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Scientific News
2nd of March 2025
Sven Bulterijs

Business/Conferences/ General news

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It's official: Senate votes to confirm RFK Jr. as HHS secretary

About a month after Donald Trump took office as the 47th US president, almost all grant-review meetings remain suspended at the US National Institutes of Health (NIH), preventing the world's largest public funder of biomedical research from spending much of its US$47 billion annual budget.

'Devastating' cuts to NIH grants by Trump's team put on hold by US judge

To further complicate grant-review efforts, the Trump administration laid off more than 1,100 employees at the NIH in the past week, representing about 6% of the agency's workforce. Many of these workers were programme officers, grant-management specialists and scientific-review officers who help to screen grant applications, conduct grant reviews and perform oversight on the 60,000 funding awards the agency issues each year.

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View the cosmos at these astrotourism destinations

Locations with low light pollution allow travelers unparalleled views of celestial objects. **In Money**

Oscars predictions: Who should win – and who will

In a year with no clear front-runners for best picture or acting roles, we give it a shot. **In Life**

KYLE TERADA/ IMAGN IMAGES

Hoops legend Taurasi leaves legacy of greatness

Retiring after 20 seasons in the WNBA, the Phoenix Mercury guard says she "lived the dream." She also changed the game, columnist says. **In Sports**

E2

USA TODAY
THE NATION'S NEWS | $3 | THURSDAY, FEBRUARY 27, 2025

US records first measles death in 10 years

Outbreak in Texas claims unvaccinated school-age child

Eduardo Cuevas
USA TODAY

Texas authorities have announced the first measles death in the state's outbreak of the highly contagious disease.

The death, of a school-age child, is the first measles death in the United States since 2015, according to the Centers for Disease Control and Prevention.

The Gaines County child died in Lubbock, according to an email from Zach Holbrooks, public health director and executive director of the South Plains Public Health District. In a statement, Lubbock city and Texas health officials confirmed the hospitalized patient was an unvaccinated school-age child who died in the past 24 hours.

In a Cabinet meeting Wednesday at the White House, Health and Human Services Secretary Robert F. Kennedy Jr. said two deaths have been reported in the outbreak. Local authorities and the CDC had confirmed only one death as of Wednesday.

One hundred twenty-four people are known to have been infected, and most of the infections are among people who weren't vaccinated or had no known vaccination status, state data showed. Eighteen people have been hospitalized.

The outbreak is believed to have

See MEASLES DEATH, Page 3A

How the disease spreads

- **In the air:** Measles is a highly contagious disease that can live up to two hours in contaminated airspace.
- **Person to person:** The virus lives in the throat and nose and is spread through mucus droplets.
- **Before symptoms appear:** Measles can infect others within four days before or after the telltale rash appears.

Source: U.S. Centers for Disease Control and Prevention

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CDC Staff Prohibited From Co-Authoring Papers With World Health Organization Personnel

It's just the latest "Orwellian" crackdown on government scientists.

By Matt Shuham

28/02/2025 05:37pm GMT

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Make America Ageless: Trump's Health Picks Take Longevity Movement Mainstream

Antiaging scientists and entrepreneurs hope the new administration will make it easier to develop treatments

By Alex Janin Follow

Jan. 15, 2025 12:01 am ET

Deputy Secretary of Health and Human Services	Jim O'Neill[38]	Awaiting Senate Confirmation

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NIH partially lifts freeze on funding process for medical research

FEBRUARY 26, 2025 · 6:41 PM ET

Rob Stein

The freeze occurred because the Trump administration had blocked the NIH from posting any new notices in the *Federal Register*, which is required before many federal meetings can be held. The stoppage forced the agency to cancel meetings to review thousands of grant applications.

The meeting freeze had stalled about 16,000 grant applications vying for around $1.5 billion in NIH funding, according to one person who is familiar with the grant-making process who did not want to be identified because of fear of retribution.

