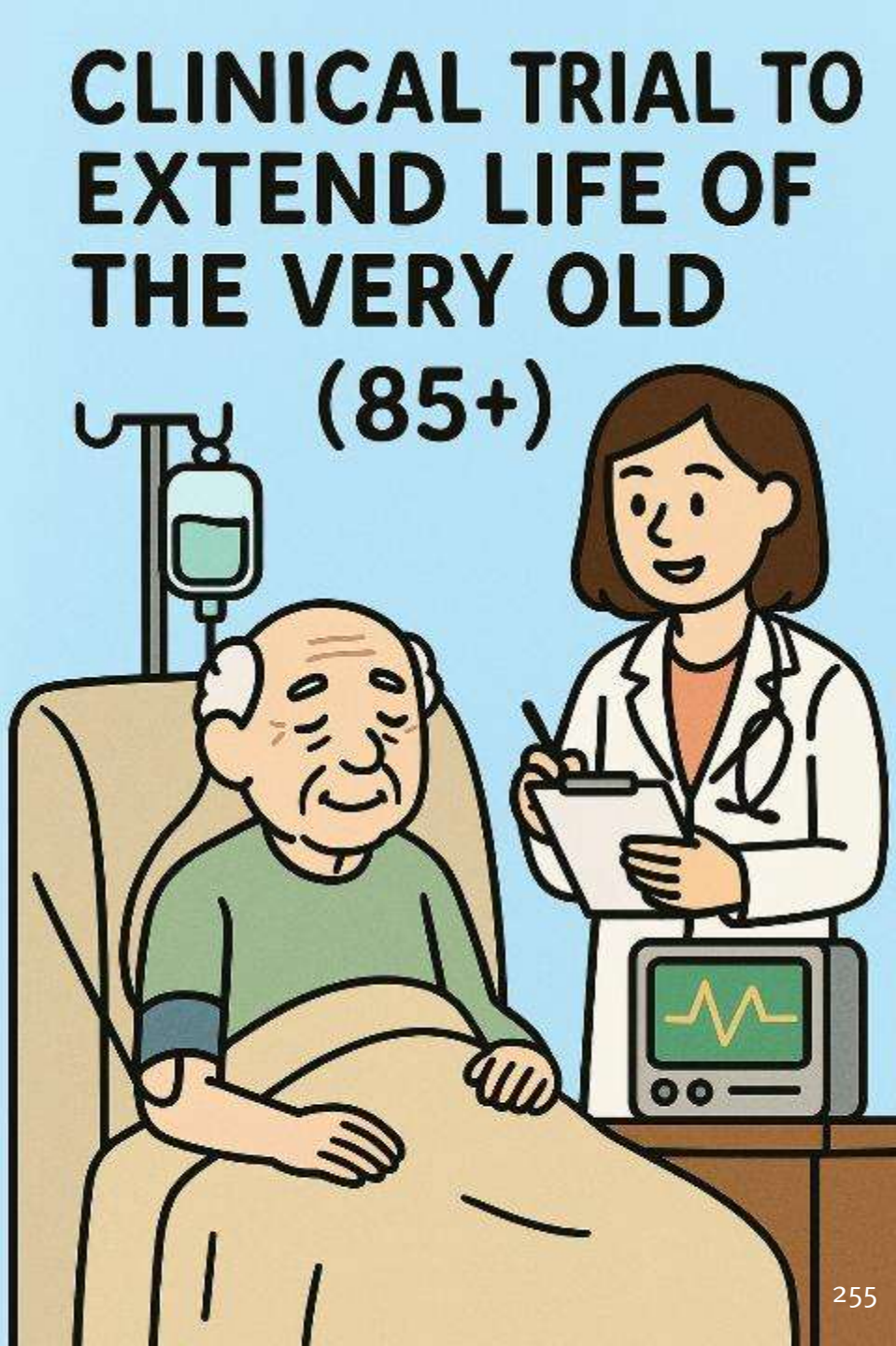
The Very Old

The first idea would be to conduct the trial on persons with **high mortality risk.** According to the U.S. Social Security Administration's *Period Life Table* (2021, latest complete dataset) and CDC *Vital Statistics*, the annual probability of death for a U.S. male at age 85 is 9.5% and a female is 7% a year. Suppose, the composite risk is 8% per annum. For 90-year-olds the event rate is even higher (15% to 20% depending on sex and country).

If one enrolled a two-arm, two-year randomized study with 1,500 85-year-olds then one should expect to see 120 deaths over the period of the trial assuming it's all-comers. Let's suppose the persons getting the intervention have a 5% mortality rate (rather than 8% in the placebo arm). The p-value of the z-score in such a trial would be 0.019. If it cost $40k per subject to enroll the study, it would cost $60mm in total to run it (plus overhead). If you moved the trial to India or China, the cost could be cut by 50% to 75%.

There are downsides, of course, to this. The elderly have numerous co-morbid conditions and may be too advanced with aging pathology to reverse it with a drug. The consenting process could be non-trivial. One would have to truly believe that a strategy could work on this population. This could make perfect sense, for example, for senolytics and cell reprogramming strategies. Presumably, one would want to start with a pilot study of some kind first.

Note: Others have written extensively about trial design for aging studies. See the Norn Group article. Also, Andrew Steele's book *Ageless* has a detailed discussion of trials. Steele disagrees with our suggested approach, arguing that the very old have multiple illnesses already, so signal generation in this population will be difficult.



Idea Two

Use Biomarkers as Surrogate Markers for the Risk of Mortality

Key Idea is to Track Biomarkers of Aging in Trials Rather than Aging Itself

Venki Ramakrishnan, Interview with Eric Topol, 2024

“And that pattern changes as we age. And they've shown that those patterns are a better predictor of many of the factors of aging. For example, mortality or symptoms of aging. They're a better predictor of that than chronological age. And then of course there are blood markers, for example, levels of various blood enzymes or blood factors, and there are dozens of these factors. So there are many different tests of many different kinds of markers which look at aging. Now the problem is these all work on a population level and they also work on an individual level for time comparison. That is to say, if you want to ask, is some intervention working? You could ask, how fast are these markers changing in this person without the intervention and how fast are they changing with the intervention?”

Source: https://erictopol.substack.com/p/venki-ramakrishnan-the-new-science

Surrogate Markers for Hard Endpoints are Used Routinely in Clinical Practice

Asmar R, Hosseini H. Endpoints in clinical trials: does evidence only originate from 'hard' or mortality endpoints? *J Hypertens Suppl*. 2009 Jun;27(2):S45-50.

'Hard' primary endpoints from randomized clinical trials, such as cardiovascular morbidity and mortality data are usually considered as the backbone of evidence for clinical practice guidelines. However, 'intermediate' or 'surrogate' endpoints, for example, biological or imaging markers are increasingly being recognized for their importance in stratifying risk and determining treatment strategy in clinical practice. In hypertension, use of validated surrogate endpoints, notably left ventricular hypertrophy (LVH), microalbuminuria, arterial stiffness and carotid intima-media thickness are discussed. These variables are among those assessed in clinical practice, and are considered as predictors of cardiovascular risk. Moreover, some antihypertensive therapies can reverse these organ-damage abnormalities and improve cardiovascular prognosis partly independently from their blood pressure lowering effect. Recognizing the importance of identifying subclinical organ damage in the prediction of cardiovascular risk provides further support to physicians making decisions in their daily clinical practice and offers possibilities for prospective studies on cardiovascular prevention in populations of middle age with low cardiovascular risk. In this article we overview the advantages and disadvantages of morbidity/mortality trials and 'hard' versus 'soft' endpoints. We also considered the relevance of analyzing not only primary endpoints but also secondary endpoints.

Source: https://pubmed.ncbi.nlm.nih.gov/19491624/

Factors to Consider When Selecting Surrogate Biomarkers that Predict Mortality Risk to Analyze Aging Interventions

Has the biomarker model been shown to predict mortality?

Is there reason to think that the factors in the model are biologically plausible?

What is the fit of the mortality model?

Is there reason to think that the surrogate mortality risk factors would move in a time associated with a typical clinical trial?

Have there been validation experiments that show model predictions of mortality effects of interventions map onto actual mortality experience?

Is it possible to map specific model variables to underlying biology that is targeted by specific interventions?

A very nice and detailed article was published by Marton Meszaros of the Norn Group on validation criteria for aging biomarkers and potential datasets to use in the process.

Expert Interviews Identified Validation and Responsiveness to Geroprotections as Key Criteria for Response Biomarkets

Biomarkers of Aging Consortium, Challenges and recommendations for the translation of biomarkers of aging. *Nat Aging.* October 2024; 4(10):1372-1383.

Biomarkers of aging (BOA) are quantitative parameters that predict biological age and ideally its changes in response to interventions. In recent years, many promising molecular and omic BOA have emerged with an enormous potential for translational geroscience and improving healthspan. However, clinical translation remains limited, in part due to the gap between preclinical research and the application of BOA in clinical research and other translational settings. We surveyed experts in these areas to better understand current challenges for the translation of aging biomarkers. We identified six key barriers to clinical translation and developed guidance for the field to overcome them. Core recommendations include linking BOA to clinically actionable insights, improving affordability and availability to broad populations and validation of biomarkers that are robust and responsive at the level of individuals.

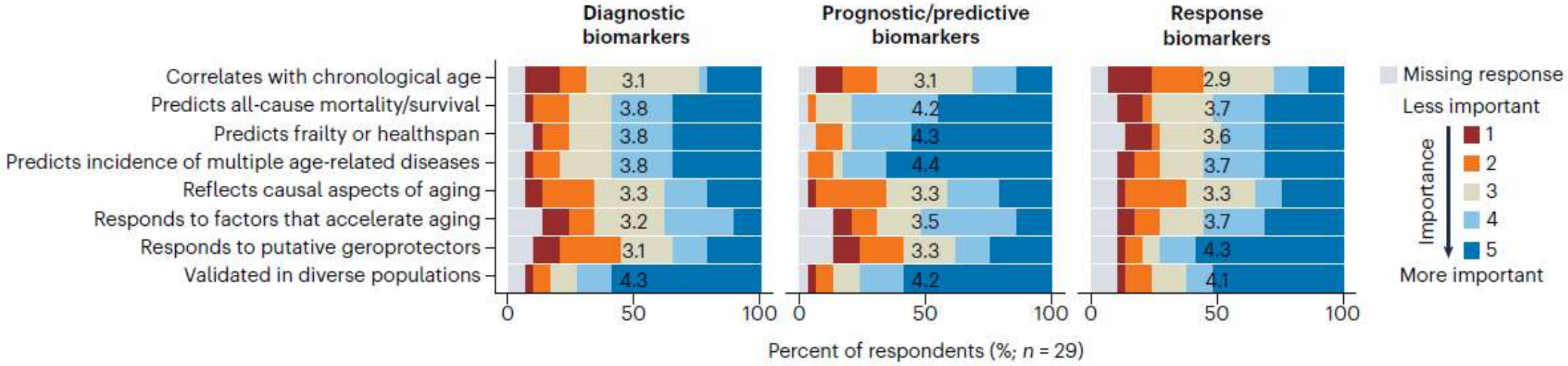
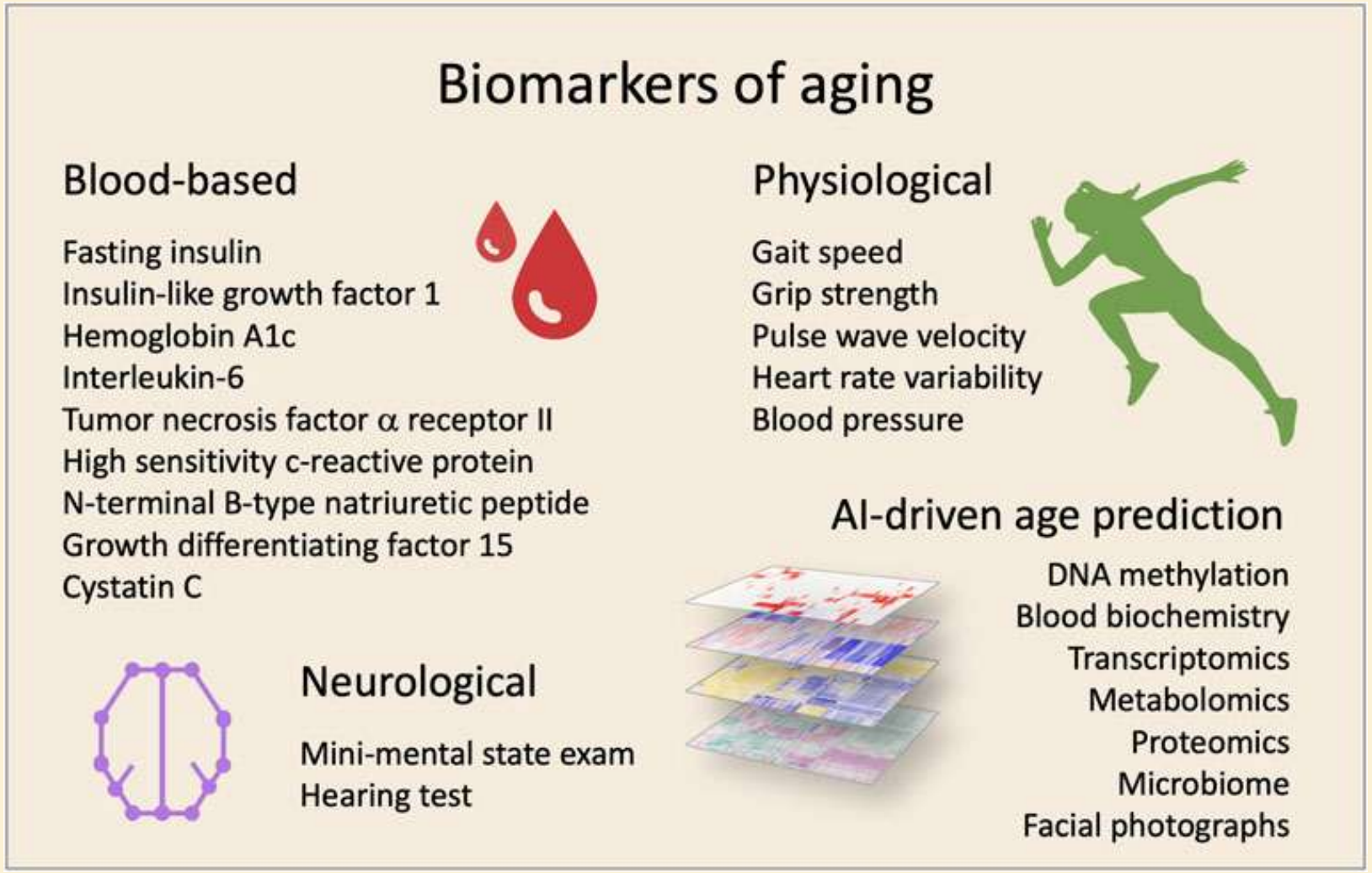


Fig. 1 | Ranking of biomarker criteria. Percentages of respondents who graded different criteria for diagnostic, prognostic–predictive and response BOA on a scale from 1 (not important at all) to 5 (extremely important). The mean score is shown for each category. Missing responses are colored gray. $n = 29$ of 34 invited participants completed the questionnaire.

Source: https://www.nature.com/articles/s43587-024-00683-3

Traditional Biomarkers of Aging

Johannes Nielsen, "Clinical Trials Targeting Aging," *Frontiers in Aging*, 2022, 3:820215.



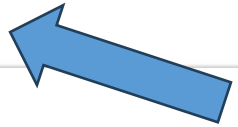
Source: https://www.frontiersin.org/journals/aging/articles/10.3389/fragi.2022.820215/full

Aging Trials Thus Far Have All Steered Clear of Measuring Mortality Effects and Have Used Highly Indirect Biomarkers

Johannes Nielsen, "Clinical Trials Targeting Aging," Frontiers in Aging, 2022, 3:820215.

Intervention	Outcome	References
CR	Glucose ↓, Blood pressure ↓	Wierik et al. (1994)
CR	Glucose ↓, Blood pressure ↓, resting metabolic rate ↓	Loft et al. (1995)
CR	Insulin ↓	Racette et al. (2006)
CR	T_3 ↓, T_4 ↓, Body temperature ↓, Mitochondria ↑, resting metabolism ↓	Civitarese et al. (2007)
CR	Cholesterol ↓, Blood pressure ↓	Lefevre et al. (2009)
CR	Insulin ↓, body temperature ↓, resting metabolic rate ↓	Heilbronn et al. (2006)
CR	DNA methylation pace of aging ↓	Waziry et al. (2021)
CR	Body mass ↓, IGF-1/IGFBP1 ↓, IGFBP1 ↑, cortisol ↓	Fontana et al. (2016)
CR	Body mass ↓, cholesterol ↓, blood pressure ↓, CRP ↓, insulin sensitivity ↑	Waziry et al. (2021)
NR + PT	NAD ↑, liver enzymes ↓, blood pressure↓	Dellinger et al. (2017)
NR + PT	No effect on muscle regeneration	Jensen et al. (2021)
NR	NAD ↑	Martens et al. (2018)
NR	NAD (blood) ↑, NAD (muscle) -, IL-2 ↓, IL-5 ↓, IL-6 ↓,TNF-α ↓	Elhassan et al. (2019)
NR	No effect	Dollerup et al. (2018), Dollerup et al. (2020)
NR	Mitochondria ↑, IL-1B ↓, IL-6 ↓, IL-18 ↓	Zhou et al. (2020)
D + Q	Gait speed ↑, Walking distance ↑, Char stand ↑	Justice et al. (2019)
D + Q	p16 ↓, p21 ↓, IL-1α, IL–2 ↓, IL–6 ↓, IL-9 ↓, MMP-2 ↓, MMP–9 ↓, MMP–12 ↓	Hickson et al. (2019)
RAD001 + BEZ235 (mTOR inhibition)	Infections ↓, Immune response ↑	Mannick et al. (2018)
Rapamycin (topical)	p16 ↓, Collagen ↑	Chung et al. (2019)
UA	Acylcarnitine ↓, mitochondria ↑	Andreux et al. (2019)
Exercise	IL-8 ↓	Balan et al. (2020)
Exercise + diet	DNA methylation age ↓	Fiorito et al. (2021)
Exercise + diet + sleep + phytochemicals	DNA methylation age ↓	Fitzgerald et al. (2021)

CR = caloric restriction
NR = nicotinamide riboside (NAD)
PT = polythenols
D = dasatinib
Q = Quercetin
UA = urolithin A



The closest we've come so far to using surrogate markers for all-cause mortality.

Source: https://www.frontiersin.org/journals/aging/articles/10.3389/fragi.2022.820215/full

The Large Clock Literature Gives Some Candidates for Aging Biomarkers

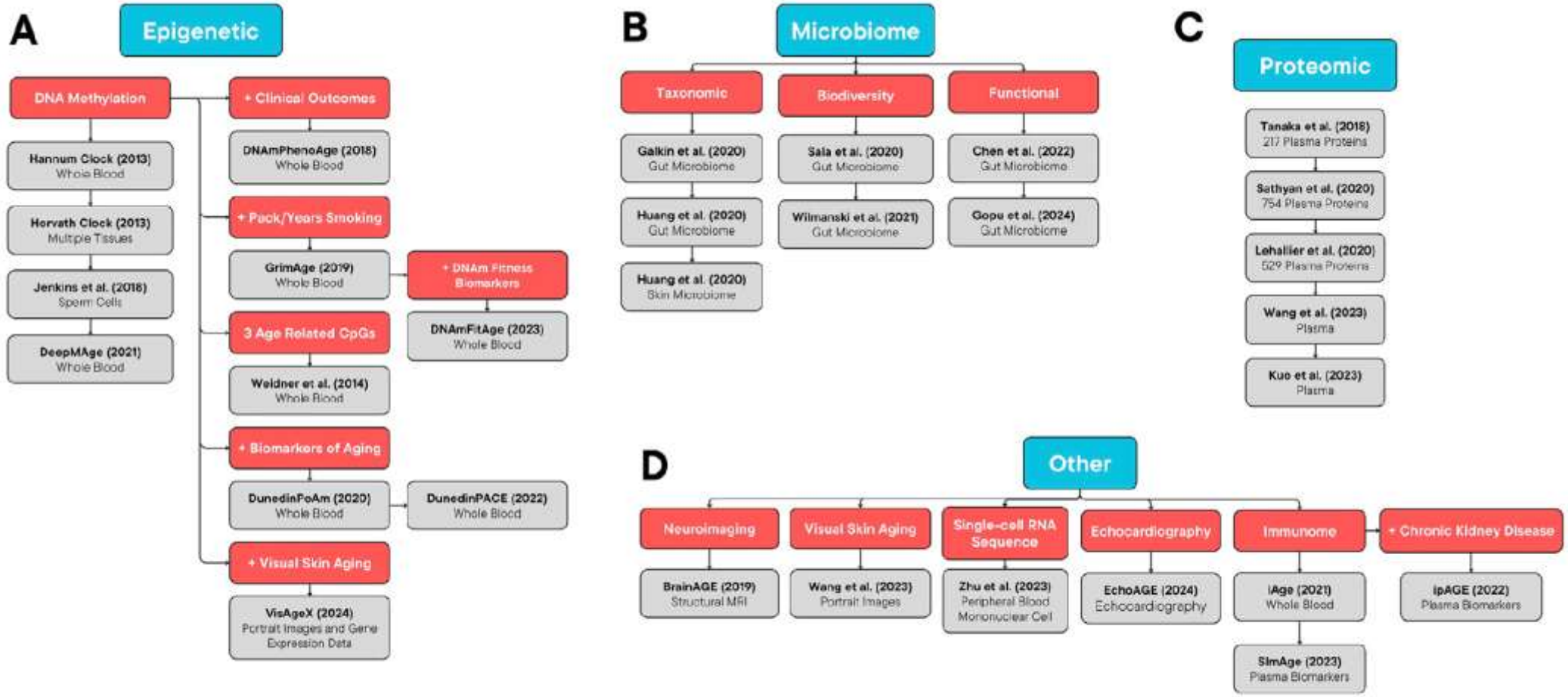


FIGURE 1
Organizational Framework of Aging Clocks. **(A)** Epigenetic, **(B)** microbiome, **(C)** proteomic, and **(D)** other aging clocks.

Source: https://www.frontiersin.org/journals/aging/articles/10.3389/fragi.2024.1487260/

Recent Review of Mortality Prediction Models Finds Some Pitfalls With Existing Approaches

Exmann et al., (2024): A total of 22 studies involving 38 unique mortality prediction models were included, of which 14 models were based on a cumulative deficit-based frailty index and 9 on machine learning. C-statistics of the models ranged from 0.60 to 0.93 for all studies versus 0.61–0.78 when a frailty index was used. Eight models reached c-statistics higher than 0.8 and reported calibration. The most used variables in all models were demographics, symptoms, diagnoses and physical functioning. Five studies accounting for eleven models had a high risk of bias.

Source: https://www.sciencedirect.com/science/article/pii/S156816372400343X

Important to Study Biomarkers of Aging with Longitudinal Validation Studies

Moqri M, et. al., "Validation of biomarkers of aging," *Nature Medicine*, February 2024; 30(2):360-372.

In contrast to cross-sectional studies, longitudinal studies collect biological measures (omics or other biomarkers), phenotypes (clinical characteristics) and adverse age-related health outcomes serially over time in the same individuals. Most longitudinal studies also include data on genetic variants, and, through Mendelian randomization studies, they may help determine whether specific biomarkers are causally related to health outcomes or rather reflect the activation of mechanisms aimed at counteracting the pathologic processes that lead to those adverse health outcomes (generally defined as 'resilience' mechanisms). Most studies collect longitudinal information on participant demographics (for example, age, sex), physiological measurements (for example, body mass index, blood pressure) and routine laboratory results (for example, complete blood count or hemograms or blood biochemistry) and may additionally collect data on mortality and cause of death as well as other aging-associated outcomes including multimorbidity, performance-based measures of physical and cognitive function, and frailty.

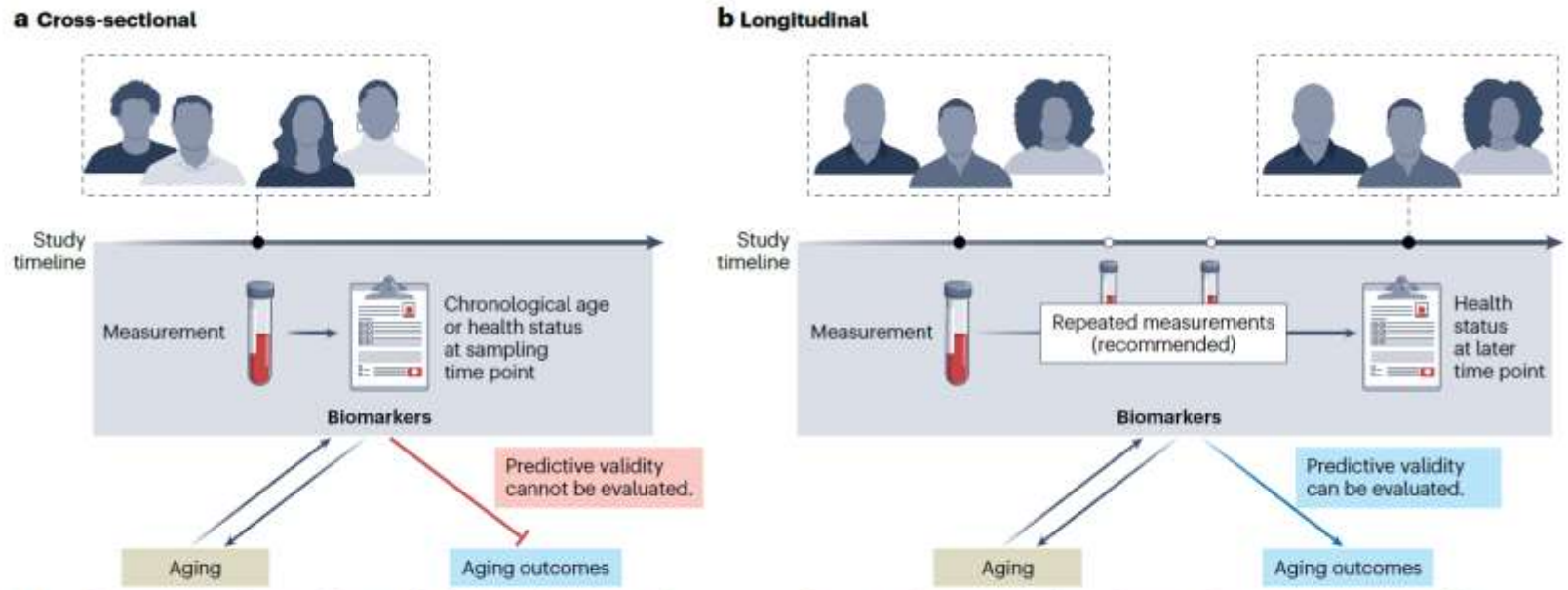


Fig. 1 | Different approaches to cohort study design in the context of biomarkers of aging. Biomarkers of aging are commonly validated using cross-sectional or longitudinal study designs. **a**, Cross-sectional studies involve measurement of biomarkers and chronological age or aging-related outcome data at a single time point. These data can only support association of these measures at that time point. **b**, Longitudinal designs, on the other hand, allow for assessment of predictive validity of biomarkers measured at one time point and future aging-related outcomes.

Source: https://www.nature.com/articles/s41591-023-02784-9

Candidate Surrogate Mortality Risk Markers

Type of Model	Description	Illustrative Models and References	Performance Metrics	Typical AUC from Population Study	Biological Plausibility?	Does it React to Interventions?	Argument to Use as Surrogate Marker	Argument Against Use as Surrogate Marker
Schonberg Models	Questionnaire model that predicts mortality based on age, BMI, self-rated health and smoking.	Schonberg et al. 2009 (Link)	Solid performance versus Age & Sex Alone	75%	Low. Smoking and weight wouldn't necessarily efficacy of aging interventions	Not likely	Easy to use	Doesn't capture underlying biology. Measures causes rather than effects.
Traditional Chemistry Risk Factors	Markers like albumin, creatinine, glucose, CRP, lymphocyte percent, alkaline phosphatase, and white blood cell count	Lind et al. 2020 (Link) (Link)	Good performance versus age and sex alone	85% to 88%	Moderate. Link from various markers to biology / medicine not always clear	Likely	Easy to use	Relationship to underlying aging biology hard to establish. Fit not great.
Traditional Chemistry Risk Factors Plus Schoenberg Model	Questionnaire model plus traditional chemistry markers / risk factors	Lee 2014 (Link)	Good performance versus age and sex alone	86% to 87%	Moderate. Link from various markers to biology / medicine not always clear	Likely	Easy to use	Relationship to underlying aging biology hard to establish. Fit not great.
Frailty Index	Measures five factors: global weakness, slowness, exhaustion, low physical activity and unintentional weight loss	Damanti 2025 (Link)	Very good performance vs. age and sex alone	75%	Highly plausible for interventions that impact frailty	Likely	Captures an important element of aging	FDA has made it clear that frailty alone is not an acceptable endpoint.
Movement Tracker	Measure of subject's movement using a device like an iPhone	Zhu et al., 2022 (Link)	Good performance versus age and sex alone	70%	Ability to move highly relevant for mitochondrial, sarcopenia stories of aging	Possible	Movement is a surprisingly good surrogate for aging	Slowdown in movement in aging happens in a specific window. Trackers would help less before.
First Generation Epigenetic Aging Clocks (e.g., Horvath)	DNA methylation markers are associated with age.	Horvath 2013 (Link)	Minimal AUC improvement vs. Age & Sex Alone	‹ 60% (link)	Fair. The story linking DNA methylation to aging is well understood.	Possible	Universality of DNA methylation with aging	These clocks measure epigenetics only and are not that predictive of mortality.
Next Generation Epigenetic Aging Clocks	DNA methylation predictors with higher fit	Mendy & Tersha 2024 (Link)	Modest AUC improvement over Age & Sex Alone	‹ 60% (link)	Fair. The story linking DNA methylation to aging is well understood.	Possible	Universality of DNA methylation with aging	These clocks measure epigenetics only and are not that predictive of mortality.
Mayo Clinic 28 Biomarker Model of Senescence	Markers that are specifically associated with cell senescence	St. Sauver et al. 2023 (Link)	Good performance versus age and sex alone	NA	Good. These markers capture cell senescence well.	Possible	Specificity to cell senescence	Would not necessarily use this panel alone to measure aging drug effects
deCODE 5 Protein Model of Mortality	Five proteins that predict mortality in Iceland	Eiriksdottir et al. 2021 (link)	Very good performance vs. age + sex	› 90% (link)	Fair. Some of the components are not well related to biology	Likely	Really powerful broad predictor of aging	Hard to interpret some of the results. Amgen has a filed patent on the use of this panel
Age-Adjusted GDF-15 Alone	Protein that is most predictive of mortality across multiple studies	Eiriksdottir et al. 2021 (link)	Very good performance vs. age + sex	› 90% (link)	Good. GDF-15 is a good proxy for mitochondrial damage and cell senescence	Likely	Linked to mitochondrial damage / senescence	While highly related to aging it is not a perfect predictor. A good marker but not the only one.
Our Proposed Three Marker Model (GDF-15/uPAR/HE4)	Three proteins that are most predictive of mortality across multiple studies	Various sources cited in Section 2	Very good performance vs. age + sex	› 90% (link)	Good. Each marker captures a different aspect of aging	Likely	Picks up multiple aspects of aging with powerful prediction	HE4 correlated with GDF-15 and underexplored. uPAR not a perfect senescence marker.

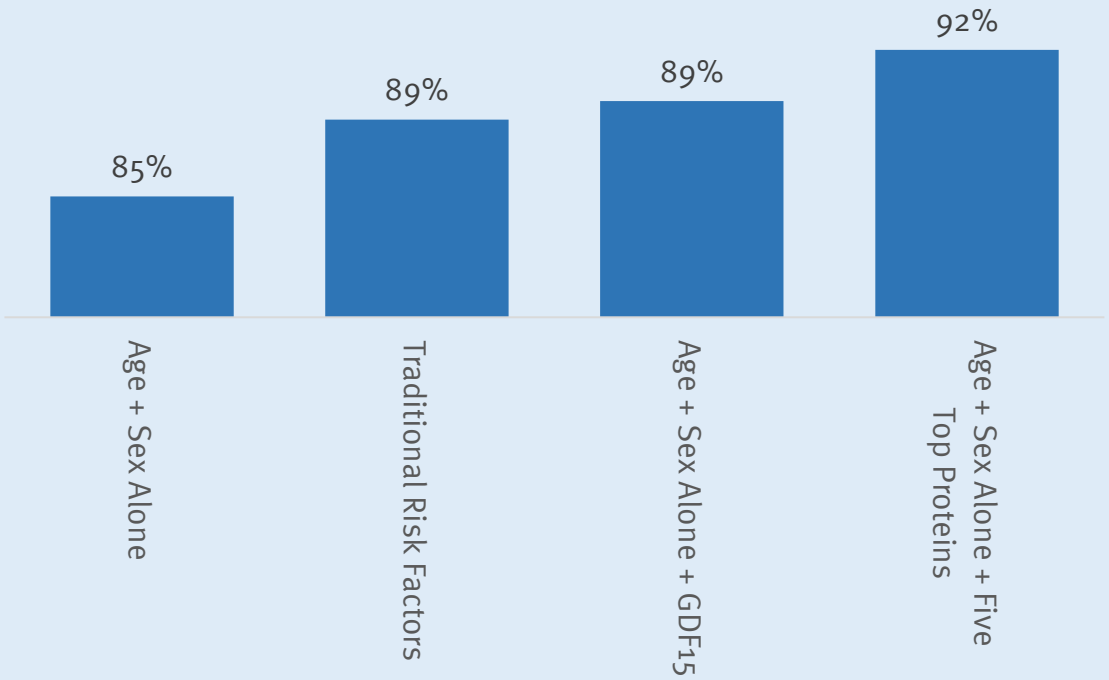
Source: Stifel Investment Banking Department.

Illustrative Discriminatory Power of Various Surrogate Biomarkers

Thus far, proteomic models combined with age and sex outgun all other model types used to predict mortality.

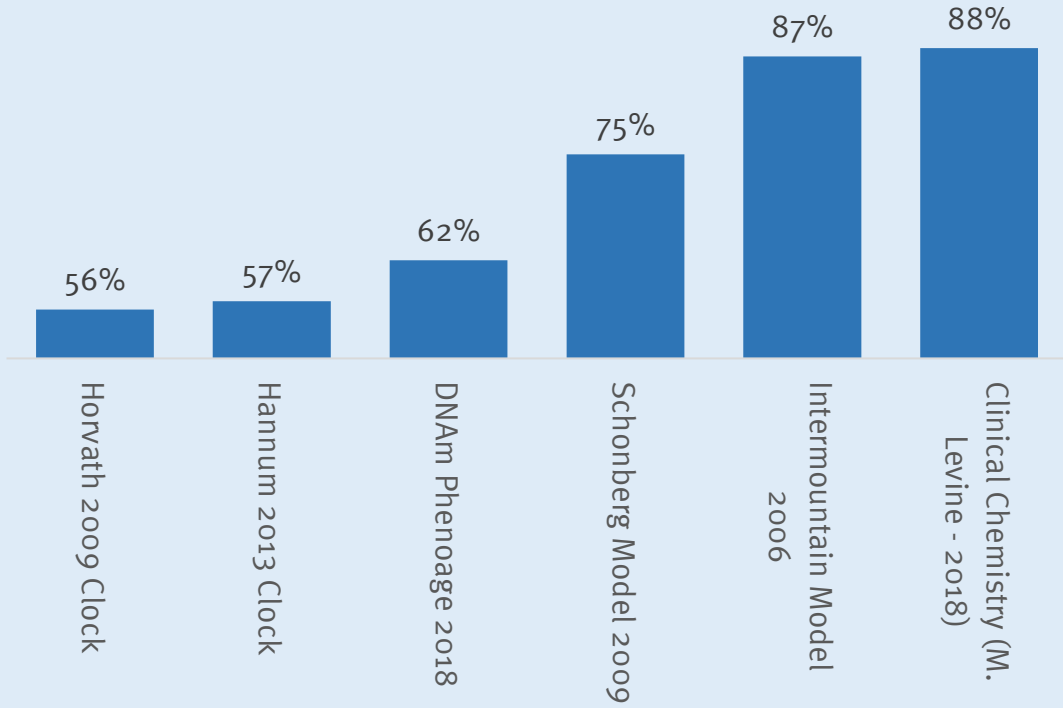
Decode (2021) Comparison of Proteomics vs. Clinical Chemistry / Traditional Markers

deCODE Comparison of AUC from Cox Regressions of Various Five-Year Mortality Predictors in Icelandic Data (N=6,893)



Qiu (2022) Analysis of Aging Clocks vs. Clinical Chemistry Approach

Qiu's 2002 Comparison of AUC from Cox Regressions of Various Mortality Predictors in NHANES 1999 to 2014 (ages 21 to 84)



Sources: deCODE (https://www.nature.com/articles/s42003-021-02289-6), Qui (https://www.nature.com/articles/s43856-022-00180-x).

Imaging Methods Have Also Shown Promise As Surrogate Biomarkers for Aging

Brain Imaging

DunedinPACNI estimates the longitudinal Pace of Aging from a single brain image to track health and disease

Nature Aging, July 1, 2025

Received: 10 October 2024

Accepted: 12 May 2025

Published online: 1 July 2025

Check for updates

Ethan T. Whitman[1,14], Maxwell L. Elliott[2,14], Annchen R. Knodt[1], Wickliffe C. Abraham[3], Tim J. Anderson[4,5,6], Nicholas J. Cutfield[7], Sean Hogan[8], David Ireland[8], Tracy R. Melzer[4,5,9,10], Sandhya Ramrakha[8], Karen Sugden[1], Reremoana Theodore[8], Benjamin S. Williams[1], Avshalom Caspi[1,11,12,13], Terrie E. Moffitt[1,11,12,13] & Ahmad R. Hariri[1]

To understand how aging affects functional decline and increases disease risk, it is necessary to develop measures of how fast a person is aging. Using data from the Dunedin Study, we introduce an accurate and reliable measure for the rate of longitudinal aging derived from cross-sectional brain magnetic resonance imaging, that is, the Dunedin Pace of Aging Calculated from NeuroImaging (DunedinPACNI). Exporting this measure to the Alzheimer's Disease Neuroimaging Initiative, UK Biobank and BrainLat datasets revealed that faster DunedinPACNI predicted cognitive impairment, accelerated brain atrophy and conversion to diagnosed dementia. Faster DunedinPACNI also predicted physical frailty, poor health future chronic diseases and mortality in older adults. When compared to brain age gap, DunedinPACNI was similarly or more strongly related to clinical outcomes. DunedinPACNI is a next-generation brain magnetic resonance imaging biomarker that can help researchers explore aging effects on health outcomes and evaluate the effectiveness of antiaging strategies.

Retinal Imaging

HEALTH AND MEDICINE *Science Advances*, Oct 24, 2025

Mendelian randomization study implicates inflammaging biomarkers in retinal vasculature, cardiovascular diseases, and longevity

Ana Villaplana-Velasco[1,2]†, Nicolas Perrot[3,4,5]†, Yu Hang[6], Michael Chong[3,4,5], Emanuele Trucco[6], Muthu R. K. Mookiah[6], Walter Nelson[7], Jeremy Petch[3,7,8,9], Hertzel C. Gerstein[3,9], Parminder Raina[10,11], Salim Yusuf[3,9], Miguel O. Bernabeu[12,13], Albert Tenesa[2], Konrad Rawlik[1], Guillaume Pare[3,4,5], Alexander Doney[14], Erola Pairo-Castineira[1,2]*†, Marie Pigeyre[3,5,9]*†

With the increasing proportion of elderly individuals, understanding biological mechanisms of aging is critical. Retinal vascular complexity, measured as fractal dimension (D_f) from fundus photographs, has emerged as a vascular aging indicator. We conducted a genome-wide association study of D_f on 74,434 participants from the Canadian Longitudinal Study on Aging, Genetics of Diabetes Audit and Research in Tayside Scotland, and UK Biobank cohorts. We identified a novel locus near *DAAM1*. We found negative genetic correlations between D_f and cardiovascular disease, stroke, and inflammation but a positive correlation with life span. By combining the genetic determinants of 1159 circulating proteins from the Prospective Urban and Rural Epidemiological cohort with those of D_f using Mendelian randomization, we identified eight causal mediators, including MMP12 and IgG–Fc receptor IIb, which link higher inflammation to lower D_f, increased cardiovascular disease risk, and shorter life span. These results extend our understanding of the biological pathways underlying aging processes and inform targets to prevention and treatment.

Organizations that Can Provide Biomarker Services for Aging Research Projects

Provider	Capability
AgeCurve	Can measure DNA damage using Tree Ring model
Alden Scientific	Does aging biomarker validation work using large epidemiologic databases
Harvard Medical School	Advanced proteomics laboratories (not a service provider – need to work through an investigator)
Mayo Clinic Kogod Center	28-protein senescence panel / SenMayo transcriptomic panel (not a service provider – would likely need to work through an investigator)
Mayo Clinic Laboratories	Offers GDF-15 assay with a physician order
Metabolon	Service provider for metabolite analysis
Nightingale	Service provider for metabolite analysis
Northeast Biolabs	CRO that does does custom panels for aging clinical trials which include GDF11, GDF-15, HE4, uPAR
Olink / Thermo Fisher	Offers 3000 protein panel including GDF-15, HE4 and uPAR
Rules-Based Medicine / IQVIA	CRO that does Does custom panels for clinical trials which include GDF-15, uPAR
Somalogic / Illumina	Service provider that measures 9000 proteins including uPAR / GDF-15 / HE4
Trajectory Biologics	Aging CRO – can coordinate aging trials and biomarkers

Source: Stifel Investment Banking Department. **Note**: If you want to personally measure your aging biomarkers, the only groups we know of that offer experimental proteomic markers like are years.co and Alden Scientific. For years.co, you have to sign up for their Ultimate Service which costs around $18k.

Idea Three

Running Studies on Genetic Diseases of Premature Aging

Progeria Could be an Interesting Area for Drug Development

Testing life-extending drugs in people with progeria is theoretically possible but highly constrained. Hutchinson–Gilford Progeria Syndrome (HGPS) mimics certain features of accelerated aging—such as vascular disease, bone fragility, and genomic instability—making it an attractive model for studying aging mechanisms over a short time frame. Because affected children experience rapid physiological decline and early mortality, researchers could in principle detect effects on survival or biological aging markers in just a few years rather than decades.

However, HGPS is a rare, genetically defined disease caused by mutations in the LMNA gene, not a simple acceleration of normal aging. The population is extremely small (fewer than a few hundred patients worldwide), and all current patients are treated with lonafarnib, the existing FDA-approved standard of care. Any experimental "aging drug" would therefore need to be tested as an add-on therapy, justified by strong preclinical data showing specific relevance to the progerin pathway, and monitored under strict ethical oversight. Safety, limited numbers, and the burden of repeated testing in fragile pediatric patients make large, powered trials unrealistic.

In practice, studies in progeria would serve more as mechanistic or supportive evidence for a gerotherapeutic than as proof of life-extension in normal humans.

A feasible design could be a small, 20–40-patient, multi-year add-on study tracking vascular stiffness, growth, or molecular biomarkers rather than mortality. The more practical use of progeria for aging research is in preclinical models and exploratory human biomarker work, not as a primary regulatory pathway for "anti-aging" approval.

HGPS is the most common form of progeria. There are other diseases where one might also explore studies.

Genetic Forms of Premature Aging

Disease	Gene(s) / Inheritance	Onset	Key Pathophysiology	Main Clinical Features	Life Expectancy	Notes / Distinctions
Hutchinson–Gilford Progeria Syndrome (HGPS)	LMNA (dominant de novo mutation ⇢ abnormal progerin protein)	Infancy (1–2 yrs)	Defective nuclear lamina; accumulation of progerin leads to nuclear instability, DNA damage, and stem-cell exhaustion	Growth failure, alopecia, lipodystrophy, sclerodermoid skin, joint stiffness, atherosclerosis, cardiovascular events	~13–20 years	Classic "childhood progeria"; normal cognition; death often from MI or stroke
Werner Syndrome (WS)	WRN gene (autosomal recessive; RecQ helicase deficiency)	Adolescence–early adulthood	Defective DNA helicase ⇢ impaired DNA repair, telomere maintenance, and genomic stability	Short stature, early graying, cataracts, diabetes, osteoporosis, atherosclerosis, increased cancer risk	~40–50 years	Sometimes called "adult progeria"; shares molecular links with normal aging
Cockayne Syndrome (CS)	ERCC6 (CSB) or ERCC8 (CSA) (autosomal recessive)	Infancy–childhood	Defective transcription-coupled nucleotide excision repair (NER) ⇢ accumulation of UV and oxidative DNA damage	Growth failure, photosensitivity, neurodegeneration, cachectic "aged" appearance, sensorineural hearing loss	10–20 years (Type I); severe neonatal form <10 yrs	Neurological and photosensitive; distinct from HGPS (affects brain, not cardiovascular)
Rothmund–Thomson Syndrome (RTS)	RECQL4 (autosomal recessive)	Infancy–childhood	DNA helicase defect ⇢ genomic instability	Poikiloderma (skin atrophy), skeletal dysplasia, sparse hair, juvenile cataracts, osteosarcoma predisposition	Variable (30–50 yrs typical)	Milder; cancer risk dominant issue
Bloom Syndrome (BS)	BLM (RecQ helicase defect)	Infancy	Chromosomal instability, high sister chromatid exchange	Growth retardation, sun-sensitive rash, immune deficiency, malignancy risk	~20–30 years	Marked cancer predisposition, not vascular aging

Source: Stifel Investment Banking Department.