POLITICS

Federal ju argument future of funding f

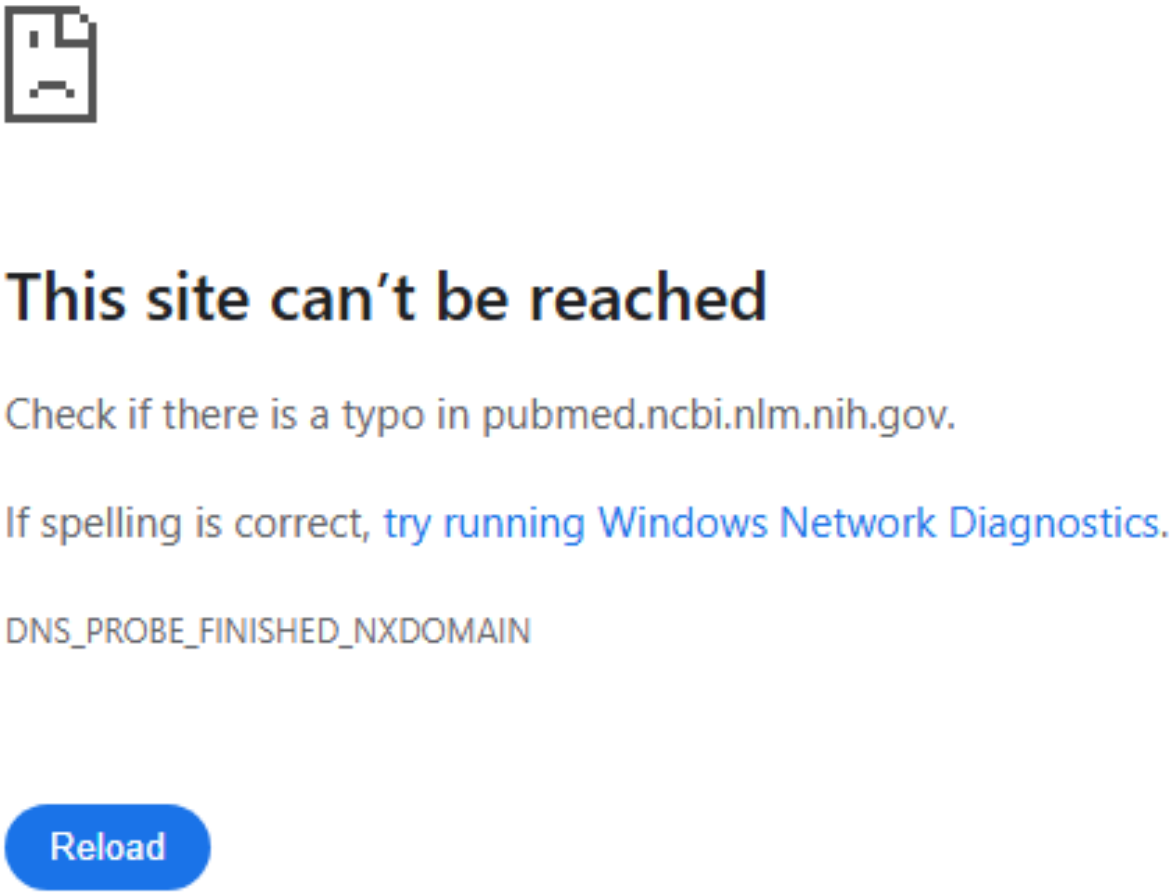
But on Wednesday the NIH released a statement saying the agency could now "begin sending notices incrementally to the Office of the Federal Register to advertise meetings of scientific review groups/study sections and begin their resumption." The agency planned to submit Federal Register Notices for the next 50 meetings, according to the statement. That will allow for the first phase of grant application reviews to start to resume.

But Federal Register notices for other types of meetings remain "on hold," which means the later stages of grant review remain frozen.