Idea Four

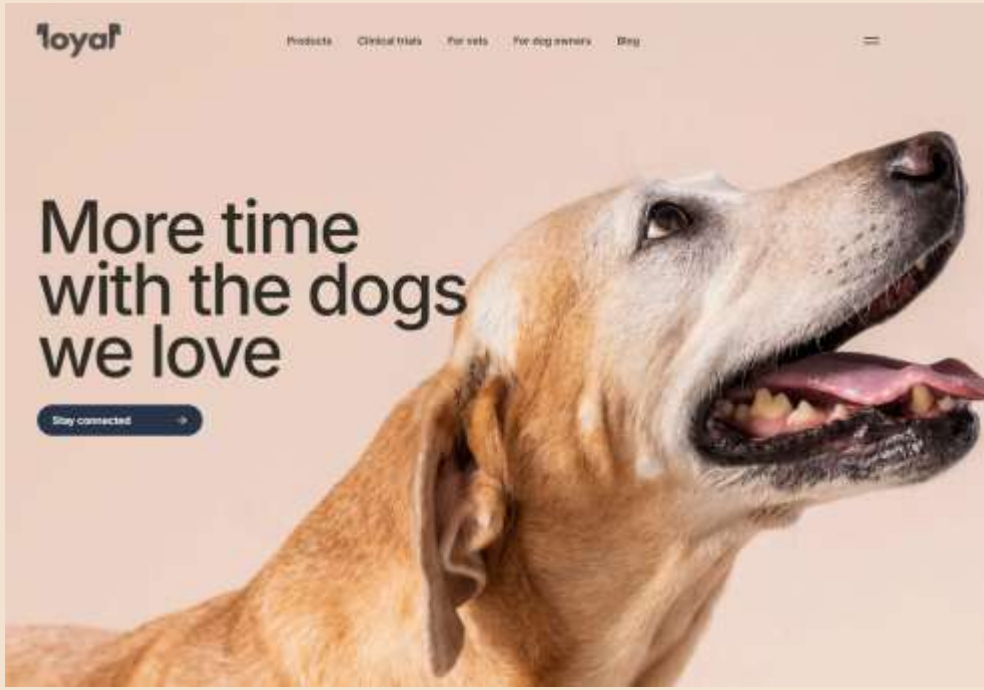
Go For An Approval of an Aging Drug in Dogs

Loyal: The First Dog Longevity Company

Loyal is a San Francisco–based veterinary biotechnology company developing drugs designed to extend the healthy lifespan of dogs. Founded in 2019 by Celine Halioua, the company's mission is to shift veterinary medicine from treating diseases late in life to targeting the underlying biological processes of aging itself.

The company's clinical pipeline centers on three major programs. LOY-002 is an oral, once-daily medication intended for senior dogs (typically over 10 years old) of small to medium size, aiming to reverse age-related metabolic dysfunction. LOY-001 and LOY-003 are designed for large and giant breeds (typically 5–7 years and older), where accelerated aging is strongly linked to elevated growth hormone and IGF-1 levels; these drugs modulate that hormonal axis to slow the biological pace of aging. Loyal's pivotal STAY trial, one of the largest longevity studies ever conducted in dogs, is enrolling more than 1,000 animals across dozens of U.S. veterinary sites to assess mortality, healthspan, and owner-reported quality-of-life endpoints.

Loyal has generated promising early clinical results. The company has published studies showing that LOY-001 and LOY-003 effectively reduce IGF-1 levels in target breeds, with acceptable safety profiles. For LOY-002, Loyal has completed dosing and safety studies that support its mechanism of improving metabolic parameters associated with age. These findings formed the basis for the U.S. FDA Center for Veterinary Medicine granting a "Reasonable Expectation of Effectiveness" determination for LOY-002 — the first time the FDA has formally recognized that a drug could plausibly extend lifespan in a healthy animal. Larger confirmatory studies are ongoing, with survival and metabolic data expected to mature over the next few years.



Pet Owners Would Spend Money for a Long-Lived Dog

Emily Anthes, *New York Times*, Nov 28, 2023 (excerpt)

It is too soon to say what longevity drugs will cost, but Ms. Halioua predicted that LOY-001 would work out to "mid-double-digit dollars per month."

For some owners, cost will not be a deterrent, said Karen Cornelius of Illinois, who has owned mastiffs and other "giant" breeds for decades. Many died when they were about 9 years old, said Ms. Cornelius, who runs several Facebook groups for owners of giant dogs.

"We were just having a discussion on one of my forums yesterday about how short-lived they were, and how people would **give almost anything** if they could extend that life," she said.

Source: https://www.nytimes.com/2023/11/28/science/longevity-drugs-dogs.html

Americans Spend Money on Their Dogs

American Pet Products Association (APPA, 2024)

1. U.S. pet market ≈ **$147 billion annually**, with dogs accounting for ›60%.
2. Median lifetime cost of a dog (food, care, vet, etc.): **$15k–$25k** for common breeds.
3. Veterinary expenditures rising ~8–10% annually, showing strong emotional price inelasticity.

Banfield Pet Hospital, "State of Pet Health Report" (2023)

Average annual medical cost for senior dogs (›10 yrs): $1,300–$2,000, often 3–5× higher in the last year of life.Common owner behavior: continuation of expensive care even with poor prognosis — a clear "grief avoidance" premium.

Veterinary Cancer Society

Median dog-cancer treatment cost: **$8k–$15k**, with some exceeding **$30k–$40k** for radiation + chemo.

ViaGen Pets (U.S.)

Cloning cost: **$50,000 for a dog**, **$35,000 for a cat**.
Waitlists routinely exceed a year, indicating strong luxury-segment demand.

Market Sizing Swag

Assume the U.S. has **90 million dogs**.

Even if **0.1%** of owners could pay $100k for a longer-lived dog, that's a **$9 billion** niche market.

If 1% of owners would pay $25k ⇢ **$22.5 billion** total potential value.

There is another market which includes working dogs (e.g., sled dogs, agricultural dogs, seeing eye dogs etc. where early death is problematic).

If One Ran a Trial on Middle-Age Dogs from Pet Owners We Think One Would Need to Wait At Two to Three Years to Get Enough of an Effect Size

Life tables of annual life expectancy and mortality for companion dogs in the United Kingdom

Nature Scientific Reports
2022, 12:6425

Kendy Tzu-yun Teng[1✉], Dave C. Brodbelt[2], Camilla Pegram[2], David B. Church[3] & Dan G. O'Neill[2]

A life table is a tabulated expression of life expectancy and mortality-related information at specified ages in a given population. This study utilised VetCompass data to develop life tables for the UK companion dog population and broken down by sex, Kennel Club breed group, and common breeds. Among 30,563 dogs that died between 1st January 2016 and 31st July 2020, life expectancy at age 0 was 11.23 [95% confidence interval (CI): 11.19–11.27] years. Female dogs (11.41 years; 95% CI: 11.35–11.47) had a greater life expectancy than males (11.07 years; 95% CI: 11.01–11.13) at age 0. Life tables varied widely between breeds. Jack Russell Terrier (12.72 years; 95% CI: 12.53–12.90) and French Bulldog (4.53 years; 95% CI: 4.14–5.01) had the longest and shortest life expectancy at age 0, respectively. Life tables generated by the current study allow a deeper understanding of the varied life trajectory across many types of dogs and offer novel insights and applications to improve canine health and welfare. The current study helps promote further understanding of life expectancy, which will benefit pet owners and the veterinary profession, along with many other sectors.

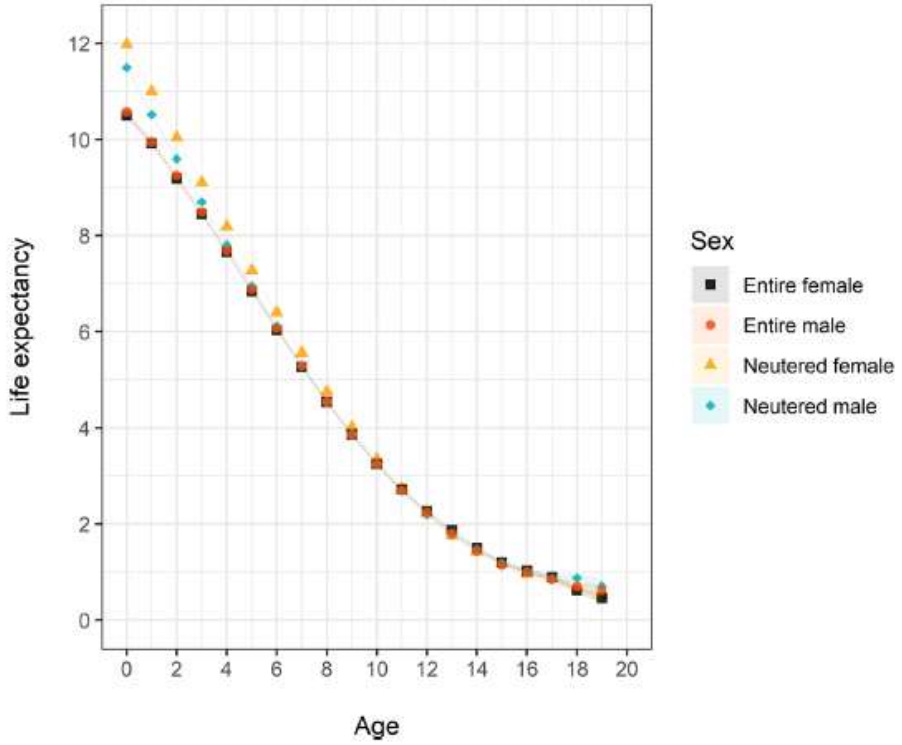


Figure 1. Life expectancy and the 95% confidence interval for female and male dogs at different ages (year) under primary veterinary care in the UK.

Source: https://www.nature.com/articles/s41598-022-10341-6

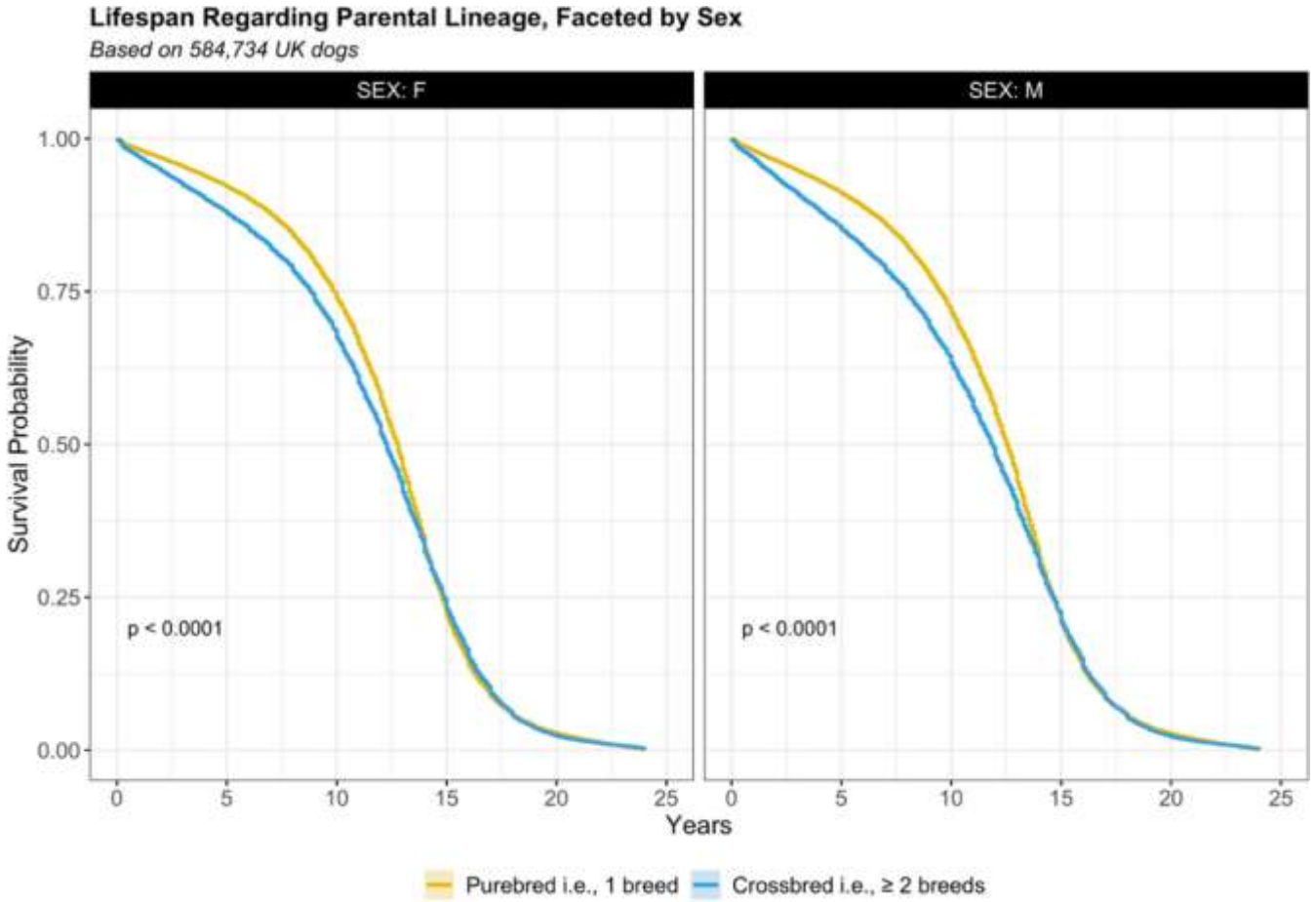
Dog Lifespans are Diverse. Survival Odds Drop Rapidly After Age 7

Longevity of companion dog breeds: those at risk from early death

Nature Scientific Reports
2024, 14:531

Kirsten M. McMillan[1]✉, Jon Bielby[2], Carys L. Williams[1], Melissa M. Upjohn[1], Rachel A. Casey[1] & Robert M. Christley[1]

The companion dog is one of the most phenotypically diverse species. Variability between breeds extends not only to morphology and aspects of behaviour, but also to longevity. Despite this fact, little research has been devoted to assessing variation in life expectancy between breeds or evaluating the potential for phylogenetic characterisation of longevity. Using a dataset of 584,734 unique dogs located within the UK, including 284,734 deceased, we present variation in longevity estimates within the following: parental lineage (purebred = 1 breed, crossbred ≥ 2 breeds), breed (n = 155), body size (large, medium, small), sex (male, female) and cephalic index (brachycephalic, mesocephalic, dolichocephalic). Survival estimates were then partitioned amongst phylogenetic clades: providing evidence that canine evolutionary history (via domestication and associated artificial selection) is associated with breed lifespan. This information provides evidence to inform discussions regarding pedigree health, whilst helping current/prospective owners, breeders, policy makers, funding bodies and welfare organisations improve decision making regarding canine welfare.



Source: https://www.nature.com/articles/s41598-023-50458-w

Cost Estimates to Get a Dog Aging Drug Approved

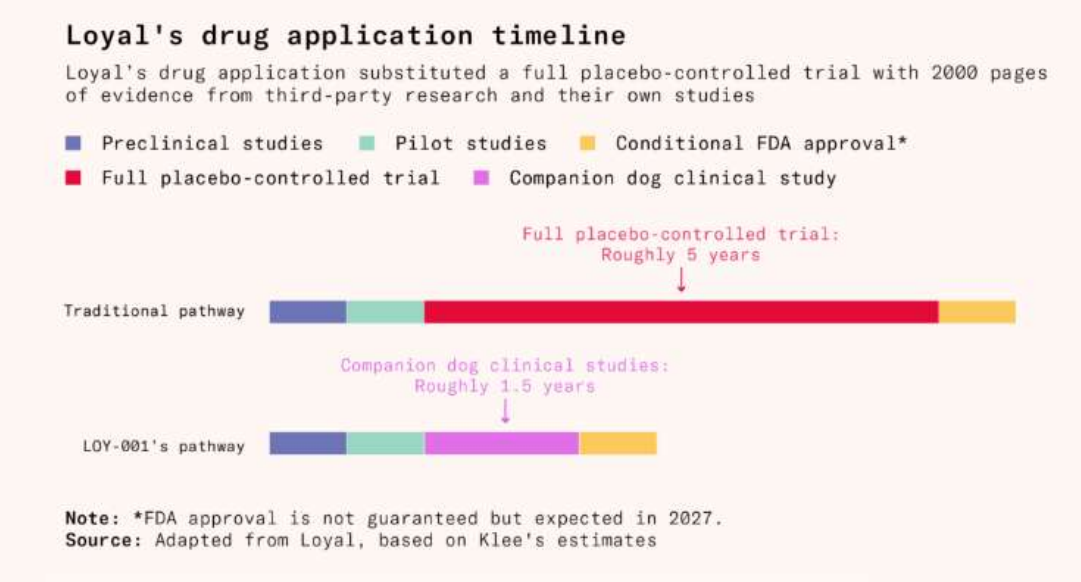
One source estimates a cost of $20mm for a full efficacy trial but a tenth this much to show reasonable expectation of efficacy as did Loyal.

By Trevor Klee, Biotech Entrepreneur, Works in Progress, June 12, 2025

Convincing the FDA of this took, by Loyal's accounting, about 2,000 pages of evidence from third-party research and their own studies. In return, the FDA agreed to waive the requirement for a full placebo-controlled trial before Loyal could legally sell LOY-001 and allowed Loyal to temporarily substitute the following completed studies instead:

1. An observational study in pet dogs showing that large dogs aged faster than small dogs;
2. A lab study in lab dogs showing that obese dogs had higher levels of a certain biomarker than non-obese dogs;
3. Third party data showing that obese dogs have shorter lifespans and healthspans than non obese dogs;
4. A third-party observational study showing that large dogs often had higher levels of that same biomarker than small dogs;
5. An interventional study in lab dogs showing that Loyal's therapeutic reduced levels of that biomarker

Based on my estimates, this shift allowed Loyal to avoid a $20 million, five-year trial for a trial lasting just 18 months at the cost of just $1 million. More importantly, it allowed Loyal to hasten their drug into the real world, gather way more evidence from a wider variety of dogs than they could ever get with lab trials alone, and earn money along the way.



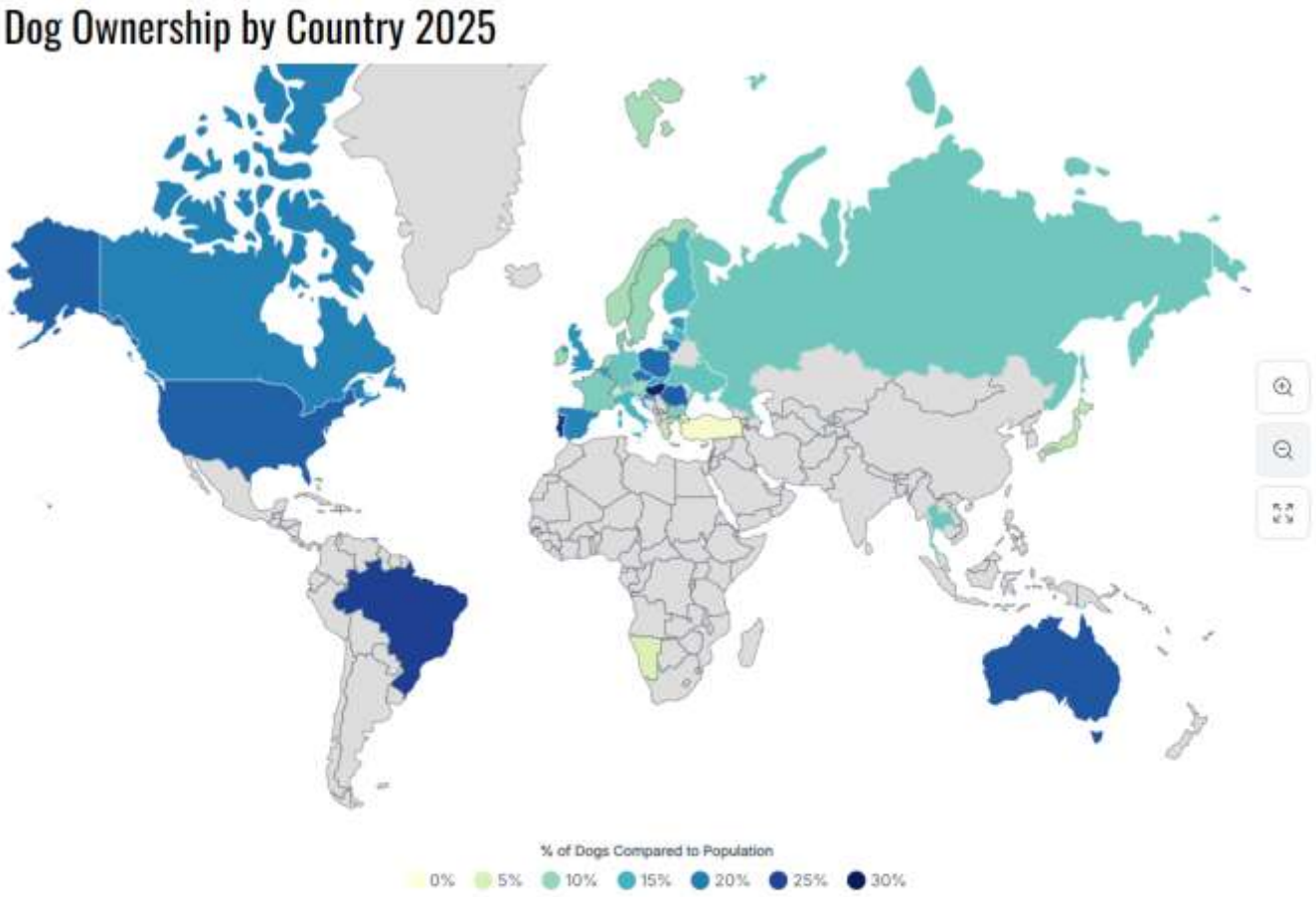
Of course, that still leaves Loyal with safety and stability trials. I'd estimate the safety trial will take at least 12 months and cost $1 million, judging by how long they want dogs to take the drug. It's hard for me to estimate how long the stability trial will take without knowing more about how the drug is manufactured. Loyal seems to anticipate approval for the drug by 2027, so it looks like they're budgeting at least two years.

Still, this is dwarfed by what the efficacy trial would require in terms of cost, complexity, and scientific risk. Proving that a drug for a novel condition is safe, shelf-stable, and affects a biomarker is a much lower bar to clear than proving that it works.

Source: https://worksinprogress.co/issue/the-secret-fast-track-for-animal-drugs/

International Trials an Option

We suspect that this cost could be reduced by running a trial in a lower cost country like Portugal, Hungary or Brazil.



5 Countries with the Most Dogs Compared to People

Hungary	Portugal	Brazil	Australia	United States
29.07%	27.28%	25.47%	23.36%	22.46%

Source: https://worldpopulationreview.com/country-rankings/dog-ownership-by-country

Idea Five

Biomarker Enhanced Approach

Study Enhancement Markers Like GDF-15, uPAR and HE4

Patient selection is a key tool to maximize the odds of success in aging trials.

We have argued that certain aging biomarkers have biological relevance. GDF-15 is a great marker for mitochondrial damage and senescence while uPAR is much more of a pure senescence marker. HE4 reflects cell disorder and an organism's fibrotic state.

Obviously, one can pick and choose your markers carefully. But you can also choose your patients to maximize the perceived odds of success.

For example, if you were to run a trial testing NAD+ on lifespan you would want to select patients who would benefit most from the intervention – those with high levels of GDF-15.

In contrast, if you were running a trial with a uPAR CAR-t, you would want to select patients with high levels of cell senescence.

Idea Six

Organ Reconditioning Market

Organ Reconditioning with Aging Drugs

The organ reconditioning market is a potential entry point for testing and deploying aging and cellular rejuvenation drugs. This was hinted in the previous news story about work in China and Russia to transplant in rejuvenated organs. There are three ways to do this. One would be to transplant the organs of younger people into older people. Another would be to generate new organs from scratch – although this is technically quite challenging (the history of the biotech Tengion provides an example). A final approach would be to take out the old organs and rejuvenate them. We are going to focus on this final idea.

In organ transplantation, donor organs are often placed in *ex vivo* perfusion systems to restore viability and assess function before transplantation. These “organs on life support” offer a controlled setting for testing rejuvenation interventions that aim to reverse age-related or stress-related molecular damage. In this setting, small molecules, gene therapies, or biologics can be administered to the organ directly, allowing researchers to evaluate improvements in tissue metabolism, proteostasis, mitochondrial function, or senescence clearance — all core hallmarks of aging — without systemic exposure in a human subject.

Companies like LyGenesis, based in Pittsburgh and spun out of the University of Pittsburgh, are already advancing the boundary between organ regeneration and reconditioning.

LyGenesis uses lymph nodes as bioreactors to grow functioning ectopic organs — for example, transplanting donor liver cells into lymph nodes of patients with end-stage liver disease to regenerate miniature liver units capable of restoring metabolic function.

This approach demonstrates that rejuvenation and organogenesis can intersect in vivo. By modulating the age or quality of donor cells before implantation — for example, applying senolytic drugs, telomerase activators, or partial reprogramming factors — researchers could further enhance organoid vitality and patient outcomes, effectively creating a regenerative feedback loop between ex vivo and in vivo biology.

Partial cell reprogramming, based on the Yamanaka factors (OCT4, SOX2, KLF4, c-MYC), has shown the ability to reset cellular epigenetic age without erasing identity when carefully controlled. Integrating this technology into organ reconditioning protocols — for example, transient delivery of OSK via mRNA, AAV, or small-molecule mimetics during ex vivo perfusion — could rejuvenate donor organs at the molecular level before transplantation. Juan Carlos Belmonte describes a similar idea in a recent seminar.

One fascinating example of what is possible is work at the Mayo Clinic through their Genesis Initiative. On our recent visit, they explained that they are the world’s #1 destination for complex organ transplants and that there just aren’t enough transplantable organs. So, they see the idea of reconditioning “old” organs as one of the best ways to go. They are making real progress in this area.

Examples of Organ Regeneration Initiatives

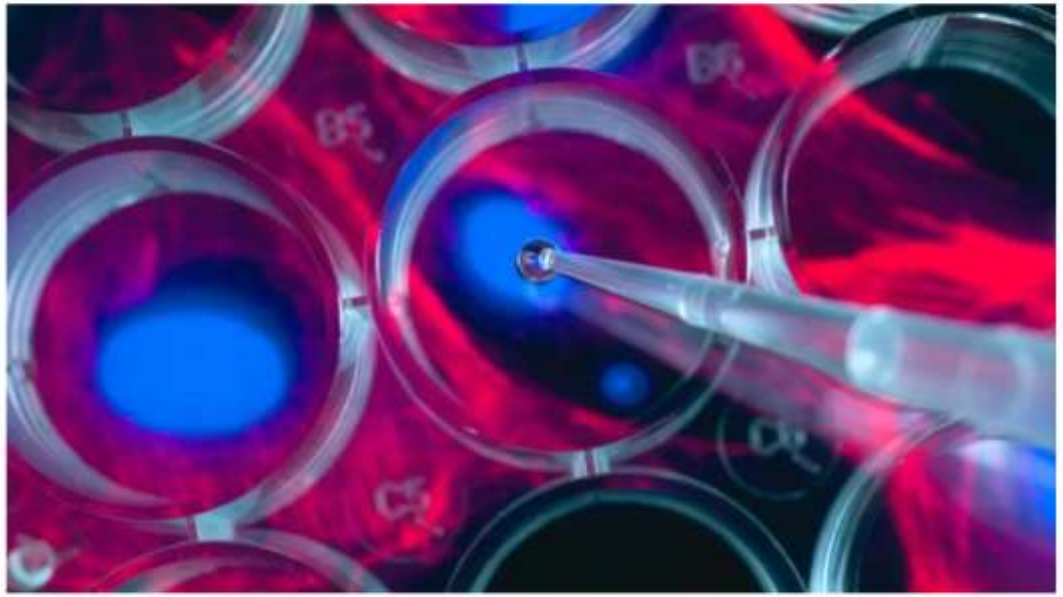
LyGenesis Announces First Patient Dosed in its Phase 2a Clinical Trial of a First-in-Class Regenerative Cell Therapy for Patients with End-Stage Liver Disease

April 2, 2024 - LyGenesis, a clinical-stage biotechnology company developing cell therapies for large unmet medical needs, announced today that the first patient has been dosed in their Phase 2a clinical trial evaluating their first-in-class allogenic regenerative cell therapy transplanted into patients' lymph nodes as a potential treatment for end-stage liver disease (ESLD).

READ MORE

Mayo Clinic researchers identify a new stem cell patch to gently heal damaged hearts

Marla Broadfoot, Ph.D.
November 5, 2025



A researcher uses a pipette to place stem cells into a multiwell plate, with an image of the cells shown beneath.

PHOENIX — Mayo Clinic researchers have developed a pioneering method to mend damaged hearts without open-heart surgery, an advance that could one day transform the treatment of heart failure.

The new approach uses lab-grown heart tissue made from reprogrammed adult stem cells, delivered through a tiny incision rather than a surgically opened chest cavity. In preclinical testing, the stem cell patch restored heart function and improved healing.

Does Organ Regeneration Have Anything to Do with Aging?

Are we seriously suggesting that people could live meaningfully longer by getting their organs reconditioned?

There are several potential scenarios to think about here.

In a trivial sense, yes, if your kidney is about to go, then an organ transplant could dramatically extend your lifespan.

Interestingly, there is very strong evidence showing that kidney and heart transplants can achieve dramatic reductions in GDF-15 levels.

But what about the China/Russia idea that one could go in and get your organs "tuned up" once in awhile so that they could take on a younger phenotype.

This may be more fiction than science to state the obvious. The reason is that the key causes of aging highlighted in this report: oxidative damage and DNA damage take place in most cells of your body. So just reconditioning a single organ is, ahem, more like moving the deck chairs around on the Titanic.

OK, perhaps we should ditch that unfortunate metaphor.

It would seem unlikely that organ regeneration would be a general solution to aging, but we could imagine situations where one visits a fancy medical institution in the future and they tell you that there are three subsystems of your body that are going to need "fixing" for you to live past 100. This institution could then schedule either *ex vivo* or *in vivo* reconditioning. The example of in vivo reconditioning being done with the heart a Mayo is fascinating. We heard a seminar on this idea while visiting there and were blown away by the data that they have showing that this works. If one could do *in vivo* reconditioning for those major weakening organ systems – that could get quite interesting. The market opportunity is a big one.

High Potential For Replacing Organs to Extend Lifespan

Lore S, Poganik JR, Atala A, Church G, Gladyshev VN, Scheibye-Knudsen M, Verdin E. Replacement as an aging intervention. *Nat Aging,* May 2025; 5(5):750-764.

Substantial progress in aging research continues to deepen our understanding of the fundamental mechanisms of aging, yet there is a lack of interventions conclusively shown to attenuate the processes of aging in humans. By contrast, replacement interventions such as joint replacements, pacemaker devices and transplant therapies have a long history of restoring function in injury or disease contexts. Here, we consider biological and synthetic replacement-based strategies as aging interventions. We discuss innovations in tissue engineering, such as the use of scaffolds or bioprinting to generate functional tissues, methods for enhancing donor-recipient compatibility through genetic engineering and recent progress in both cell therapies and xenotransplantation strategies. We explore synthetic approaches including prostheses, external devices and brain-machine interfaces. Additionally, we evaluate the evidence from heterochronic parabiosis experiments in mice and donor-recipient age-mismatched transplants to consider whether systemic benefits could result from personalized replacement approaches. Finally, we outline key challenges and future directions required to advance replacement therapies as viable, scalable and ethical interventions for aging.

Source: https://www.nature.com/articles/s43587-025-00858-6

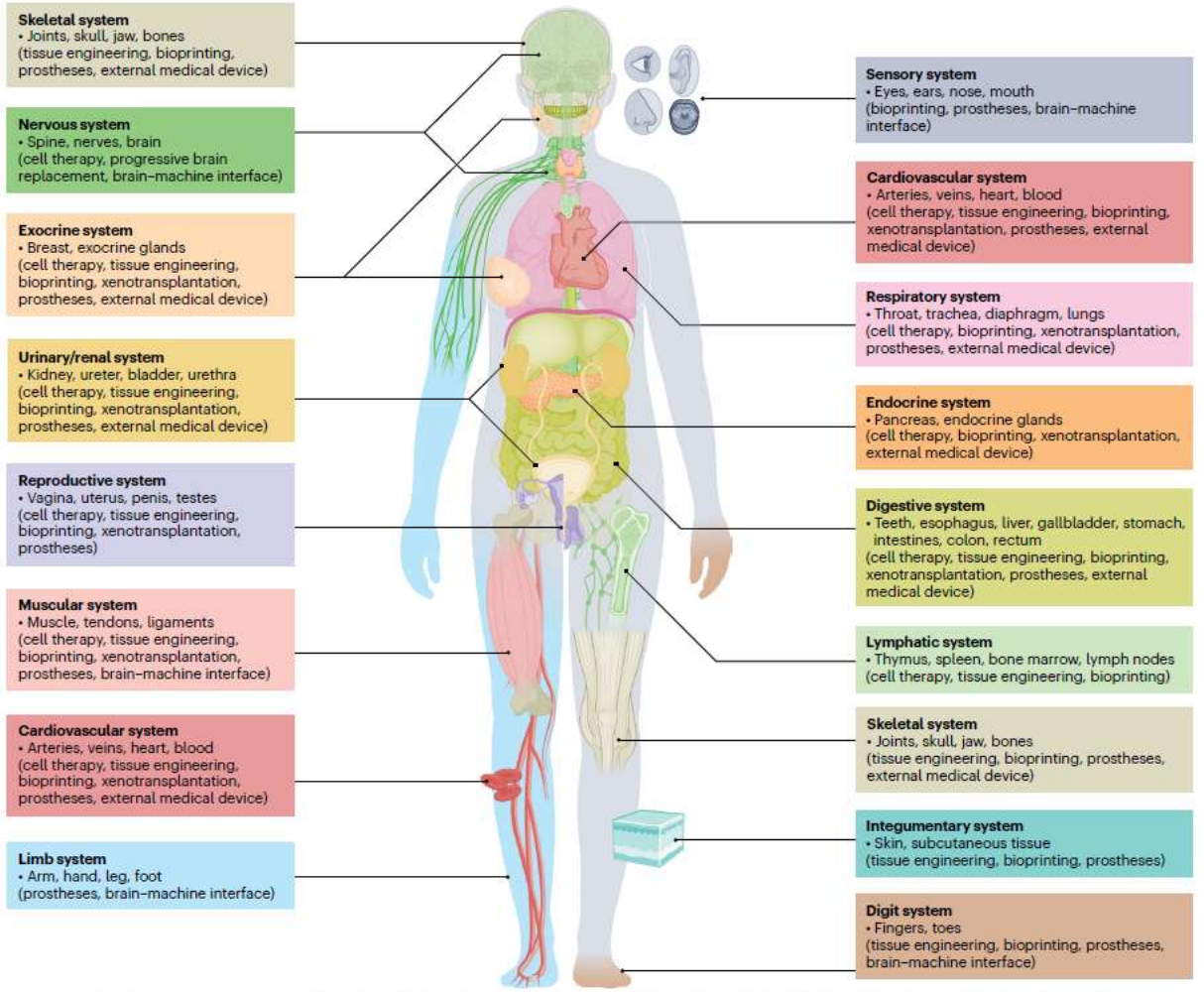


Fig. 3 | Overview of anatomical systems and potential replacement methods. This schematic maps potential replacement methods to key anatomical systems in the human body. Examples include the skeletal system (for example, prostheses for joint replacements), the nervous system (for example, brain–machine interfaces for neural implants) and the urinary–renal system (for example, xenotransplantation for the kidney). Color-coded anatomical icons emphasize the diversity of potential synthetic and biological replacement technologies aimed at addressing aging. Note that, although the figure highlights many organs and body parts, not every structure or potential replacement approach is represented. Adapted from an original created in BioRender. Vega, G. (2025) https://BioRender.com/m80t259.

Synthetic Man: A Range of Replacement Ideas in Development

Lore S, Poganik JR, Atala A, Church G, Gladyshev VN, Scheibye-Knudsen M, Verdin E. Replacement as an aging intervention. *Nature Aging*, May 2025; 5(5):750-764.

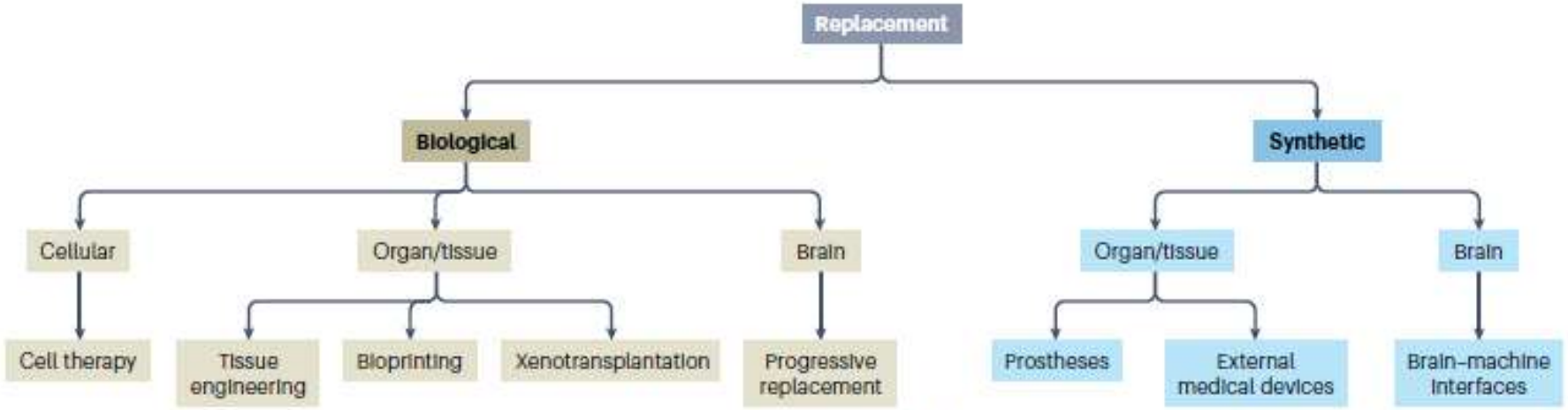


Fig. 1 | Overview of approaches for replacement interventions in aging. Approaches at the cellular level, the organ–tissue level and the brain. A combination of biological and synthetic interventions may be required for multitissue replacement. Note that the brain is an organ, but we have chosen to classify it separately for the sake of clarity.

Perusing the current literature on replacing parts of humans with reconditioned organs and machine interfaces, of course, quickly brings flashbacks to the 1970s TV series on the first bionic man. Maybe the show wasn't so crazy after all.

Source: https://www.nature.com/articles/s43587-025-00858-6

Regulatory Agency Pathways for Aging Drug Approvals

So You Actually Can Run an Aging Trial, But Will the FDA Ever Approve Such a Drug if Your Trial Works?

Important question. The FD&C Act does not prohibit the FDA from approving a drug for aging. Yet, many say that the FDA does not consider aging to be a disease. Therefore, the narrative goes, that the FDA would not consider a drug for aging as approvable. This view is widespread.

We spoke to a senior FDA official in January 2024 (obviously, the last Administration) and posed the question: could you approve a drug for aging?

The answer was an unequivocal yes. The official pointed out that the FDA had already approved the protocol for Nir Barzilai's TAME Trial.

The official noted that the way this trial works is that the primary endpoint is a composite of events from cardiovascular disease, cancer, cognitive disease, and mortality. Interestingly, this trial is not one that has its composite endpoint of mortality from multiple causes. Barzilai took the safer route.

The FDA would, in theory, accept all-cause mortality as an endpoint but only for patients with a specific condition. But this could be a very broad condition like hypertension or sarcopenia (both of which the FDA consider to be diseases). However, one could run a trial like the TAME trial where all-cause mortality was a *secondary* endpoint.

This is all very similar to what Lilly and Novo are going through with obesity drugs today. The FDA wants to see benefits from these drugs in specific contexts like diabetes, heart disease, sleep apnea etc. You can't get a drug approved for obesity alone.

It is well-known that the FDA prefers hard endpoints like cardiac events or mortality to soft endpoints. For example, the FDA generally does not accept loneliness as an endpoint for trials. However, the FDA has made increasing progress on endpoints like frailty and intrinsic capacity. In general, the FDA will approve drugs that hit endpoints like frailty as long as the specific endpoints are well validated and clearly hit in a well-designed trial.

Today's U.S. administration is particularly receptive to efforts to extend lifespan (a topic of high interest to HHS Secretary Kennedy). HHS held a MAHA conference in November 2025 which featured a full panel on longevity and lifespan expansion.

We also spoke to the FDA official about biomarkers. He was highly encouraging but noted that once the agency accepts biomarkers as a proxy for all-cause mortality for aging drugs, everyone will want to use such a marker panel. So, the bar on doing this is not going to be low. He said that the FDA would require extensive validation of any biomarkers prior to their use and noted that the validatory context should be similar to that of any proposed clinical trial.

Multiple Paths Possible for Aging Drug Approvals

Guarente L, Sinclair DA, Kroemer G. Human trials exploring anti-aging medicines. *Cell Metabolism*, Feb 6, 2024; 36(2):354-376.

We believe that the next few years will present a tipping point, when the most viable approaches will become evident and move us toward a more widespread use of interventions targeting aging processes. While aging is not a disease as prescribed by the FDA, one might expect approval of these interventions to treat aging-fostered diseases. Off-label use may allow a more general application to combat aging and its effects (Figure 2). In the future, the burgeoning field of aging biomarkers, such as DNA methylation, glycation, metabolomics, and proteomics, may lead to FDA approval of these agents for aging processes per se. Given the momentum in human studies targeting aging, we are optimistic that the course of human health could be fundamentally changed.

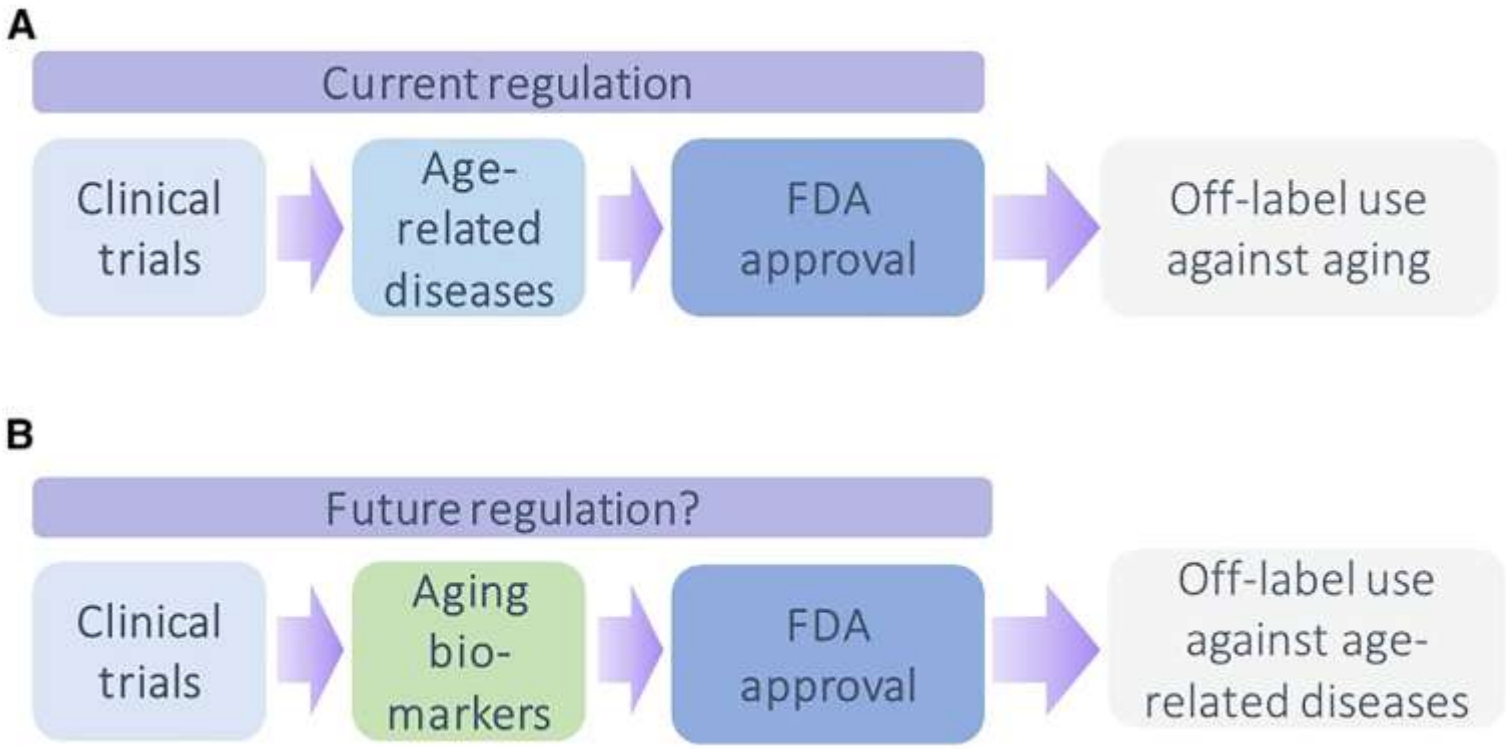


Figure 2. Current and future paths to FDA approval for interventions to slow (or reverse) aging processes

(A) In compliance with current FDA regulations, interventions must be tested for their effects on aging-dependent diseases. If approved, they could be used off label for more widespread applications.

(B) In the future, the acceptance of aging biomarkers would allow drugs to be tested and approved for aging itself, and then be used off label to treat diseases.

Source: https://linkinghub.elsevier.com/retrieve/pii/S1550-4131(23)00458-8

Other Possibilities for Regulatory Pathways

Muscedere J, Shorey CL, Duque G, Kim P, Lorbergs AL, McGlory C, Merchant RA, Newman JC, Rolland Y, Vellas B., "Advancing Geroscience Research - A Scoping Review of Regulatory Environments for Gerotherapeutics," *J Nutr Health Aging*. September 2025; 29(9):100637.

Decline in Intrinsic Capacity is in ICD-11

While aging itself is not a disease, it is the largest risk factor for many chronic diseases and conditions, including frailty and diminished intrinsic capacity. Notably, the International Classification of Diseases (ICD-11) now includes "aging-associated decline in intrinsic capacity" (MG2A) as a classification, replacing the previous term "old age" [19]. This shift provides a potential regulatory foundation for future gerotherapeutic drug approvals, as it establishes a recognized target for interventions aimed at mitigating age-related declines. Similarly, sarcopenia, a condition characterized by the progressive loss of skeletal muscle mass and function, has been assigned an ICD-10-CM code (M62.84) although consensus on measurement remains elusive [20]. The distinction between disease and the aging process matters for regulators, as current therapeutic approvals are tied to specific conditions (e.g., sarcopenia), whereas therapies designed to target aging biology would fall outside existing disease-based frameworks. If aging is accepted as a therapeutic target, regulatory agencies may need to revise approval pathways, expand eligible endpoints, and support trial designs that reflect the complexity of aging biology rather than traditional single-disease models.