Funding freeze is threatening the ITP

And it gets worse: in an email to a member of the Rapamycin News forum, head of the ITP Richard Miller explained that 'current NIH plans appear not to involve any new awards, and the ITP is funded on an annual basis via a 'non-competing renewal.' What this means is that the NIH cuts/freeze are even hitting projects that are already approved: due to a technicality, one of the most important aging research programs, the ITP, is refunded annually. The freeze on grants means it won't be.

PubMed down… a sign for troubles ahead???



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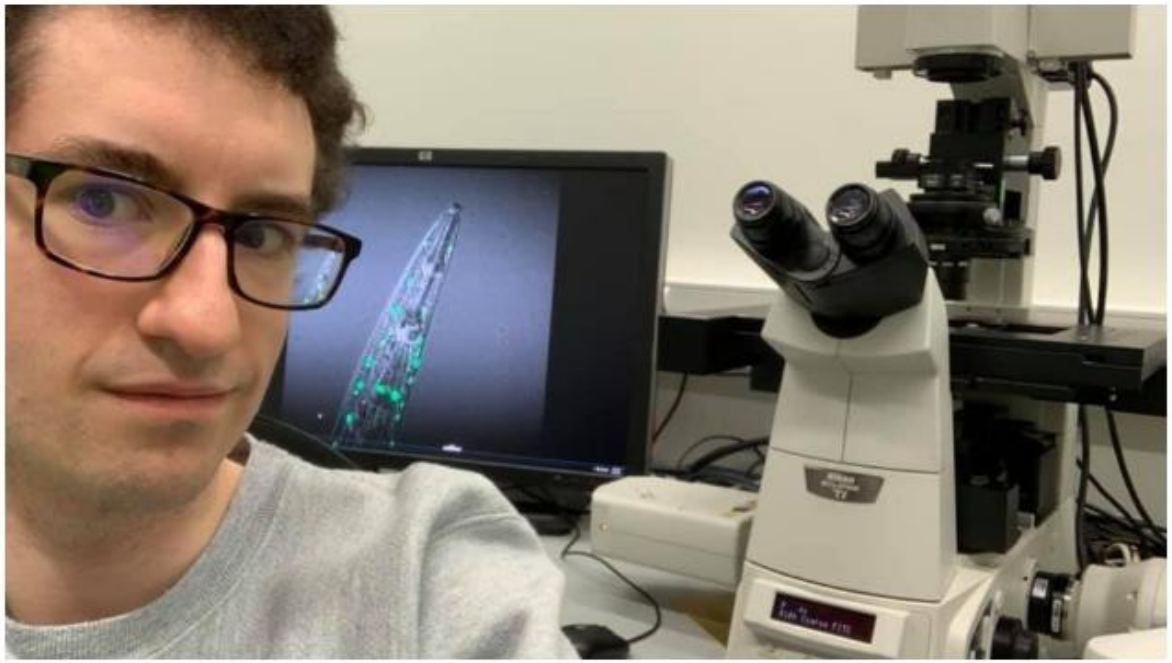