Work with ARPA-H's PROSPR Program

As regulatory frameworks develop and evolve, incorporating adaptive approval pathways and trial designs that accommodate the complexity of aging will be key to accelerating progress. Innovative regulatory pathways are in place in agencies around the world in response to unmet needs or perceived urgency such as the EMA's Adaptive Pathway or the FDA Accelerated Approval Program. While these would be difficult to adapt to an aging indication since they are based on regulatory processes already in place, they demonstrate the willingness of agencies to adapt to needs or new evidence. This could be provided by the PROSPR program in the United States that aims for the development of novel clinical trial designs, real-world resilience metrics, and biomarker strategies as a strategy for accelerating gerotherapeutic development. Although its success remains to be seen, PROSPR offers a model for how regulatory and scientific innovation could converge to support healthspan-focused therapies. Without regulatory frameworks, researchers and industry stakeholders will likely face continued uncertainty, limiting progress in translating geroscience advances into clinical practice.

Source: https://linkinghub.elsevier.com/retrieve/pii/S1279770725001629

The Ability to Reliably Measure and Classify Differentials in Intrinsic Capacity in Clinical Trials is Getting Good

de Souto Barreto P, IHU HealthAge INSPIRE/Open Science study group, "Reference centiles for intrinsic capacity to monitor clinical health outcomes in real-world primary care cohorts," *Nat Aging*. 2025 Jul;5(7):1217-1231.

Intrinsic capacity (IC) refers to physical and mental capacities that determine healthy aging. IC is the central element of the World Health Organization care pathway 'Integrated Care for Older People' (ICOPE). However, the operationalization of a composite IC measurement in clinical settings remains to be defined. We used screening data from ICOPE implementation in a real-life population of 27,706 adults 60 years or older that were users of primary care services to elaborate and cross-validate IC scores and centile values for men and women. Here, we show that IC centiles were cross-sectionally associated with comorbidity, frailty and limitations in both activities of daily living and instrumental activities of daily living. External validation using populations from high-income (French INSPIRE-T cohort) and upper-middle-income (ICOPE Brazil) countries validated the associations between IC centiles and clinical outcomes. The IC centiles developed using ICOPE screening data constitute a standardized parameter to monitor individual and population IC through a clinically friendly approach.

Table 2 | Comparison of IC centile groups in the training and test samples of the ICOPE Care cohort based on three IC approaches

	Training sample	Test sample	*P*
Score from CFA bifactor model			
>P90	1,200 (10.4%)	517 (10.4%)	0.307
P76–P90	1,741 (15.1%)	726 (14.7%)	
P51–P75	2,748 (23.8%)	1,258 (25.4%)	
P26–P50	3,003 (26.0%)	1,229 (24.8%)	
P11–P25	1,743 (15.1%)	748 (15.1%)	
≤P10	1,115 (9.7%)	479 (9.7%)	
ICOPE Step 1 score			
>P90	1,838 (11.1%)	764 (10.8%)	0.389
P76–P90	1,612 (9.7%)	649 (9.2%)	
P51–P75	4,608 (27.8%)	1,934 (27.4%)	
P26–P50	4,586 (27.7%)	1,973 (28.0%)	
P11–P25	2,369 (14.3%)	1,074 (15.2%)	
≤P10	1,537 (9.3%)	666 (9.4%)	

Source: https://www.nature.com/articles/s43587-025-00861-x

Does FDA Approval Even Matter in Aging Drugs?

Of course, the FDA matters. We don't know any sponsors who would prefer not to get an FDA approval for a drug if its possible. This facilitates reimbursement and has certain risk advantages in the case of product liability suits.

But we wonder if the aging field is a bit different. Recall our argument that billionaires might drive this field. So, let's suppose we have a pill that will add ten years to a billionaire's life, and we are going to charge a billion dollars for the pill. And, further let's suppose that reputable medical professionals have reviewed the data package for the drug and agree that it's reward to risk ratio is favorable.

Presumably, we could enroll and consent the person into a study, get them in their yacht into international waters and have them take the pill outside of the jurisdiction of any agency. Or, as shown at right, we could make this a liquid drink so billionaires could just drink from the fountain of youth.

This isn't how any of us would want the market to work. We are simply making the point that the lack of an FDA approval is not necessarily the death knell for an aging drug.

Further Thoughts on the Regulatory Process for Aging Drugs

So, as already mentioned, the FDA is absolutely willing to approve drugs for aging as has been proposed in Nir Barzilai's TAME Trial. The idea is that the FDA is open to stacking diseases in composite endpoints. If you claim your drug will cure both kidney and liver disease, the FDA is perfectly willing to consider a trial that includes patients with both conditions with a single composite endpoint.

However, the FDA has not yet said that you can take a group of people without explicit disease and run a study of an aging drug to impact all-cause mortality. We aren't sure that the FDA would decline to allow a sponsor to run such a study.

This is arguably based on antiquated regulatory science. We have noted on page 18 of this report that most overt diseases have subclinical origins that could impact aspects of human physiology.

Carina Kern of Linkgevity makes the point far more eloquently than we, noting in her recent seminar at the Royal Institution (see minute 14:50) that the notion of associating a single disease with a single pathway and single drug makes little sense.

We would guess that the FDA would be open to altering their views, particularly in the current Administration. There would, most likely, need to be a process of thought, guidances and the like.

Another obvious question is what do other countries think on this topic? China, in particular comes to mind. If the top leadership in China has an explicit interest in aging therapeutics, one would imagine that the CFDA would be open to creating guidance for the approval of such drugs.

We would note that while the European Medicines Agency does not recognize "aging" as an indication, but it has done more than anyone else on frailty, intrinsic capacity and geriatric medicines. EMA has provided a statement on medicines for old people. EMA has also provided a policy paper on defining frailty – which is obviously highly relevant if one wishes to test a drug for its effect on frailty. In general, regulatory agencies are behind the science in this area. The most up-to-date synthesis is the 2025 scoping review "Advancing Geroscience Research – A Scoping Review of Regulatory Environments for Gerotherapeutics" (Muscedere et al.). It specifically looked for aging-focused regulatory frameworks in the US, Europe, Canada and elsewhere and concluded: "In 3,780 publications screened, no regulatory frameworks for gerotherapeutics were found, and there is a lack of recognition of biological aging as a formal target plus an absence of clear regulatory pathways for aging-focused therapies." This is pretty stark: nowhere in the world is there a codified regulatory path for "a drug for aging"—only geriatric/ frailty / intrinsic-capacity–related guidance that you can try to "hack" into a pathway.

Selected Biopharmas and Pipeline in the Aging Field

Deepening Pipeline of Aging Drugs in Development

Source: Stifel Investment Banking Department.

Large Pharma Has Emerging Interest in Aging Biology

Boehringer Ingelheim has shown growing interest in aging biology and healthy longevity, although its programs are framed around healthspan and age-related disease rather than explicit “anti-aging” drugs. The company’s Research Beyond Borders initiative seeks disease-modifying and neuroprotective therapies that could extend both lifespan and quality of life, and its “AI for Healthy Aging” projects apply artificial intelligence to address the needs of aging populations. Boehringer is also involved in regenerative medicine collaborations and supports fundamental research on aging, DNA repair, and epigenetics through the Institute of Molecular Biology in Mainz. It has also invested in aging biotechs such as Refoxy.

Novartis has publicly declared that aging (or “healthy lifespan for older adults”) is a strategic frontier for them.

They struck a large deal with BioAge Labs (which holds large human-biobank/AI longevity data) to fuel discovery of longevity therapeutics.

Mechanistic interest: targeting determinants of healthy lifespan, presumably via pathways regulating aging biology (metabolism, resilience, cellular maintenance) rather than just a late-disease indication.

See a nice article on Novartis’ ambitions: https://www.swissinfo.ch/eng/healthcare-innovation/novartis-bets-on-ageing-as-next-frontier-in-drug-development/89353154

Roche commissioned a major study titled “The Value of Innovation in the Era of Longevity: How Can Europe Invest Better to Manage Ageing and Longevity?” The report discusses ageing populations, health-system sustainability, and the importance of keeping people healthier for longer.

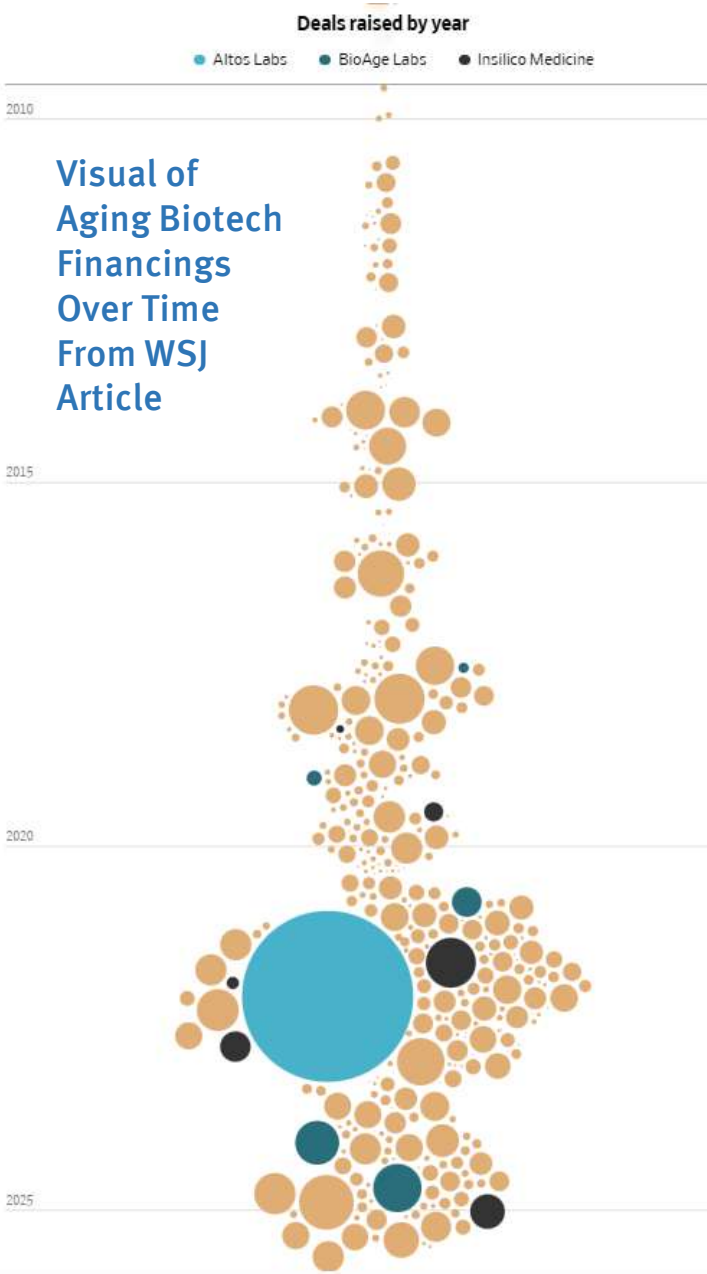
Roche’s public messaging emphasizes that as people live longer (and populations age), the “real game” is not just adding years, but adding healthy years — keeping people productive and out of chronic disease. For example: “While living longer is a triumph, it presents a challenge: to maintain sustainable health systems at a time of ageing populations…”

Other Notes:

AbbVie has a publicly stated collaboration with Calico Life Sciences aimed at aging biology but appears to have exited this.
AstraZeneca has recently hired a leading aging researcher from academia and is showing interest in the area.
Eli Lilly participated in New Limit’s recent $45 million raise. This is a cell reprogramming company. Lilly has some interest in the aging field.
Pfizer has published on anti-aging genes but is not showing any aging drugs in its pipeline.
Taisho partnered with Insilico Medicine on an AI-powered senolytic drug discovery program aimed at therapeutics against aging.
Grifols, the blood product company, has been exploring whether transfusions of young blood can help Alzheimer’s Disease.

Largest Private Financings of Aging Biotechs

Company	Amount	Round	Date	Select investors
ALTOS	$3000M	Series A	January 2022	ARCH Venture Partners. Private Individuals
Calico	$2500M	Corporate	September 2018	Alphabet, AbbVie
Retro	$180M	Seed	April 2022	Sam Altman
BIOAGE	$170M	Series D	February 2024	Sofinnova Ventures, Andreessen Horowitz, Longitude
JUVENESCENCE	$150M	Series B–III	April 2025	M42
NewLimit	$130M	Series B	May 2025	Kleiner Perkins, Founders Fund, Khosla Ventures
Insilico Medicine	$123M	Series E	January 2025	Pudong Development Group, Wuxi Capital Group
Cambrian	$100M	Series C	October 2021	Anthos Capital, Apeiron, Future Ventures, SALT Fund
life BIOSCIENCES	$82M	Series C	January 2022	AlphaWave Global
Centenara Labs	$75M	Series B	September 2023	Apeiron, Catalio Capital, Mubadala Capital



Visual of Aging Biotech Financings Over Time From WSJ Article

Source: Stifel Investment Banking Department. Chart at right shows individual financings for aging biotechs. Sourced from Shane Shiffett, Amy Docker Marcus and Alex Janin, "The Billionaires Fueling the Quest for Longer Life," *Wall Street Journal*, Sep 6 2025 (link)

Selected Profiles of Aging Biotech Companies

Aeovian PHARMACEUTICALS

Company Overview

Aeovian Pharmaceuticals is a privately held clinical-stage biopharmaceutical company based in the Bay Area. The company was spun out of the Buck Institute for Aging and was previously known as Delos Pharma. Aeovian is developing targeted and highly selective small molecules to restore cellular metabolic quality control, thereby addressing the dysregulated growth and hyperactive signaling found in certain rare genetic and age-related diseases. The company is specifically focused on overcoming challenges with first-generation mTOR inhibitors such as rapamycin. Aeovian's lead development candidate, is a first-in-class CNS penetrant selective mTORC1 inhibitor being developed for the treatment of TSC refractory epilepsy and is currently being evaluated in a Phase 1 trial. TSC is a rare genetic disorder caused by the hyperactive signaling of mTORC1.

Pipeline

Therapy	*MOA*	*Stage*	*Indication*
AV-078	mTORC1 inhibitor	Phase 1b/2	TSC Epilepsy

Broader pipeline of selective mTORC1 inhibitors (sometimes referred to as next-generation rapalogs) for neurological and age-related diseases; specific additional candidates are largely undisclosed but referenced in investor and foundation communications as a "robust pipeline" of selective mTORC1 modulators. Also developing CD38 inhibitors for aging-related diseases.

Publication(s)

Gulieva RE, Ahmadvand P, Freedman BS. A novel rapalog shows improved safety vs. efficacy in a human organoid model of polycystic kidney disease. *Stem Cell Reports*. 2025 Feb 11;20(2):102395.

Buttermore ED, Srinivasan GR, Jumo H, Swanson AC, O'Kelly B, Makhortova NR, Sahin M, Tzannis ST. mTORC1-selective inhibitors rescue cellular phenotypes in TSC iPSC-derived neurons. *Front Neuroscience,* July 28, 2025; 19:1595880.

Location / People / Capital

Location: Berkeley, California
Website: https://www.aeovian.com/

Last Raise: Raised $50 million in 2024
($87mm total raised in Series A)
Employees: 5+

Leadership

Allison Hulme	Chief Executive Officer
John Kincaid	Chief Scientific Officer
Davis Ryman	Chief Medical Officer
Micah Zajic	Chief Financial Officer
Richard Gaster	Chairman / VenBio
Lars Ekman	Director / Sofinnova
Justin Gover	Director
Bill Greene	Director / Hevolution
Nils Regge	Director / Apollo

Investors

APOLLO HEALTH VENTURES
HEVOLUTION
SOFINNOVA INVESTMENTS
venBio

Aeternum Pharma

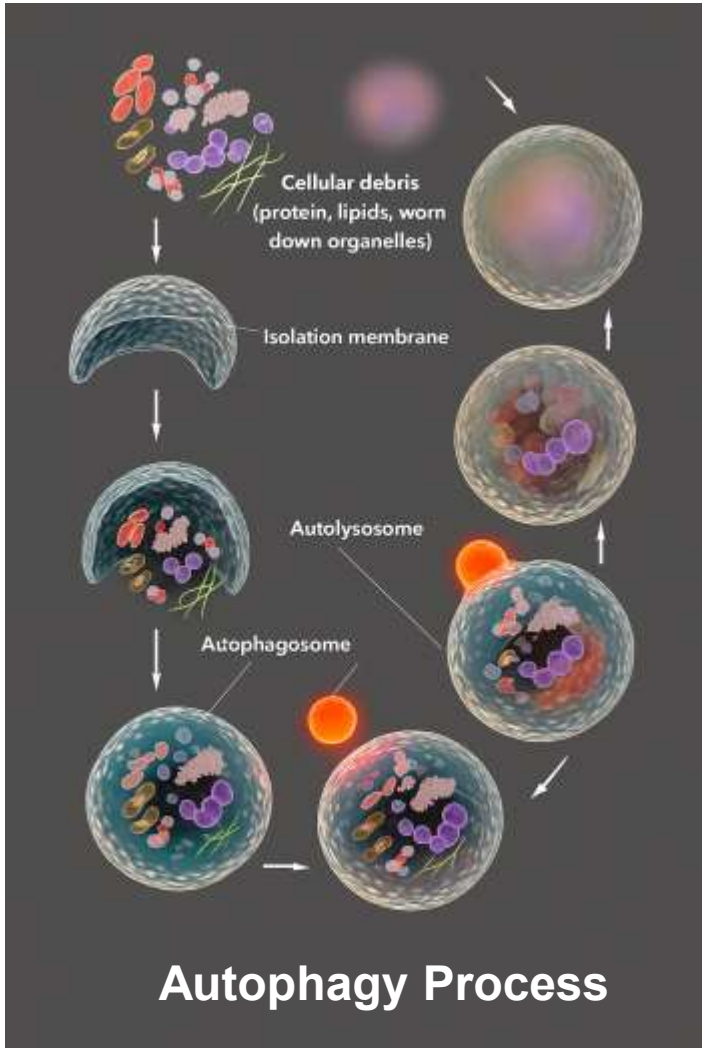
Company Overview

Aeternum Pharma is a privately held biotechnology platform company based in St. Louis, MO focused on discovering and developing novel autophagy-enhancing small-molecule drugs to treat neurodegenerative and age-related diseases.

Its scientific vision is rooted in the insight that autophagy — the cellular system responsible for degrading damaged proteins, lipids, and organelles — declines with age, contributing to disorders such as Huntington's, Parkinson's, Alzheimer's, and frontotemporal dementia. The company's founders, David H. Perlmutter, MD (Executive Vice Chancellor and Dean of the Washington University School of Medicine) and Gary A. Silverman, MD, PhD (Chair of Pediatrics, WashU), are internationally recognized leaders in autophagy research and high-throughput screening of protein-aggregation diseases.

At the core of Aeternum's discovery engine is its Autophagy-enhancing Caenorhabditis Elegans Screener (ACES) platform — a validated, automated in vivo system using fluorescent C. elegans models of misfolded α1-antitrypsin (ATZ) to identify compounds that clear protein aggregates. This platform has yielded several lead series, including LC-115, LC-603, LC-567, and LC-699, which have demonstrated activity in models of Huntington's, Parkinson's, Alzheimer's, and α1-antitrypsin deficiency. These compounds appear to enhance autophagy through activation of the TFEB (Transcription Factor EB) pathway, promoting lysosomal clearance of toxic proteins. In mice, orally administered LC analogs rapidly accumulate in the brain and liver at concentrations hundreds-fold above their IC_{50} values, and exhibit favorable pharmacokinetics, oral bioavailability, and safety margins.

Aeternum's lead program targets Huntington's disease as a first clinical "beachhead," leveraging clear mechanistic biomarkers — mononuclear cell huntingtin levels and neurofilament light chain (NfL) — to demonstrate proof of mechanism. The company plans to advance IND-enabling studies by 2025, supported by a $15 million fundraising initiative to finance translational research, lead optimization, and preclinical efficacy testing in additional CNS indications.



Company Overview

Altos Labs is a biotechnology company founded in 2022 with the mission to restore cell health and resilience through cellular rejuvenation. The company operates global research centers in the San Francisco Bay Area, San Diego, Cambridge (UK), and Japan. Its structure blends academic freedom with industrial precision, allowing scientists to explore the fundamental mechanisms of aging and regeneration while advancing discoveries toward therapeutic use.

The core scientific concept driving Altos Labs is "cellular rejuvenation programming"—a process that seeks to return aged or damaged cells to a younger, healthier state without erasing their identity. This strategy integrates stem-cell biology, epigenetics, computational biology, and regenerative medicine. The company has assembled an exceptional team of Nobel laureates, renowned scientists, and data-science experts who are mapping the molecular and transcriptional networks that govern cell health, resilience, and recovery from stress.

Altos Labs launched with roughly $3 billion in funding, making it one of the most well-capitalized ventures in the history of biotechnology. Its initial focus is on understanding and reversing the molecular damage of aging rather than rushing products to market. The long-term vision is to transform medicine by creating therapies that rejuvenate cells, repair tissues, and extend the healthy human lifespan—turning the biology of resilience into a new frontier for disease prevention and longevity.

Publication(s)

Memczak S, Izpisua Belmonte JC, Graepel T., "Escaping ageing through Cell Annealing-a phenomenological model," *Cell Research,* August 2025;35(8):535-538.

Sahu SK, Reddy P, Lu J, Shao Y, Wang C, Tsuji M, Delicado EN, Rodriguez Esteban C, Belmonte JCI, "Targeted partial reprogramming of age-associated cell states improves markers of health in mouse models of aging," *Sci Translational Medicine* Sep 11, 2024; 16(764):eadg1777.

Location / People / Capital

Location: Redwood City, CA
Website: https://www.altoslabs.com/

Last Raise: Raised $3 billion in 2022 in a Series A
Employees: 585

Leadership

Hal Barron	Chief Executive Officer
Hans Bishop	President
Rick Klausner	Chief Scientific Advisor
Juan Carlos Belmonte	Founding Scientist
Dolo Diaz	SVP, Drug Discovery
Dan Elkes	SVP, Head of Inst of Tech
Hana El-Samad	SVP, Inst. Of Computation
Laurie Hill	General Counsel
Joan Mannick	Chief Medical Officer
Kevin Sin	CFO / CBO

Investors

ARCH VENTURE PARTNERS

Selected Recent Output from Altos Labs

Altos Labs has raised $3bn and has over 500 employees and has been running for roughly four years. There is a lot of curiosity as to what the company is up to given its resource base. Presumably, there have been some interesting discoveries that are kept confidential in order to avoid competition. Despite this, there has been some interesting output which is listed, in part, below.

Escaping ageing through Cell Annealing—a phenomenological model

Sebastian Memczak[1], Juan Carlos Izpisua Belmonte[1] and Thore Graepel[2]
[1]Altos Labs San Diego, Institute of Science, San Diego, USA. [2]Altos Labs Cambridge, Institute of Computation, Cambridge, UK.
email: smemczak@altoslabs.com

Cell Research, July 8, 2025

Cellular rejuvenation shows great promise for treating age-related diseases and disabilities. However, the underlying molecular mechanisms and how and where information for youthful, healthy cells might be stored remain poorly understood. This is largely due to the complexity of ageing which involves numerous molecular modalities, their interactions, and a wide array of phenotypes, making it challenging to model or even conceptualise these processes. Here, we introduce “Cell Annealing”, a phenomenological model that builds on the Waddington Landscape and features of Hopfield Networks. It provides a novel perspective on ageing, aims to deepen our understanding of **cell state information storage and retrieval, and offers a framework for cell rejuvenation and therapeutic interventions.**

Inventor: Sanjeeb Kumar Sahu, Pradeep Reddy DUBBAKA VEN
Juan Carlos Izpisua Belmonte, Masakazu Kurita

Current Assignee : Altos Labs Inc

Targeted expression of regeneration factors in aged/senescent cells

WIPO Filing: Mar 28, 2025

Abstract

Provided are materials and methods for rejuvenating senescent cells. Senescent cells are transduced with a viral vector to express Oct4 and Sox2 proteins for partial cell reprogramming and/or to suppress a senescence-associated secretory phenotype. The materials and methods provided can be used to treat progeria syndrome, signs and symptoms of premature aging or natural aging or to rejuvenate tissue in subjects experiencing premature aging or having an agerelated disease.

This patent describes a two-transcription factor reprogramming process with 90 subclaims. Fairly detailed simplified approach to reprogramming is laid out.

BOOSTER THERAPEUTICS

Company Overview

Booster Therapeutics is a biotechnology company pioneering a new class of proteasome activator medicines to treat neurodegenerative and other diseases, launched with the support of a $15 million financing led by Apollo Health Ventures and Novo Holdings. The company is developing small molecule therapeutics that boost the innate activity of proteasomes to restore the body's ability to remove a wide range of disease-causing proteins. Proteasomes, the cell's natural quality control machinery, play a critical role in removing damaged or misfolded proteins. When proteasome function is impaired, misfolded proteins accumulate and increase the risk of serious disease as the buildup of toxic proteins overwhelms the cell's natural clearance mechanisms. Booster's approach is a departure from current targeted protein degradation methods, which tag single disease proteins with the marker protein ubiquitin, leading to their degradation via 26S proteasomes. This can be effective, particularly in diseases driven by a single errant protein. But complex diseases are often driven by multiple protein dysfunctions. To achieve more widespread degradation of unwanted proteins, Booster's compounds directly activate 20S proteasomes, which naturally recognize disordered proteins without the need for ubiquitin tagging.

Proteasomes, the cell's natural quality control machinery, play a critical role in removing damaged or misfolded proteins. When their function is impaired, misfolded proteins accumulate and increase the risk of serious disease. Booster's approach is a departure from current targeted protein degradation methods, which tag single disease proteins with the marker protein ubiquitin, leading to their degradation via 26S proteasomes. This can be effective, particularly in diseases driven by a single errant protein. But complex diseases are often driven by multiple protein dysfunctions. To achieve more widespread degradation of unwanted proteins, Booster's compounds directly activate 20S proteasomes, which naturally recognize disordered proteins without the need for ubiquitin tagging.

Booster is discovering small molecules through its DGRADX™ platform, which combines proprietary methods for automated high-throughput screening with advanced structural and computational tools. The company has built an extensive library of activator compounds with therapeutic potential and aims to develop a multi-disease pipeline to address proteinopathies.

Location / People / Capital

Location: Berlin, Germany
Website: https://www.boostertx.com/

Last Raise: Raised $15 million in 2024 (seed round)
Employees: 5+

Leadership

Diogo R. Feleciano	Chief Executive Officer
Emanuele Gabellieri	Head, Medicinal Chem.
Sonia Poll	Head, Translational Sci.
João Ribas	Chief Business Officer
Darci J. Trader	Co-Founder
Marianne E. Mertens	Managing Director

Investors and Strategic Partners

APOLLO HEALTH VENTURES

novo holdings

Calico

Company Overview

Calico Labs is a privately held research and development company founded in 2013 by former Genentech CEO Arthur Levinson with backing from Alphabet, dedicated to understanding the biology of aging and translating that knowledge into interventions that extend healthy lifespan. The company's style is to develop drugs by modulating age-related pathways such as IGF-1, ISR, IL-11 and the like. Calico operates as a hybrid between an academic institute and a biotech company: it houses over 350 scientists and leverages deep collaborations to pursue drug discovery across multiple age-related domains.

Calico apparently has recently exited a collaboration with AbbVie. However, details have not been released. Calico's internal research programs have produced dozens of high-impact publications in journals such as Nature, Cell, and Science, detailing new insights into proteostasis, senescence, mitochondrial function, DNA damage response, and immune aging. The company has advanced several therapeutic candidates into Phase 1 and Phase 2 studies, including small molecules designed to modulate protein homeostasis and inflammation in neurodegenerative and fibrotic disorders. Beyond drug candidates, Calico has built powerful multi-omics, computational, and model-organism platforms—spanning *C. elegans*, *Drosophila*, mice, and primates—to map how molecular aging trajectories differ between species and to identify tractable intervention points.

Pipeline

Therapy	*MOA*	*Stage*	*Indication*
Fosigotifator (Abbvie)	eIF2B (ISR)	Phase 1b/2	Vanishing White Matter
ABBV-CLS-484 (AbbVie)	PTPN2	Phase 1	Solid Tumors
ABBV-CLS-628 (AbbVie)	PAPP-A mAb	Phase 2	ADPKD
9MW3811	IL-11 mAb	Phase 1	Age-Related

Publication(s)

Many. See https://www.calicolabs.com/publications/ for details.

Location / People / Capital

Location: South San Francisco, California
Website: https://www.calicolabs.com/

Last Raise: Has raised $2.5 billion in committed funding
Employees: 335

Leadership

Arthur Levinson	CEO
Michael Lenardo	CSO
Jonathan Lewis	CBO
John Whiting	CFO
Cynthia Kenyon	VP, Aging Research
Matt Onsum	Head, Computational Sci
Karen Rolfes	Head, HR
Jonathan Powell	Head, Development
Robert Cohen	Calico Fellow
Dan Eaton	Head Discovery Tech
Philip Kym	Head Drug Discovery

Investors

Alphabet

Rationale for Calico Program in Polycystic Kidney Disease Pathology: IGF-A Aging Pathway Plays a Decisive Role in ADPKD

Metalloproteinase PAPP-A regulation of IGF-1 contributes to polycystic kidney disease pathogenesis

Sonu Kashyap,[1] Kyaw Zaw Hein,[1] Claudia C.S. Chini,[1] Jorgo Lika,[1] Gina M. Warner,[1] Laurie K. Bale,[2] Vicente E. Torres,[3] Peter C. Harris,[3] Claus Oxvig,[4] Cheryl A. Conover,[2] and Eduardo N. Chini[1]

[1]Department of Anesthesiology and Robert and Arlene Kogod Center on Aging, [2]Division of Endocrinology and Metabolism, Endocrine Research Unit, Mayo Clinic, Rochester, Minnesota, USA. [3]Division of Nephrology and Hypertension and Robert M. and Billie Kelley Pirnie Translational PKD Center, Rochester, Minnesota, USA. [4]Department of Molecular Biology and Genetics, Aarhus University, Aarhus, Denmark.

JCI Insight. 2020 Feb 27;5(4):e135700.

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of end-stage renal disease (ESRD). The treatment options for ADPKD are limited. We observed an upregulation in several IGF-1 pathway genes in the kidney of *Pkd1*$^{RC/RC}$ mice, a model of ADPKD. Pregnancy-associated plasma protein A (PAPP-A), a metalloproteinase that cleaves inhibitory IGF binding proteins (IGFBPs), increasing the local bioactivity of IGF-1, was highly induced in the kidney of ADPKD mice. PAPP-A levels were high in cystic fluid and kidneys of humans with ADPKD. Our studies further showed that PAPP-A transcription in ADPKD was mainly regulated through the cAMP/CREB/CBP/p300 pathway. *Pappa* deficiency effectively inhibited the development of cysts in the *Pkd1*$^{RC/RC}$ mice. The role of PAPP-A in cystic disease appears to be regulation of the IGF-1 pathway and cellular proliferation in the kidney. Finally, preclinical studies demonstrated that treatment with a monoclonal antibody that blocks the proteolytic activity of PAPP-A against IGFBP4 ameliorated ADPKD cystic disease in vivo in *Pkd1*$^{RC/RC}$ mice and ex vivo in embryonic kidneys. These data indicated that the PAPP-A/IGF-1 pathway plays an important role in the growth and expansion of cysts in ADPKD. Our findings introduce a therapeutic strategy for ADPKD that involves the inhibition of PAPP-A.

October 2, 2025

Calico Life Sciences Announces U.S. FDA Fast Track Designation for Investigational Treatment of Autosomal Dominant Polycystic Kidney Disease

ABBV-CLS-628, an investigational human monoclonal antibody designed to inhibit PAPP-A activity, is being evaluated for the treatment of ADPKD. ABBV-CLS-628 has completed a Phase 1 study in healthy volunteers (ACTRN12622001550796) in which it was shown to be safe and well tolerated with no significant adverse events reported to be associated with the drug.

The ongoing Phase 2 study (NCT06902558) is now enrolling across approximately 95 sites globally. Participants receive intravenous ABBV-CLS-628 or placebo every 4 weeks for 92 weeks, with safety follow-up for up to 15 weeks. This study is designed to evaluate the safety, tolerability, and potential efficacy of ABBV-CLS-628 in slowing disease progression in ADPKD.

Sources: https://www.calicolabs.com/press/calico-life-sciences-announces-u-s-fda-fast-track-designation-for-investigational-treatment-of-autosomal-dominant-polycystic-kidney-disease/, https://insight.jci.org/articles/view/135700

Cambrian

Company Overview

Cambrian Bio is a next-generation biotechnology company focused on extending human healthspan by developing therapies that repair or prevent cellular damage underlying age-related diseases. Cambrian has attracted strong investor interest since emerging from stealth in 2021, when it raised $60 million in seed financing, followed by a $100 million Series C round later that year. Its hub-and-spoke model combines elements of a biotech company, venture fund, and incubator—creating and funding multiple semi-independent "daughter" companies built around novel mechanisms of aging. This structure allows Cambrian to diversify risk while pursuing multiple therapeutic strategies in parallel. The company's guiding philosophy is that aging itself is the root cause of chronic disease, and that medicine must evolve from reactive treatment to proactive maintenance of cellular integrity. Cambrian's programs aim to address different forms of biological deterioration—metabolic, immune, mitochondrial, and proteostatic—before clinical disease emerges. Its portfolio spans obesity, respiratory, oncology, and immunology indications, unified by the goal of reversing or slowing the molecular damage that accumulates with time. Among Cambrian's eight pipeline companies, Amplifier Therapeutics and Tornado Therapeutics are the most advanced. Amplifier's lead candidate, ATX-304, is a small-molecule activator of AMPK and mitochondrial metabolism designed for cardiometabolic disease prevention; it is currently in a Phase 1b trial in overweight and pre-diabetic participants in Europe. Tornado, launched in 2022, is developing TOR-101, a selective mTOR inhibitor aimed at respiratory infections and potentially broader anti-aging applications. It recently launched Telos Therapeutics focused on short telomeres.

Pipeline

Therapy / Portfolio Company	*MOA*	*Stage*	*Indication*
ATX-304 (Amplifier Tx)	pan-AMPK activator	Phase 1b	Obesity / Prediabetes
TOR-101 (Tornado Tx)	TORC1 inhibitor	Preclinical	Respiratory Infections
TOR-103 (Tornado Tx)	TORC1 inhibitor	Preclinical	Oncology / Respiratory
IST-101 (Isterian)	TG2 inhibitor	Preclinical	IPF
VTA-400 (Vita)	Allogeneic Cell	Preclinical	FSHD

Location / People / Capital

Location: New York, NY
Website: https://www.cambrianbio.com/

Last Raise: $100mm. Has raised $160 million
Employees: 28 (LinkedIn)

Leadership

James Peyer	Chief Executive Officer
Ying Li	VP, Operations
Juliette Han	CFO/COO
Mark Nuttall	Chief Business Officer
Eric Schneider	VP, BD & Strategy
Ruth Thieroff-Ekerdt	EVP, Clinical Development

Investors and Strategic Partners

ANTHOS
APEIRON INVESTMENT GROUP
CATALIO CAPITAL MANAGEMENT
galaxy
SALT
FUTURE VENTURES
MOORE CAPITAL MANAGEMENT, LP

CELLJEVITY

Company Overview

Celljevity is a biotechnology company developing autologous epigenetic cell therapies designed to reverse biological aging and restore tissue function. Its core approach involves taking a small skin sample from a patient, reprogramming the cells in the lab by partially resetting their epigenetic clock, and reinfusing them through an IV drip.

This process is carried out in a clinic in China led by Dr. Yi Eve Sun, an accomplished stem-cell researcher formerly at Harvard and UCLA. Anecdotal results in some patients have been impressive. This process uses small-molecule modulation of transcripts related to pathways such as Wnt, Hedgehog and TGF-β to restore youthful cellular behavior without reverting cells to a risky pluripotent state. The result is a patient's own multipotent repair cells, capable of regenerating cartilage, bone, muscle, and blood vessels while avoiding the immune rejection and tumor risks of donor or pluripotent stem cells.

The company combines this biological approach with advanced analytics and personalized care. It operates a growing network of high-end regenerative clinics in Europe and the MidEast offering individualized rejuvenation treatments that integrate molecular biomarkers, imaging data, and AI-driven health monitoring. Celljevity reports encouraging early data from more than a thousand infusions, suggesting improvements in cellular function, telomere length, and tissue regeneration in conditions such as osteoarthritis, osteoporosis, and neurodegeneration. Its leadership team brings together expertise in regenerative biology, single-cell omics, and translational neuroscience.

By positioning itself at the intersection of longevity medicine, regenerative therapy, and digital health, Celljevity aims to redefine aging as a treatable biological process rather than an inevitable decline. Its strategy reflects a blend of frontier science and precision medicine, supported by emerging partnerships and validation studies intended to secure clinical credibility.

While the approach remains in the investigational stage, the company's early traction, scientific ambition, and integration of autologous cell therapy with data-driven health optimization mark it as a visionary entrant in the growing longevity field.

Location / People / Capital

Location: Antibes, France
Website: https://celljevity.life/

Employees: 10+
Funds Raised: Not disclosed

Leadership

Diederik van der Reijt	Chief Executive Officer
Digvijay Gahtory	Chief Business Officer
Henk Viëtor	Chief Medical Officer
David Maman	Chief Operational Officer
Christopher Juel-Jensen	Chief Integration Officer
Dan Fobes	Chief Technology Officer

Investors and Strategic Partners

REVEFJES

MPG

Lin Dayen-Hsu

clock.bio

Company Overview

Clock.bio is a biotechnology company focused on reversing cellular aging by decoding and targeting the genetic networks that control rejuvenation. Their strategy integrates genomics, AI, and cell biology into a platform that systematically identifies and validates genes and pathways that impact biological age in human cells. The company's founder, Mark Kotter is a serial entrepreneur with some good companies under his belt and a Professor at Cambridge University.

Clock goes far beyond the initial work of Yamanaka, focused on fully mapping all genes which regulate cell age. The company has built an Atlas of Rejuvenation Factors, identifying 151 genetic regulators across the genome. These regulators are clustered in core pathways such as autophagy, metabolism, RNA processing, and epigenetic remodeling, linking directly to hallmarks of aging and multiple age-related diseases.

At the center of their preclinical work is the imAgeScore platform, an AI-powered system that quantifies cellular age from imaging data. By training on known interventions that accelerate or reverse aging, imAgeScore predicts the biological impact of drugs or genetic changes with high accuracy, correlating strongly with established epigenetic clocks. This enables scalable, phenotypic screening in human somatic cells—allowing virtually any compound to be tested for its rejuvenating potential. The technology provides a bridge between molecular targets and measurable improvements in cellular function.

Clock.bio's third pillar, clinAge, aims to accelerate translation of rejuvenation discoveries into human applications. The platform is initially being tests on drug candidates using adaptive clinical trial models. The company's initial focus on skin rejuvenation topicals. This will allow it to move quickly, generate human data, and demonstrate measurable reversal of biological age. Equipped with new data in neurodegeneration it has initiated its first clinical development programs.

By linking genetic discovery, phenotypic validation, and rapid clinical translation, clock.bio positions itself as a full-stack rejuvenation engine—one designed to move anti-aging science from the lab to early human benefit efficiently and systematically.

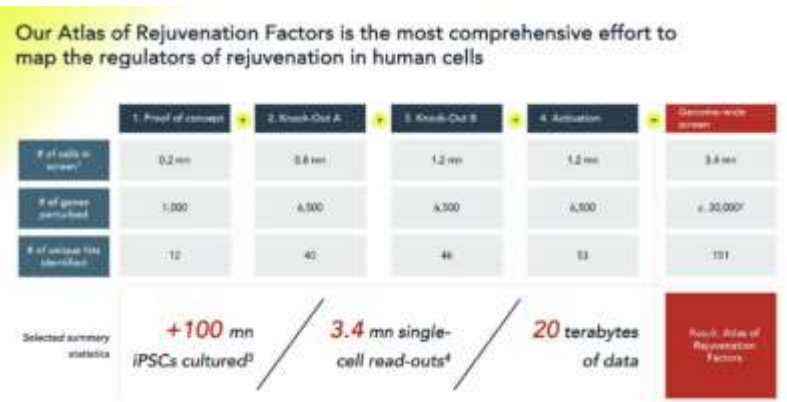
Location / People / Capital

Location: Cambridge, UK
Website: https://www.clock.bio/

Last Raise: $8.5mm.
Employees: 11

Leadership

Markus Gstöttner	Chief Executive Officer
Michael Boehler	Chief Business Officer
Mark Kotter	Executive Chairman
Mary Vinson	Chief Development Officer
Rodrigo Santos	Chief Technology Officer
Koby Baranes	Head of Science
Joana Tavares	Head of Target Validation
Fabio D'Orazio	Head of Informatics
Jack Brelstaff	Senior Scientist



DECIDUOUS THERAPEUTICS

Company Overview

Deciduous is a privately held biotech based in the Bay Area spun out of UCSF that is developing small-molecule immunotherapies that reactivate a built-in immune surveillance program to clear senescent cells and treat age-related disease. Rather than killing these cells directly with "senolytic" drugs, they prime an innate-like T-cell population (invariant Natural Killer T cells, iNKT) to find and remove them. The company holds at least two patent filings regarding small molecules for the activation of iNKT's to eliminate inflammatory senescent cells. Although conventional NK cells can kill senescent cells, Deciduous' published and public materials focus on iNKT cells, a distinct lymphocyte that recognizes lipid antigens presented by CD1d. Activating iNKT cells has been shown to reduce senescent-cell burden and improve pathology in mice.

In healthy tissues, iNKT cells patrol for abnormal lipid signatures; with age and metabolic stress, this surveillance wanes. Deciduous aims to pharmacologically activate iNKT cells (via lipid-antigen/CD1d signaling) so they selectively eliminate pathologic senescent cells and then return to quiescence—offering a potentially self-limiting, systemic approach.

Pipeline

Therapy	*MOA*	*Stage*	*Indication*
iNKT Cell Therapeutic	Senolytic	Preclinical	Human Aging

Publication(s)

Arora S, Thompson PJ, Wang Y, Bhattacharyya A, Apostolopoulou H, Hatano R, Naikawadi RP, Shah A, Wolters PJ, Koliwad S, Bhattacharya M, Bhushan A., "Invariant Natural Killer T cells coordinate removal of senescent cells," *Med.* Aug 13, 2021;2(8):938-950.

Location / People / Capital

Location: San Francisco, California (MBC Biolabs)
Website: https://www.deciduoustx.com/

Last Raise: $6 million in 2019 (seed round)
Employees: 2+

Leadership

Robin Mansukhani	CEO
Leah Makley	Operations Lead
Anil Bhushan (UCSF)	Scientific Founder

Scientific and clinical advisors include leaders in iNKT biology such as Mitchell Kronenberg, PhD, Steven Porcelli, MD, and others.

Investors

THE LONGEVITY FUND · BOLD CAPITAL PARTNERS · crv · FORMIC VENTURES · global brain · age1

genflow biosciences
longer better life

Company Overview

Genflow Biosciences is a publicly traded UK-based biotechnology company founded in 2020, headquartered in London, with research and development facilities in Belgium. Genflow specializes in developing gene therapy and biologic interventions that target the upstream biology of aging, rather than solely treating individual age-related diseases. Their core technology centers around a centenarian variant of the SIRT6 gene—an isoform identified in long-lived individuals—which the company aims to leverage in both human and veterinary settings to enhance repair, metabolic resilience, and tissue homeostasis.

Genflow's pipeline is still in the pre-clinical stage and spans multiple programs including a lead human gene therapy candidate (GF-1002) for metabolic dysfunction-associated steatohepatitis (MASH), a veterinary counterpart for aging dogs (GF-1004), and future indications in muscle aging (sarcopenia) and ophthalmology using non-viral or mRNA-based delivery of the SIRT6 variant. The company's pipeline includes a program for MASH and companion-animal indications (aged dogs) to extend healthspan.

Pipeline

Therapy	*MOA*	*Stage*	*Indication*
GF-1002	SIRT6 gene therapy	Preclinical	MASH
GF-1003	SIRT6 topical	Preclinical	Werner Syndrome
GF-1004	SIRT6 gene therapy	Phase 1	Aging in dogs

Publication(s)

Tian X et al. "SIRT6 Is Responsible for More Efficient DNA Double-Strand Break Repair in Long-Lived Species," *Cell,* April 18, 2019; 177(3):622-638.e22.

Mao Z et al., "SIRT6 promotes DNA repair under stress by activating PARP1," *Science*, June 17, 2011; 332(6036)

Location / People / Capital

Location: London UK and Belgium
Website: https://genflowbio.com/

Last Raise: $5 million in 2022 (IPO)
Other: Raised $8 million in Belgian grant funding

Leadership

Eric Leire	Chief Executive Officer
Cedric Szpirer	Head of CMC
Tamara Joseph	Board Chair
Guy Fanneau de la Horie	Director
Peter King-Lewis	Director
Yassine Bendiabdallah	Director

Key Metrics

Ticker:	LSE: GENF
Market Capitalization:	$12.7mm
Employees:	2+

Company Overview

Life Bio's lead program is a gene therapy called ER-100,which allows for expression of three transcription factors, Oct-4, Sox-2, and Klf-4 ("OSK"), which induces partial epigenetic reprogramming to modify the epigenome of cells. These are three of the four Yamanaka Factors.

By targeting a root cause of aging at the epigenetic level, this approach offers the potential to address a wide range of age-related diseases across organs and systems.

Life is evaluating ER-100 in two optic neuropathies, non-arteritic anterior ischemic optic neuropathy (NAION) and primary open angle glaucoma (POAG), with plans to initiate the first human clinical studies in the second half of 2025. Life Biosciences is exploring the potential of our partial epigenetic reprogramming platform in additional age-related indications. Each additional indication pursued is based on evidence of epigenetic changes in an age-related disease that impacts healthspan.

Pipeline

Therapy	*MOA*	*Stage*	*Indication*
ER-100	AAV Partial Reprogramming	Preclinical	Glaucoma
ER-300	AAV Partial Reprogramming	Preclinical	MASH

Publication(s)

Lu Y et.al, "Reprogramming to recover youthful epigenetic information and restore vision," *Nature*, Dec 2020; 588(7836):124-129.

J.H. Yang et al., "Loss of epigenetic information as a cause of mammalian aging," *Cell,* Feb 29, 2024;187(5):1312-1313.

Location / People / Capital

Location: Boston, MA
Website: https://www.lifebiosciences.com/

Last Raise: $82mm in 2021 (approx. $150 raised)
Employees: 2+

Leadership

Jerry McLaughlin	Chief Executive Officer
Michael Ringer	Chief Operating Officer
Sharon Rozenzweig-Lipson	Chief Scientific Officer
Amit Shashank	Chief Administrative Officer
Michael Wathier	SVP, CMC

Investors

Abundance Partners LLC
Alpha Wave
Hybridge Capital Management
IMO Ventures

LinkGevity

Company Overview

LinkGevity is a biotechnology company with a mission to bring about systemic healthspan regeneration. The company has developed drugs that block the cellular necrosis process implicated in aging, organ failure, and chronic disease. The company's science originated at the Babraham Research Campus, Cambridge, UK, where researchers identified a calcium-driven molecular pathway responsible for necrotic cell death and mapped key potential druggable targets to it.