Longevity Trends: February 2025

Sven Bulterijs
PhD student in Biology of Aging

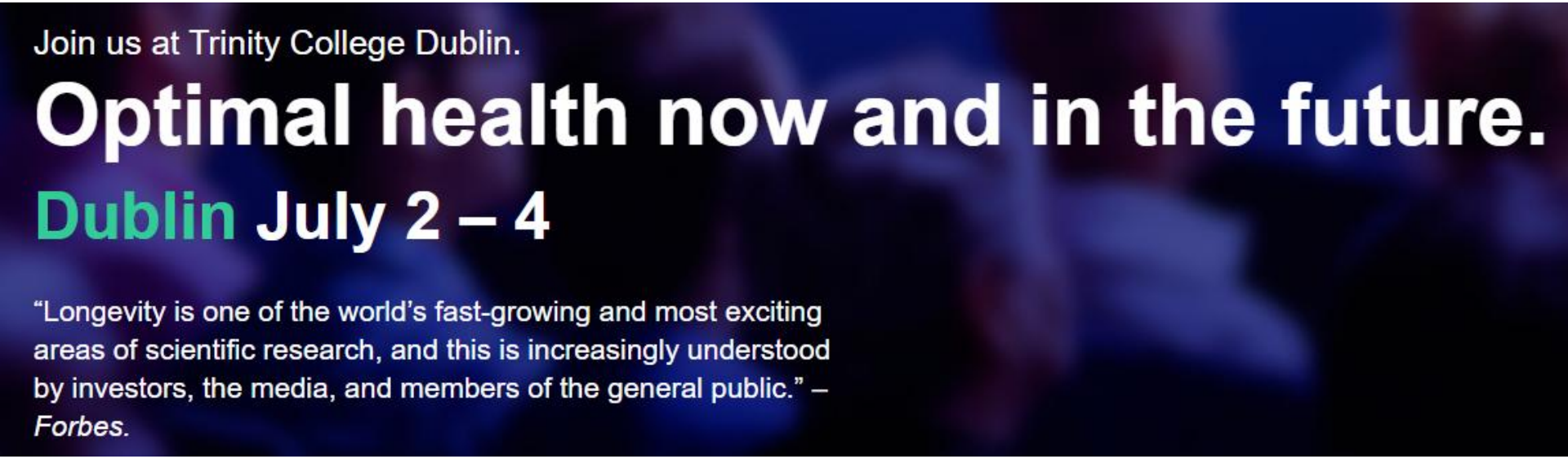
March 1, 2025

Introduction

Last month, I hosted a journal club (DM me to sign up for future journal clubs) focused on **organ-specific proteomic clocks**—an exciting and emerging area in longevity research. Given the growing interest in this topic, it seemed fitting to dedicate this month's newsletter to it.

Upcoming conferences

I'll be there!



Aging research articles

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Integrating the environmental and genetic architectures of aging and mortality

Both environmental exposures and genetics are known to play important roles in shaping human aging. Here we aimed to quantify the relative contributions of environment (referred to as the exposome) and genetics to aging and premature mortality. To systematically identify environmental exposures associated with aging in the UK Biobank, we first conducted an exposome-wide analysis of all-cause mortality (n = 492,567) and then assessed the associations of these exposures with a proteomic age clock (n = 45,441), identifying 25 independent exposures associated with mortality and proteomic aging. These exposures were also associated with incident age-related multimorbidity, aging biomarkers and major disease risk factors. Compared with information on age and sex, polygenic risk scores for 22 major diseases explained less than 2 percentage points of additional mortality variation, whereas the exposome explained an additional 17 percentage points. Polygenic risk explained a greater proportion of variation (10.3–26.2%) compared with the exposome for incidence of dementias and breast, prostate and colorectal cancers, whereas the exposome explained a greater proportion of variation (5.5–49.4%) compared with polygenic risk for incidence of diseases of the lung, heart and liver. Our findings provide a comprehensive map of the contributions of environment and genetics to mortality and incidence of common age-related diseases, suggesting that the exposome shapes distinct patterns of disease and mortality risk, irrespective of polygenic disease risk.

Proteomic organ-specific ageing signatures and 20-year risk of age-related diseases: the Whitehall II observational cohort study

Prof Mika Kivimäki, FMedSci [a,d] · Philipp Frank, PhD [a] · Jaana Pentti, MSc [d,f] · Prof Markus Jokela, PhD [e] · Solja T Nyberg, PhD [d] · Acer Blake, MSc [b,c] · Joni V Lindbohm, MD PhD [a,d,g] · Hamilton Se-Hwee Oh, PhD [h,i,j] · Prof Archana Singh-Manoux, PhD [a,l] · Prof Tony Wyss-Coray, PhD [i,j,k] · Prof Linda Partridge, FMedSci [b,c] Show less

Methods

In this observational cohort study, to assess the biological age of an individual's organs relative to those of same-aged peers, ie, organ age gaps, we collected plasma samples from 6235 middle-aged (age 45–69 years) participants of the Whitehall II prospective cohort study in London, UK, in 1997–99. Age gaps of nine organs were determined from plasma proteins via SomaScan (SomaLogic; Boulder, CO, USA) using the Python package organage. Following this assessment, we tracked participants for 20 years through linkage to national health records. Study outcomes were 45 individual age-related diseases and multimorbidity.