Using AI-driven cheminformatics, literature mining, and high-throughput complex human organoid screening, LinkGevity discovered first-in-class dual-target necrosis inhibitors. Preclinical data demonstrated up to 90% inhibition of necrosis without toxicity, enabling tissue regeneration. Its lead program uses kidney disease as the first indication because the kidney ages more rapidly and shares core aging mechanisms with other organs., providing a scientifically grounded path to secure the first regulatory approval for an aging drug.

Extensive studies have demonstrated the anti-necrotic's ability to protect cells across the body under inflammatory, oxidative, and ischemic stress. Preclinical in vivo models developed with leading experts in nephrology and regenerative medicine from Harvard, the Mayo Clinic, and Imperial College London demonstrated the compound's ability for near complete re-instatement of kidney function, with no observed adverse events.

Publications

See https://www.linkgevity.com/news for details.

Pipeline

Program	Indication	Discovery	Hit validation	Lead identification	Lead optimisation	Preclinical & safety studies	Phase 2 clinical trial	Phase 3 clinical trial
LINK-001	Kidney Disease	Preclinical studies completed						
LINK-001	Approval for Ageing	Preclinical studies completed						
LINK-004	Undisclosed	Discovery Phase						

Location / People / Capital

Location: Cambridge, UK
Website:
https://www.linkgevity.com/
Employees: 7+
CRO/Subcontractors: 30+

Leadership

Carina Kern	Chief Executive Officer
Serena Kern-Libera	Chief Operating Officer
Greg Jarzabek	Chief Financial Officer
Lukasz Rzeczkowski	Chief Commercial Officer
Nikodem Grzesiak	Chief Technology Officer
Bill Davis	Chief R&D Officer

Investors and Backers

Rationale for LinkGevity Program in Kidney Disease: A model to gain regulatory approval as the first drug for aging

The kidney ages faster than other organs and mirrors universal aging pathways, providing a clear, well-understood mechanism and an indication where clinical trials can be completed in under two years—making kidney disease the optimal first path to regulatory approval for an aging-targeted drug. This has drawn global attention, including the anti-necrotic being selected as one of only 12 global innovations for the NASA Space-Health Program, as well as funding from the UK Space Agency to take the anti-necrotic into space for its potential to counteract astronaut degeneration during long-duration missions.

nature › oncogene ›

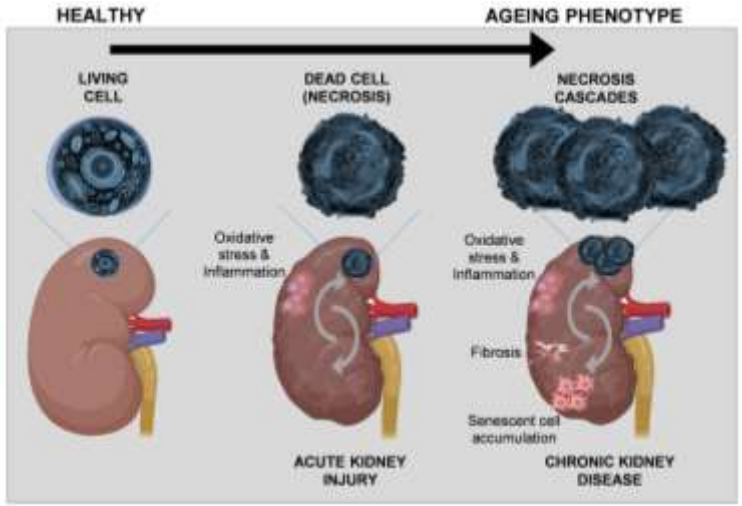
Necrosis as a fundamental driver of loss of resilience and biological decline: what if we could intervene?

Carina Kern, Joseph V. Bonventre, Alexander W. Justin, Kianoush Kashani, Elizabeth Reynolds, Keith Siew, Bill Davis, Halime Karakoy, Nikodem Grzesiak & Damian Miles Bailey

LinkGevity, Babraham Research Campus, Cambridge, UK; Division of Renal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; Harvard Stem Cell Institute, Harvard, Boston, MA, USA; Harvard-MIT Health Sciences and Technology, Cambridge, MA; MRC Laboratory of Molecular Biology, Cambridge Biomedical Campus, Cambridge, UK; Division of Nephrology and Hypertension, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Rochester, MN, USA; Starburst Aerospace, USA; NASA Human Research Program, Microsoft and Translational Research Institute for Space Health Space-H Program, USA; London Tubular Centre, Royal Free Hospital, London, UK; UCL Centre for Kidney and Bladder Health, University College London, London, UK; Neurovascular Research Laboratory, Faculty of Life Sciences and Education, University of South Wales, Pontypridd, UK; Bexorg Inc, New Haven, CT, USA; Life Sciences Working Group, European Space Agency

Abstract

Necrosis is uncontrolled cell death that marks the irreversible threshold of biological degeneration. Rooted in the Greek *nekros* (death), it is a pivotal mechanism underlying numerous diseases, including cancer, as well as renal, cardiac, neuronal, and hepatic disorders, and more broadly, the aging process. Despite its profound impact on morbidity and mortality, necrosis remains untreatable and has long been viewed as a chaotic, unavoidable aspect of biology. This review examines the mechanisms of necrosis and outlines its far-reaching impact on health, as revealed by emerging evidence. Furthermore, we explore its potential as a game-changing therapeutic target. Inhibiting necrosis could revolutionize treatments for acute and chronic age-related conditions like cancer, kidney disease, cardiovascular disease (including heart attacks and strokes), and neurodegeneration, while also preserving resilience—and even slowing aging itself. Beyond Earth, where microgravity, cosmic radiation, and oxidative stress accelerate cellular decline, targeting necrosis may also hold the key to preserving astronaut resilience and health on long-duration space missions, offering insights that could reshape human longevity both on and off the planet.



BJCP British Journal of Clinical Pharmacology

Beyond GLP-1s: The blueprint for systemic therapeutics that will reshape aging and medicine

Carina C. Kern, Annalisa Jenkins, D. Nageshwar Reddy, Bill Davis, Nikodem Grzesiak, Richard Faragher, Tina Woods, John Ayrton, Justin Stebbing

"Necrosis represents a central node within the network of degeneration: once triggered, it unleashes damaging cascades. Unlike beneficial programmed cell death, which follows tightly regulated genetic programs, necrosis is unregulated, pathological and initiated by cellular damage.

Various intrinsic and/or extrinsic stressors—including oxidative stress, metabolic stress, ischemia and lipotoxicity—can converge to induce necrosis, even within the same tissue."

"At the tissue level, necrotic cells release harmful intracellular contents, including DAMPs and proteases, in an uncontrolled manner. This promotes further necrosis, chronic inflammation, senescent cell accumulation and fibrosis."

Sources: https://www.nature.com/articles/s41388-025-03431-y;

https://bpspubs.onlinelibrary.wiley.com/doi/10.1002/bcp.70312

METROBIOTECH

Company Overview

Metro International Biotech is a privately-owned clinical-stage pharmaceutical company advancing a leading portfolio of proprietary NAD+ precursors. As NAD+ levels decline with age, restoring them offers broad therapeutic potential for health and metabolism. NAD+ levels have been shown to decline as humans age and research and preclinical models have demonstrated the broad therapeutic potential of increasing NAD+ to preserve health and normal metabolism. MetroBiotech's platform focuses on restoring and sustaining NAD+ levels, a critical cofactor for mitochondrial function, gene regulation, and cellular resilience. Early human trials demonstrated up to 200% increase in NAD+ levels within 14 days, without any drug-related serious adverse events (SAEs). Metro's lead drug candidate, MIB-626, is a novel, patented crystalline NAD+ booster with scalable manufacturing capabilities. It is currently in three Phase 2 clinical trials for Alzheimer's disease, chronic kidney disease, and muscle strength and endurance.

Pipeline

Therapy	*MOA*	*Stage*	*Indication*
MIB-626	NAD+ Potentiator	Phase 2	Diabetic Kidney Disease
MIB-626	NAD+ Potentiator	Phase 2a	Muscle Endurance
MIB-626	NAD+ Potentiator	Phase 1b	Friedrich's Ataxia
MIB-626	NAD+ Potentiator	Phase 2	Alzheimer's Disease
MID-725	NAD+ Potentiator	Phase 1	Cardiorenal Diseases

Publication(s)

Pencina KM, et.al, "Oral MIB-626 (β Nicotinamide Mononucleotide) Safely Raises Blood Nicotinamide Adenine Dinucleotide Levels in Hospitalized Patients With COVID-19 and Acute Kidney Injury: A Randomized Controlled Trial," *FASEB BioAdvances,* Jun 18, 2025; 7(8): 1-11.

Pencina KM, et.al, "Nicotinamide Adenine Dinucleotide Augmentation in Overweight or Obese Middle-Aged and Older Adults: A Physiologic Study," *J Clin Endocrinol Metab.* Jul 14, 2023;108(8):1968-1980.

Location / People / Capital

Location: Worcester, MA
Website: https://www.metrobiotech.com/

Raises: $250 million+
Employees: 25+

Leadership

Edward Schulak	Chairman
David J. Livingston, MBA, PhD	CEO
David B. Pryor, MD	CMO
Bruce Szczepankiewicz, PhD	VP Chem

Advisors include Rajendra Apte, Johan Auwerx, James Ellis, Nick Lane, Jeffrey Lieberman, David Sinclair, Li-Huei Tsai, Lindsay Wu

Investors

MetroBiotech has raised substantial capital from high net worth individuals including a number of major European family offices.

NewLimit

Company Overview

NewLimit is a biotechnology company dedicated to extending human healthspan by reversing the molecular and cellular effects of aging. Founded with the vision of tackling the root causes of biological aging, its goal is not just to treat individual diseases but to restore youthful function across tissues and organs. The company views age-related decline as a process that can be measured, modeled, and ultimately modified — aiming to make humans live longer, healthier lives by reprogramming how cells behave rather than by managing symptoms of disease.

The scientific foundation of NewLimit lies in the idea that much of aging is encoded in the epigenome — the system of gene regulation that determines which genes are active or silent in each cell. By identifying the molecular changes that distinguish young and old cells, the company hopes to "reset" aged cells without changing their identity.

Using high-throughput single-cell sequencing, computational modeling, and machine-learning tools, NewLimit maps how transcription factors and chromatin states change over time. These insights are then used to design therapeutic interventions that restore a youthful gene-expression program.

In practical terms, NewLimit's research centers on discovering combinations of transcription factors and regulatory molecules that can rejuvenate specific cell types. Early focus areas include hepatocytes in the liver, T cells in the immune system, and vascular cells that line blood vessels — all tissues that play major roles in the systemic effects of aging. The company employs mRNA-based delivery systems and other emerging modalities to introduce these rejuvenating factors into cells.

Location / People / Capital

Location: South San Francisco, CA
Website: https://www.newlimit.com/

Last Raise: Raised $130mm, Series B
Employees: 43 (LinkedIn)

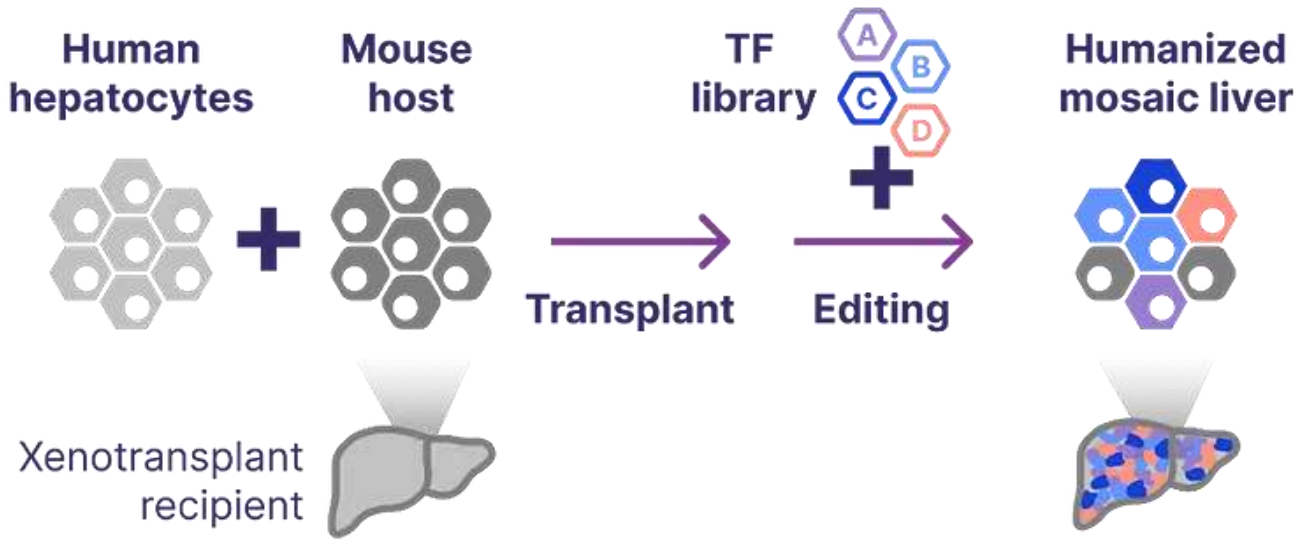
Leadership

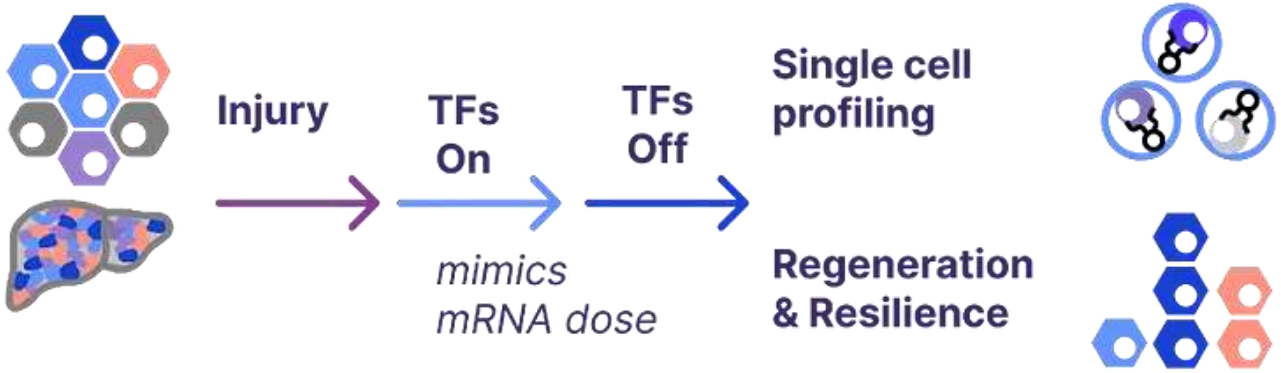
Brian Armstrong	Chief Executive Officer
Blake Byers	Co-Founder
Cathy O'Hare	Head of Operations
Jacob Kimmel	President

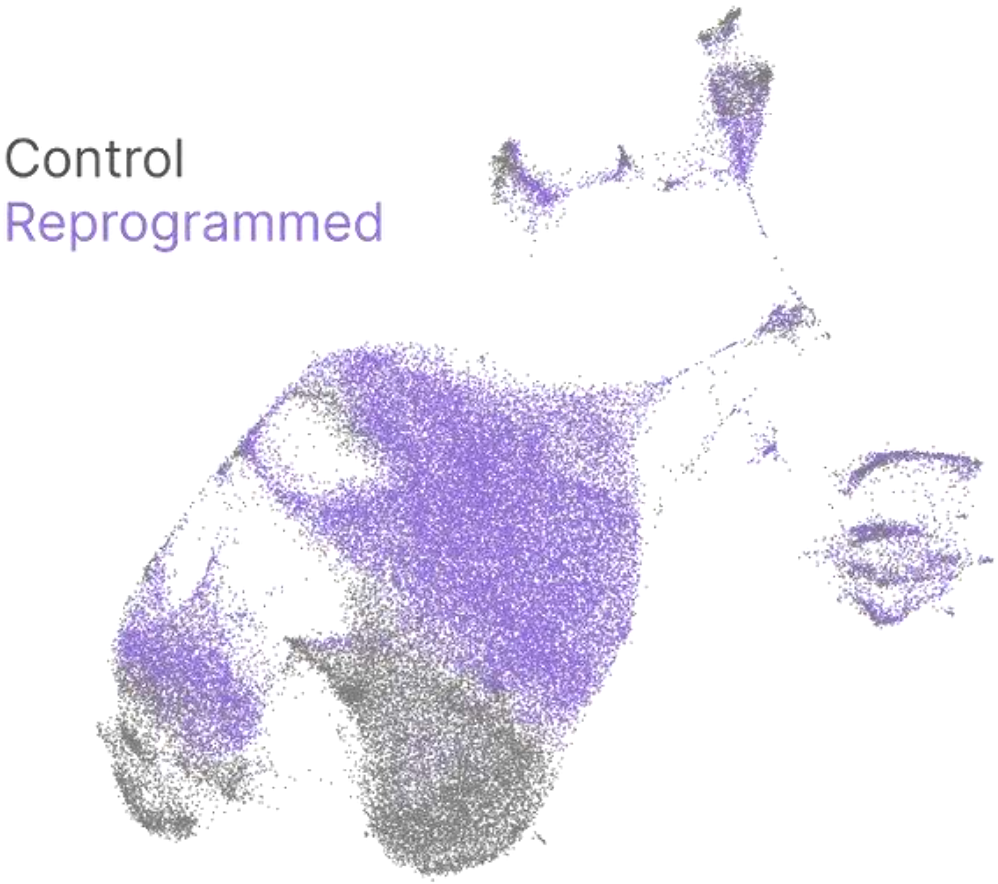
Investors

DIMENSION
Lilly
FOUNDERS FUND
khosla ventures
VALOR EQUITY PARTNERS
KLEINER PERKINS

NewLimit Focused on Delivering Reprogrammed Cells to the Liver







Niagen. BIOSCIENCE

Company Overview

Niagen Bioscience is a Los Angeles–based bioscience company focused on technologies that elevate cellular NAD^+, a coenzyme essential to mitochondrial function, metabolism, DNA repair, and cellular resilience. Niagen is an unusual aging therapeutics company in that it is generating solid revenue and growth, posting $34mm in revenue for Q3 2025.

Its patented NAD^+ precursor nicotinamide riboside (NR) — branded Niagen® — has provided the foundation for its evolution into a longevity-focused company.

Niagen operates through several interconnected business lines. Its consumer segment markets Tru Niagen®, a supplement designed to raise NAD^+ levels in humans, while its ingredient business supplies NR to a global network of third-party manufacturers.

It also maintains an analytical standards and services division that provides high-precision phytochemical reference materials — a legacy business that continues to generate diversified revenue. This multi-segment structure allows Niagen Bioscience to blend B2B and B2C models while anchoring its brand in clinically tested metabolic science.

Niagen's scientific strategy emphasizes NAD^+ replenishment as a means of counteracting the natural decline in mitochondrial efficiency and metabolic stability that accompanies aging. Through a combination of peer-reviewed studies, regulatory submissions, and international safety clearances, the company seeks to differentiate NR from more generic or unproven NAD^+ boosters. This science-driven positioning is designed to appeal both to consumers seeking healthy-aging solutions and to institutional partners evaluating metabolic interventions.

Location / People / Capital

Location: Los Angeles, CA
Website: https://www.niagenbioscience.com/
Employees: 43 (LinkedIn)

Leadership

Rob Fried	Chief Executive Officer
Ozan Pamir	Chief Financial Officer
Andrew Shao	SVP Regulatory/Science
Carlos Lopez	Chief Counsel

Key Metrics

Ticker:	NAGE
Market Capitalization:	$557mm
Revenue (LTM):	$124mm
EBITDA (LTM):	$20mm
Employees:	104

OMEICOS THERAPEUTICS

Company Overview

OMEICOS is a Berlin- and Boston-based clinical-stage biotech company developing first-in-class, fully synthetic analogues of omega-3 fatty-acid metabolites. Founded in 2013, the company has built a comprehensive IP estate extending to 2041. Its lead candidate, OMT-28, is a small-molecule, orally dosed modulator of S1PR1 that also activates SIRT1 and SIRT3, thereby improving mitochondrial function and reducing chronic inflammation. The molecule has demonstrated excellent safety and tolerability in more than 185 individuals, with clean chronic toxicity data, predictable pharmacokinetics, and low manufacturing cost. The first Phase II study in a typically aged population of atrial fibrillation patients showed significant reductions of IL-6, hsCRP and GDF-15 in GDF-15 high individuals. OMEICOS approach to mitochondrial disease obviously has potential for development in aging.

The company is advancing OMT-28 for Primary Mitochondrial Diseases (PMD)—a heterogeneous, multisystem group of rare genetic disorders with no approved pharmacologic therapies for most major subtypes. In the completed Phase 2a PMD-OPTION study (29 patients, multiple mtDNA mutation types), OMT-28 did not meet the GDF-15 biochemical endpoint but showed a strong safety profile and meaningful clinical improvements in functional measures such as the 12-Minute Walk Test and 5x Sit-to-Stand, particularly in a clearly identifiable responder subgroup. Responders exhibited significant increases in NAD+/NADH and GSH/GSSG ratios, tightly linking pharmacological activity to clinical benefit via enhanced mitochondrial metabolism and reduced oxidative stress. These biomarker and functional correlations provide a de-risked foundation for next-phase development.

OMEICOS plans a pivotal Phase 2b/3 trial starting in 2026, testing 160–200 PMD patients with myopathy and/or cardiomyopathy across EU and US sites.

Location / People / Capital

Location: Berlin, Germany
Website: https://omeicos.com/
Employees: 5+

Leadership

Robert Fischer	Chief Executive Officer
Simon Russell	Chief Business Officer
Hnk Streefkerk	Chief Medical Officer
Karen Uhlmann	VP Operations

Investors

REMIGES VENTURES

VESALIUS BIOCAPITAL

Forbion.

源生生物 ORISOMES BIOTECH

Company Overview

Orisomes Biotech (Qingdao) is a Chinese biotechnology company founded by Academicians Guangju Ji and Dan Zhang with the mission of reversing aging and treating age-related diseases through advanced cellular and nucleic acid technologies. Built on a foundation of mechanistic research, the company combines expertise in stem-cell biology, small-RNA therapeutics, and translational clinical development. Its work aims to overturn the traditional concept that cellular senescence is irreversible, instead demonstrating that senescent cells can be re-entered into the cell cycle and rejuvenated. The company maintains close collaborations with leading hospitals such as Peking Union Medical College Hospital and the PLA General Hospital.

Orisomes' leading candidate, OS110, is a microRNA-based therapy that reverses cellular senescence and restores youthful cell function. In preclinical studies, aged C57BL/6J mice treated with OS110 showed striking rejuvenation: smoother hair coats, improved motor function and cognition, and extended median lifespan from 28 to 33 months—an effect equivalent to roughly a 20 percent increase in human lifespan. Organ-level analysis revealed reversal of fibrosis, reduced inflammatory cytokines, and a sharp decline in senescence markers (SA-β-Gal) across tissues such as kidney, liver, skin, and brain. The company's broader pipeline includes exosome- and RNA-based therapeutics targeting pulmonary fibrosis and rare immune diseases (e.g., MDA5 syndrome), as well as consumer-facing anti-aging formulations and veterinary longevity applications.