Findings

Over 123 712 person-years of observation (mean follow-up 19·8 years [SD 3·6]), after excluding baseline disease cases and adjusting for age, sex, ethnicity, and age gaps in organs other than the one under investigation, individuals with large organ age gaps showed an increased risk of 30 diseases. Six diseases were exclusively associated with accelerated ageing of their respective organ: liver failure (hazard ratio [HR] per SD increment in the organ age gap 2·13 [95% CI 1·41–3·22]), dilated cardiomyopathy (HR 1·65 [1·28–2·12]), chronic heart failure (HR 1·52 [1·40–1·65]), lung cancer (HR 1·29 [1·04–1·59]), agranulocytosis (HR 1·27 [1·07–1·51]), and lymphatic node metastasis (HR 1·23 [1·06–1·43]). 24 diseases were associated with more than one organ age gap or with organ age gaps not directly related to the disease location. Larger age gaps were also associated with elevated HRs of developing two or more diseases affecting different organs within the same individual (ie, multiorgan multimorbidity): 2·03 (1·51–2·74) for the arterial age gap, 1·78 (1·48–2·14) for the kidney age gap, 1·52 (1·38–1·68) for the heart age gap, 1·52 (1·12–2·06) for the brain age gap, 1·43 (1·16–1·78) for the pancreas age gap, 1·37 (1·17–1·61) for the lung age gap, 1·36 (1·26–1·46) for the immune system age gap, and 1·30 (1·18–1·42) for the liver age gap.

Enhanced paracrine action of FGF21 in stromal cells delays thymic aging

Age-related thymic involution precedes aging of all other organs in vertebrates and initiates the process of declining T cell diversity, which leads to eventual immune dysfunction. Whether FGF21, a liver-derived pro-longevity hormone that is also produced in thymic stroma, including by adipocytes, controls the mechanism of thymic demise is incompletely understood. Here, we demonstrate that elevation of FGF21 in thymic epithelial cells (TECs) and in adipocytes protects against thymic aging, whereas conditional hepatic overexpression did not impact thymic biology in aged mice. Notably, elevation of thymic FGF21 increased naïve CD8 T cells in aged animals and extended healthspan. Mechanistically, thymic FGF21 overexpression elevated TECs and reduced fibroadipogenic cells. Ablation of β-klotho, the obligatory co-receptor for FGF21 in Foxn1^{+} TECs, accelerated thymic aging, suggesting regulation of TECs by FGF21 is partially required for thymic lymphopoiesis. These findings establish that paracrine FGF21 improves thymic function and delays immune aging.

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Paracrine FGF21 dynamically modulates mTOR signaling to regulate thymus function across the lifespan

Consequences of age-associated thymic atrophy include declining T-cell responsiveness to pathogens and vaccines and diminished T-cell self-tolerance. Cortical thymic epithelial cells (cTECs) are primary targets of thymic aging, and recent studies suggested that their maintenance requires mTOR signaling downstream of medullary TEC (mTEC)-derived growth factors. Here, to test this hypothesis, we generated a knock-in mouse model in which FGF21 and mCherry are expressed by most mTECs. We find that mTEC-derived FGF21 promotes temporally distinct patterns of mTORC1 and mTORC2 signaling in cTECs, promotes thymus and individual cTEC growth and maintenance, increases T-cell responsiveness to viral infection, and diminishes indicators of peripheral autoimmunity in older mice. The effects of FGF21 overexpression on thymus size and mTOR signaling were abrogated by treatment with the mTOR inhibitor rapamycin. These results reveal a mechanism by which paracrine FGF21 signaling regulates thymus size and function throughout the lifespan, as well as potential therapeutic targets for improving T-cell function and tolerance in aging.

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Infusion of young donor plasma components in older patients modifies the immune and inflammatory response to surgical tissue injury: a randomized clinical trial

Methods

This double-blind, placebo-controlled study enrolled and randomized 38 patients undergoing major joint replacement surgery. Patients received four separate infusions of a plasma protein fraction derived from young donors, or placebo one day before surgery, before and after surgery on the day of surgery, and one day after surgery. Blood specimens for proteomic and immunological analyses were collected before each infusion. Based on the high-content assessment of circulating plasma proteins with single-cell analyses of peripheral immune cells, proteomic signatures and cell-type-specific signaling responses that separated the treatment groups were derived with regression models.

Results

Elastic net regression models revealed that administration a young plasma protein fraction significantly altered the proteomic (AUC = 0.796, $p = 0.002$) and the cellular immune response (AUC 0.904, $p < 0.001$) to surgical trauma resulting in signaling pathway- and cell type-specific anti-inflammatory immune modulation. Affected proteomic pathways regulating inflammation included JAK-STAT, NF-kappa B, and MAPK ($p < 0.001$). These findings were confirmed at the cellular level as the MAPK and JAK/STAT signaling responses were diminished and IkB, the negative regulator of NFkB, was elevated in adaptive immune cells.

Individual and additive effects of vitamin D, omega-3 and exercise on DNA methylation clocks of biological aging in older adults from the DO-HEALTH trial

While observational studies and small pilot trials suggest that vitamin D, omega-3 and exercise may slow biological aging, larger clinical trials testing these treatments individually or in combination are lacking. Here, we report the results of a post hoc analysis among 777 participants of the DO-HEALTH trial on the effect of vitamin D (2,000 IU per day) and/or omega-3 (1 g per day) and/or a home exercise program on four next-generation DNA methylation (DNAm) measures of biological aging (PhenoAge, GrimAge, GrimAge2 and DunedinPACE) over 3 years. Omega-3 alone slowed the DNAm clocks PhenoAge, GrimAge2 and DunedinPACE, and all three treatments had additive benefits on PhenoAge. Overall, from baseline to year 3, standardized effects ranged from 0.16 to 0.32 units (2.9–3.8 months). In summary, our trial indicates a small protective effect of omega-3 treatment on slowing biological aging over 3 years across several clocks, with an additive protective effect of omega-3, vitamin D and exercise based on PhenoAge.

Multi-dimensional evidence from the UK Biobank shows the impact of diet and macronutrient intake on aging

Background

The role of diet in aging is crucial, yet research findings on how specific diets influence human aging remain inconsistent. Understanding the relationship between dietary factors and aging could inform interventions to promote healthier aging outcomes.

Methods

We analyzed data from the UK Biobank baseline survey and a 24-hour dietary assessment survey to investigate the association between diet and aging. The study examined 18 individual food intakes, 6 dietary patterns, 3 macronutrient intakes, and 3 dietary quality scores. High-dimensional Fixed Effects (HDFE) models were used to assess associations between dietary factors and aging measures, including telomere length, phenotypic age, and brain grey/white matter volumes. Multivariable Mendelian Randomization (MVMR) was employed to explore causal links between macronutrient consumption and aging outcomes.

Results

Our results show that healthier diets are generally associated with improved aging outcomes from HDFE analyses. Plant-based food consumption correlates with increased telomere length and reduced phenotypic age, while animal-based food intake is linked to adverse aging effects. MVMR results confirm the causal benefits of carbohydrate intake, including reductions in phenotypic age ($\beta = -0.0025$; 95% CI = $[-0.0047, -0.0003]$; $p = 0.0253$) and increases in whole-brain grey matter volume ($\beta = 0.0262$; 95% CI = $[0.007, 0.046]$; $p = 0.0087$). The latter association remains significant after multiple testing correction.