Professor Guangju Ji is the leader from Orisomes and is an academician of the Chinese Academy of Sciences, has led major breakthroughs in stem-cell differentiation, disease signaling, and anti-aging research, with over 150 publications in journals such as Nature and Science and more than 35 patents.

Location / People / Capital

Location: Beijing, China
Employees: 30+

Leadership

Guangju Ji	Chief Executive Officer
Dan Zhang	Chief Operating Officer

Publications

Bi Y, Qiao X, Cai Z, Zhao H, Ye R, Liu Q, Gao L, Liu Y, Liang B, Liu Y, Zhang Y, Yang Z, Wu Y, Wang H, Jia W, Zeng C, Jia C, Wu H, Xue Y, Ji G. Exosomal miR-302b rejuvenates aging mice by reversing the proliferative arrest of senescent cells. *Cell Metab*. 2025 Feb 4;37(2):527-541.e6.

Li Z, Duan Y, Yan S, Zhang Y, Wu Y. The miR-302/367 cluster: Aging, inflammation, and cancer. *Cell Biochem Funct.* 2023 Oct;41(7):752-766.

REFOXY PHARMA

Company Overview

Refoxy Pharma is a privately held German biotechnology company founded in 2020 and headquartered in Cologne. Refoxy is a preclinical stage company developing small molecule activators of the FOXO3 transcription factor for the treatment of age-related diseases.

FOXO3 is a master regulator of cellular stress responses, longevity pathways, metabolism and tissue homeostasis. Foxo 3 is the most cited gene in relation to longer lifespan.

Refoxy's proprietary discovery platform (called "F.act finder" for "FOXO activator finder") is designed to identify and optimize drug-like compounds that selectively activate FOXO3, thereby influencing multiple downstream pathways implicated in age-related disease.

The company raised a €9.1 million seed-extension financing in 2024 led by Boehringer Ingelheim Venture Fund (BIVF), and joined by co-founding investor Apollo Health Ventures and other investors to advance the development of novel therapeutic medicines in diverse indications, starting with idiopathic pulmonary fibrosis (IPF).

The company's initial therapeutic focus is on idiopathic pulmonary fibrosis (IPF) and other age-associated fibrotic disorders, but its platform is designed to support expansion into multiple aging-related disease indications.

Location / People / Capital

Location: Cologne, Germany
Website: https://www.refoxy.com/

Last Raise: Raised €9.1 million in 2024 (seed round)
Employees: 2+

Leadership

Victor Bustos	Chief Executive Officer
Wolfgang Link	Scientific Co-Founder
Niklas Czeloth	Director / Boehringer
Anela Vukoja	Director / Apollo
Vera Mehler-de Graaff	Director / NRW

Investors

APOLLO HEALTH VENTURES
Boehringer Ingelheim
HTGF
NRW.Venture
Ein Fonds der NRW.BANK
KORIFY CAPITAL

REGERNA™ Therapeutics

Company Overview

Regerna Therapeutics is a next-generation regenerative-medicine biotech focused on restoring functional and endurant muscle in injury, aging, and muscle-wasting diseases. Its discovery platform centers on AUF1, a first-in-class mRNA-binding protein therapeutic that acts as a "master regulator" of muscle regeneration. AUF1 enhances satellite-cell proliferation, promotes myofiber growth and maturation, stimulates mitochondrial biogenesis, and accelerates neuromuscular re-innervation and vascularization.

The company's early pipeline targets high-value indications such as severe muscle injury, disuse atrophy, Duchenne and limb-girdle muscular dystrophies (DMD and LGMD), and ultimately sarcopenia and GLP-1–associated muscle loss.

Mechanistically, Regerna's AUF1 therapy replaces or supplements the declining endogenous protein that controls stability and translation of key muscle and mitochondrial mRNAs. In preclinical models, AUF1 supplementation blocked muscle atrophy, restored normal muscle strength, improved mitochondrial structure and endurance capacity, and achieved functional regeneration superior to micro-dystrophin or exon-skipping approaches. The company is advancing multiple formulations—AAV and lentiviral vectors for long-term systemic delivery, and lipid nanoparticles (LNPs) for local, repeatable mRNA delivery—allowing both chronic and acute applications and distinct pricing strategies per indication.

Publications

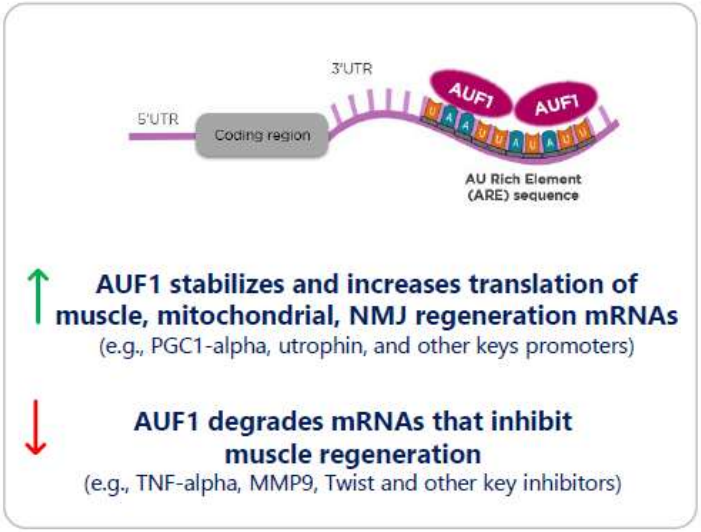
Abbadi, Dounia, "mRNA binding proteins join the longevity pipeline: Rebuilding muscle through the power of mRNA binding protein therapeutics," *Science,* April 4, 2025; 388(6742):41.

Location / People / Capital

Location: New York, NY
Employees: 3+

Leadership

Ken Moch	Chief Executive Officer
Robert Schneider	President
Dounia Abbadie	Chief Scientific Officer
Manisha Narasimhan	Senior Advisor



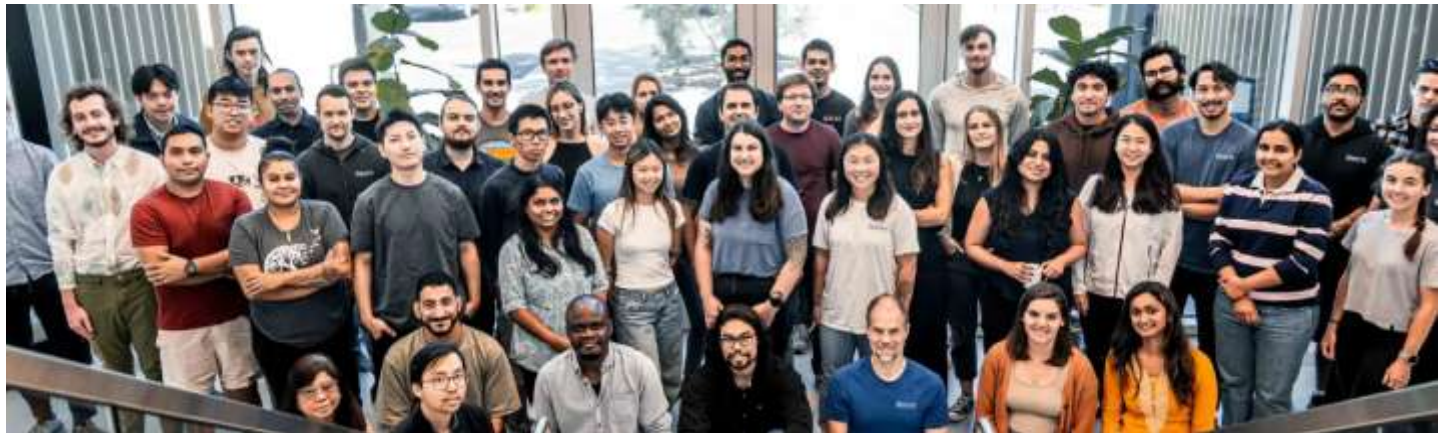
Company Overview

Retro Bio is a privately held biotechnology company focused on developing therapies to reverse or repair cellular aging processes by leveraging advances in cellular reprogramming, autophagy modulation, and stem-cell–derived regenerative biology. Its pipeline spans multiple preclinical programs, including small-molecule autophagy enhancers for neurodegenerative disease (RTR242), iPSC-derived microglial progenitors for CNS repair (RTR888), iPSC-derived hematopoietic stem cells for blood disorders (RTR890), and AAV-delivered gene therapies designed to reprogram aged tissues for rejuvenation in osteoarthritis and hearing loss. Founded with a mission to extend healthy human lifespan by restoring youthful cell function, Retro Bio applies a translational, platform-driven approach that integrates synthetic biology, stem-cell engineering, and longevity science to tackle diseases of aging at their root cause rather than treating symptoms downstream.

Pipeline

Therapy	*MOA*	*Stage*	*Indication*
RTR242	Autophagy Enhancer	Preclinical	Alzheimer's Disease
RTR888	Microglial Progenitors	Preclinical	Neurologic Conditions
RTR890	iPSC Hematopoetic Cells	Preclinical	Hematologic Conditions

Team:



Location / People / Capital

Location: Redwood City, CA
Website: https://retro.bio/

Raises: Has raised over $250 million, including from Sam Altman of OpenAI
Employees: 60+

Leadership

Joe Betts-Lacroix	CEO
Alex Trapp	Comp Bio
Sheng Ding	Scientist
Peng Liu	Scientist
Shirley Telebrico	Finance

Advisors include Alejandro Ocampo, Vadim Gladyshev, Jeff Kindler, Kristen Fortney, Dan Goodman, Filipe Pereira, Alejo Rodriguez-Fraticelli, Brian Stolz, David Rubinzstein.

Company Overview

Rubedo Life Sciences is a privately held clinical-stage biotechnology company focused on developing small-molecule therapies that target pathological, senescent cells that contribute to aging and related diseases like chronic inflammation, fibrosis, and dermatologic conditions.

Rubedo leverages its proprietary AI-driven discovery platform called ALEMBIC™, which identifies druggable pathways in senescent cells and enables the design of first-in-class modulators aimed at restoring tissue homeostasis rather than just treating symptoms.

Rubedo's lead candidate is RLS-1496, a selective GPX4 modulator intended to clear senescent cells through ferroptosis sensitization, and the company has reported clearance of an IND by the U.S. U.S. Food & Drug Administration for a Phase 1b/2a trial in actinic keratosis. Rubedo is also exploring the effect of RLS-1496 on psoriasis in a Phase 1 clinical trial underway in Europe.

Pipeline

Therapy	*MOA*	*Stage*	*Indication*
RLS-1496	GPX-4 / Ferroptosis Modulator	Phase 1	Actinic Keratosis
RBO-2xx	Not Described	Preclinical	Respiratory Conditions

Publications

Marco Quarta and Marco Demaria, "On the past, present and future of senotherapeutics," *NPJ Aging*, Feb 3, 2024;10(1):11.

Donovan LJ, Brewer CL, Bond SF, Laslavic AM, Pena Lopez A, Colman L, Jordan CE, Hansen LH, González OC, Pujari A, de Lecea L, Quarta M, Kauer JA, Tawfik VL. Aging and injury drive neuronal senescence in the dorsal root ganglia. *Nat Neurosci*ence, May 2025;28 (5):985-997.

Location / People / Capital

Location: Cambridge, MA
Website: https://www.rubedolife.com/

Last Raise: $40M
Employees: 33 (LinkedIn)

Leadership

Frederick Beddingfield III	Chief Executive Officer
Marco Quarta	Chief Scientific Officer
Alex Laslavic	Chief Technology Officer
Julianne Averill	Chief Financial Officer
Ali Siam	Chief Business Officer
Mary Spellman	Chief Medical Officer
Ofir Moreno	SVP Drug Discovery

Investors

Ahren khosla ventures

THYMOFOX

Company Overview

Thymofox is developing targeted, orally available therapies that induce thymic regeneration and rejuvenation to restore immune function in aging people and immunocompromised patients. The age-related involution and degeneration of the thymus impair its ability to produce new T-cells, which is thought to contribute to older people's weakened resistance to new immune threats. Therefore, thymic regeneration could protect aging people against infectious disease and cancer.

Thymofox is a privately held biotechnology company. Apollo Health Ventures co-founded the company at the beginning of 2022 with Drs. Marcel van den Brink (President, City of Hope) and Jarrod Dudakov (Hutchinson Cancer Center) and financed it together with Memorial Sloan Kettering Investment Office as well as Thomas Ebeling (Ex CEO of Novartis).

As the immune system ages, thymic involution (a genetically programmed aging process in which the thymus shrinks) leads to a decline in naïve T cell production, impairing immune surveillance and response. The thymus is a particularly attractive target because it is one of the earliest and most visibly aging organs, and because it has shown regenerative potential when FOXN1 is restored. Several players have emerged around the excitement for the potential of thymus regeneration, but they have taken the approach of investing in cell therapy and biologics, which require inordinately large up-front investments and risk for a field that is in the nascent stages of clinical development. Thymofox is taking the approach of finding small molecule modulators across a diverse target space that converge on functional FOXN1 activation: the key biologic node for thymus regeneration. The small molecule approach mitigates risk for the critical early inflection points of drug development (PKPD, exposure, CMC), which will allow Thymofox to test and revise the clinical thesis, and eventually expand into the largest unmet patient segments that are not scalable for cell therapies and biologics.

Location / People / Capital

Location: Cambridge, MA
Website: https://www.thymofox.com/

Last Raise: NA
Employees: 5+

Leadership

Chris Shepard	Chief Executive Officer
Wolfgang Link	Scientific Co-Founder
Niklas Czeloth	Director / Boehringer
Anela Vukoja	Director / Apollo
Vera Mehler-de Graaff	Director / NRW

Investors

APOLLO HEALTH VENTURES
City of Hope
Fred Hutch Cancer Center
Memorial Sloan Kettering Cancer Center

Vandria

Company Overview

Vandria SA is a privately held Swiss-based biotech company focused on developing first-in-class small molecule mitophagy inducers—compounds designed to selectively trigger the removal and renewal of damaged mitochondria (mitophagy) to rejuvenate cells and treat age-related and chronic diseases.

Mitochondria are double-membrane organelles that play a critical role in generating most of cellular energy. Mitophagy is a key pathway by which portions of damaged mitochondria are eliminated and recycled using the autophagy machinery, and is required to maintain proper mitochondrial function.

Their lead candidate, VNA-318, is a brain-penetrant drug developed for central nervous system (CNS) indications such as cognitive impairment, Alzheimer's and Parkinson's disease; it's claimed to combine an immediate improvement in memory and learning with longer-term disease-modifying effects such as reduced neuroinflammation and improved mitochondrial function. Vandria's pipeline extends beyond the CNS to cover additional programs in muscle, lung and liver diseases, all anchored around a proprietary screening platform that identifies compounds targeting a novel mitophagy-relevant target.

Pipeline

Therapy	*MOA*	*Stage*	*Indication*
VNA-318	Brain Mitophagy Inducer	Phase 1	MCI
VNA-052	Muscle Mitophagy Inducer	Preclinical	Sporadic IBM
VNA-438	Liver Mitophagy Inducer	Preclinical	MASH
VNA-710	Lung Mitophagy Inducer	Preclinical	IPF
VNA-897	Ferroptosis Program	Preclinical	Undisclosed

Location / People / Capital

Location: Lausanne, Switzerland
Website: https://www.vandria.com/

Last Raise: $30.7mm in 2024 (Total: $52 million)
Employees: 11

Leadership

Klaus Dugi	Chief Executive Officer
Pénélope Andreux	Chief Scientific Officer
Peter Harboe-Schmidt	Head, BD and Finance
Leila Mirmohamadsadeghi	Director, Preclinical Ops

Investors

DOLBY FAMILY VENTURES
HEVOLUTION
ND Capital

Funding Sources in the Aging Field

Selected Dedicated Financing Groups Focused on Longevity

Also see (courtesy of Maximon):

- https://www.longevityinvestors.ch/post/the-global-longevity-investment-landscape-leading-investors-by-deal-count
- https://longevity.technology/investment/report/annual-longevity-investment-report-2024/
- https://www.finews.com/news/english-news/68320-longevity-investors-lucia-kupcova-lic-2025-gstaad-interview-marc-p-bernegger-tobias-reichmuth

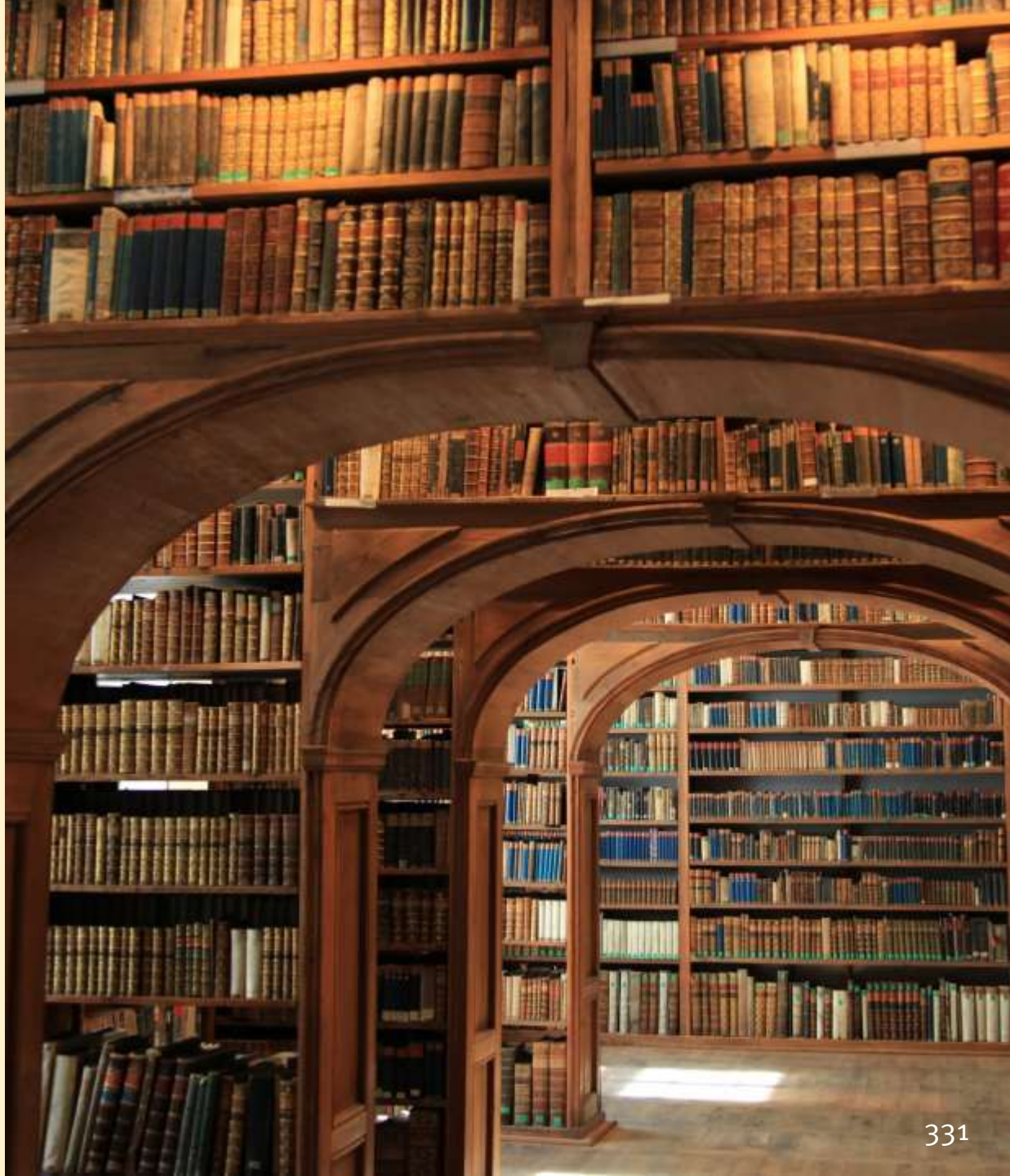
Appendix 1:

Accessing Other Reports From Stifel's Healthcare Investment Banking Group

Past Issues

To get on the mailing list for this publication feel free to contact Jenna Hill (hillje@stifel.com). Past issues of this publication can be read online at:

Nov 3, 2025 (China Update)
Oct 6, 2025 (Biotech Bull Market)
Sep 16, 2025 (Fixing Pharma's Image)
Aug 18, 2025 (Cardiovascular Drugs)
Jul 14, 2025 (Top 40 Pharma)
Jun 23, 2025 (Science and Truth)
May 12, 2025 (MFN Policy)
May 5, 2025 (NIH Cuts, China Tariffs)
Apr 28, 2025 (Eyes on Washington DC)
Apr 21, 2025 (FDA Shifts, Buyside Update)
Apr 14, 2025 (Wild Week in Market)
Apr 7, 2025 (Biotech Market Break)
Mar 31, 2025 (China Biotech Update)
Mar 24, 2025 (Healthcare Reform)
Feb 24, 2025 (Retail Pharma Trends)
Feb 10, 2025 (Pharma Earnings)
Jan 27, 2025 (Women's Health, Obesity)
Dec 17, 2024 (Biotech Blues)
Nov 25, 2024 (Biotech Balance Sheets)
Nov 18, 2024 (New Administration)
Nov 4, 2024 (Election, Obesity)
Oct 21, 2024 (China, Pfizer)
Oct 7, 2024 (VC update)
Sep 23, 2024 (The Fed Rate Cut)
Sep 9, 2024 (Sector Outlook)
Aug 12, 2024 (Biotech Market)
July 8, 2024 (Obesity Market Update)
June 17, 2024 (Lab Market)
June 8, 2024 (Oncology Review)
May 27, 2024 (GLP-1's)
May 20, 2024 (Returning Capital)
May 13, 2024 (Brain, AlphaFold 3)
May 6, 2024 (Earnings, Obesity)
April 29, 2024 (M&A, Japan)
April 22, 2024 (Pharma Pricing)
April 15, 2024 (AI in Pharma)
April 8, 2024 (The Buyside)
April 1, 2024 (Biotech Balance Sheets)
March 25, 2024 (Women's Health)
March 18, 2024 (Inflammasome)
March 11, 2024 (IRA, Immunology)
March 4, 2024 (Biotech Employment)
Feb 26, 2024 (Biotech Strategy)
Feb 19, 2024 (Big Drugs, Autoantibodies)
Feb 12, 2024 (Fibrosis, Endometriosis)
Feb 5, 2024 (Severe Disease in Women)
Jan 29, 2024 (Pharma R&D Productivity)
Dec 18, 2023 (Expectations for Future)
Dec 11, 2023 (ASH, R&D Days)
Dec 4, 2023 (Big Pharma, CEA)
November 20, 2023 (M&A)
November 13, 2023 (AHA, Bear Market)
November 7, 2023 (Unmet Needs)
October 30, 2023 (ADCs)
October 23, 2023 (ESMO Review)
October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)



Links to Stifel Biopharma Special Topic Publications

Breast Cancer

[Oct 28, 2025]

Medicine, Progress & AI

[Sep 11, 2025]

Obesity Drug Update

[July 9, 2025]

Oncology Update

[Jun 5, 2025]

Healthcare Future

[May 30, 2025]

Aging Biology, Part I

[Mar 26, 2025]

2025 Biotech Outlook

[Jan 8, 2025]

Why Invest in Biotech?

[November 22, 2023]

Disclosure

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