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PREPRINT

Blood mitochondrial health markers cf-mtDNA and GDF15 in human aging

Altered mitochondria biology can accelerate biological aging, but scalable biomarkers of mitochondrial health for population studies are lacking. We examined two potential candidates: 1) *cell-free mitochondrial DNA* (cf-mtDNA), a marker of mitochondrial signaling elevated with disease states accessible as distinct biological entities from plasma or serum; and 2) *growth differentiation factor 15* (GDF15), an established biomarker of biological aging downstream of mitochondrial energy transformation defects and stress signaling. In a cohort of 430 participants aged 24-84 (54.2% women), we measured plasma and serum cf-mtDNA, and plasma GDF15 levels at two timepoints 5 years apart, then assessed their associations with age, BMI, diabetes, sex, health-related behaviors, and psychosocial factors. As expected, GDF15 showed a positive, exponential association with age ($r=0.66$, $p<0.0001$) and increased by 33% over five years. cf-mtDNA was not correlated with GDF15 or age. BMI and sex were also not related to cf-mtDNA nor GDF15. Type 2 diabetes was only positively associated with GDF15. Exploring potential drivers of systemic mitochondrial stress signaling, we report a novel association linking higher education to lower age-adjusted GDF15 ($r=-0.14$, $p<0.0034$), both at baseline and the 5-year follow up, highlighting a potential influence of psychosocial factors on mitochondrial health. Overall, our findings among adults spanning six decades of lifespan establish associations between age, diabetes and GDF15, an emerging marker of mitochondrial stress signaling. Further studies are needed to determine if the associations of blood GDF15 with age and metabolic stress can be moderated by psychosocial factors or health-related behaviors.

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PREPRINT

Mitophagy at the oocyte-to-zygote transition promotes species immortality

The quality of inherited mitochondria determines embryonic viability[1], metabolic health during adulthood and future generation endurance. The oocyte is the source of all zygotic mitochondria[2], and mitochondrial health is under strict developmental regulation during early oogenesis[3–5]. Yet, fully developed oocytes exhibit the presence of deleterious mitochondrial DNA (mtDNA)[6,7] and mitochondrial dysfunction from high levels of endogenous reactive oxygen species[8] and exogenous toxicants[9]. How fully developed oocytes prevent transmission of damaged mitochondria to the zygotes is unknown. Here we discover that the onset of oocyte-to-zygote transition (OZT) developmentally triggers a robust and rapid mitophagy event that we term mitophagy at OZT (MOZT). We show that MOZT requires mitochondrial fragmentation, activation of the macroautophagy system and the mitophagy receptor FUNDC1, but not the prevalent mitophagy factors PINK1 and BNIP3. Oocytes upregulate expression of FUNDC1 in response to diverse mitochondrial insults, including mtDNA mutations and damage, uncoupling stress, and mitochondrial dysfunction, thereby promoting selection against damaged mitochondria. Loss of MOZT leads to increased inheritance of deleterious mtDNA and impaired bioenergetic health in the progeny, resulting in diminished embryonic viability and the extinction of descendent populations. Our findings reveal FUNDC1-mediated MOZT as a mechanism that preserves mitochondrial health during the mother-to-offspring transmission and promotes species continuity. These results may explain how mature oocytes from many species harboring mutant mtDNA give rise to healthy embryos with reduced deleterious mtDNA.

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PREPRINT

A Quantitative Approach to Mapping Mitochondrial Specialization and Plasticity

Anna S. Monzel, Jack Devine, Darshana Kapri, Jose Antonio Enriquez, Caroline Trumpff, Martin Picard

Mitochondria are a diverse family of organelles that specialize to accomplish complimentary functions [1-3]. All mitochondria share general features, but not all mitochondria are created equal [4].Here we develop a quantitative pipeline to define the degree of molecular specialization among different mitochondrial phenotypes – or *mitotypes*. By distilling hundreds of validated mitochondrial genes/proteins into 149 biologically interpretable MitoPathway scores (MitoCarta 3.0 [5]) the simple mitotyping pipeline allows investigators to quantify and interpret mitochondrial diversity and plasticity from transcriptomics or proteomics data across a variety of natural and experimental contexts. We show that mouse and human multi-organ mitotypes segregate along two main axes of mitochondrial specialization, contrasting anabolic (liver) and catabolic (brain) tissues. In cultured primary human fibroblasts exhibiting robust time-dependent and treatment-induced metabolic plasticity [6-8], we demonstrate how the mitotype of a given cell type recalibrates i) over time in parallel with hallmarks of aging, and ii) in response to genetic, pharmacological, and metabolic perturbations. Investigators can now use MitotypeExplorer.org and the associated code to visualize, quantify and interpret the multivariate space of mitochondrial biology.

Exploring the Plasma Proteome: Identifying Hub Proteins linking Aging, Homeostasis, and Organ Function

Juan Jiao[1†], Fei Gao[2†], Hongye Zhao[3†], Mingjun Jiang[4†], Yan Zhou[5†], Dizhi Liu[6], Sihang Fang[6], Danni Gao[6], Zhaoping Wang[6], Ze Yang[6], Huiping Yuan[6]

As effectors of interactions between genes and the environment, plasma proteins can monitor homeostasis and reflect the aging state of an organism. However, biomarkers of aging that are associated with homeostasis are still unclear. This study investigates the phenotype-related plasma proteome profiles of healthy individuals and to identify proteins that are specifically related to aging and physiological indices and their expression patterns across the lifespan. From September 2020 to March 2021, 71 participants aged over 20 to 100 years were enrolled in this cross-sectional study. Data were analyzed from April 2021 to December 2023. The plasma proteome was analyzed to identify proteins that are specifically related to aging and their expression patterns across the lifespan. Then, hub proteins were screened through correlation of aging proteins with physiological and biochemical phenotypes. Based on levels of plasma proteins, physiological indices are associated with age. Additionally, these differences in protein expression correlate with age and physiological indices. Finally, we identified 20 hub proteins that correlate with both physiological indices and age, and these proteins are involved in oxidative stress, inflammation and metabolism. Bibliometric analysis confirmed that 8 hub proteins (CD44, CD14, IGF2, CFD, LBP, IGFBP3, EFEMP1, and AHSG) associated with age affect organ function by mediating homeostasis. Plasma proteins associated with both age and physiological indices are involved in oxidative stress, inflammation, and metabolism. This is the first investigation to link aging and homeostasis based on plasma proteins.

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The Multiomics Blueprint of Extreme Human Lifespan

The indexed individual, from now on termed M116, was the world's oldest verified living person from January 17th 2023 until her passing on August 19th 2024, reaching the age of 117 years and 168 days (https://www.supercentenarian.com/records.html). She was a Caucasian woman born on March 4th 1907 in San Francisco, USA, from Spanish parents and settled in Spain since she was 8. Although centenarians are becoming more common in the demographics of human populations, the so-called supercentenarians (over 110 years old) are still a rarity. In Catalonia, the historic nation where M116 lived, the life-expectancy for women is 86 years, so she exceeded the average by more than 30 years (https://www.idescat.cat). In a similar manner to premature aging syndromes, such as Hutchinson-Gilford Progeria and Werner syndrome, which can provide relevant clues about the mechanisms of aging, the study of supercentenarians might also shed light on the pathways involved in lifespan. To unfold the biological properties exhibited by such a remarkable human being, we developed a comprehensive multiomics analysis of her genomic, transcriptomic, metabolomic, proteomic, microbiomic and epigenomic landscapes in different tissues, comparing the results with those observed in non-supercentenarian populations. The picture that emerges from our study shows that extremely advanced age and poor health are not intrinsically linked and that both processes can be distinguished and dissected at the molecular level.

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Lipid-induced condensate formation from the Alzheimer's Aβ peptide triggers amyloid aggregation

Greta Šneiderienė, Alicia González Díaz, Sourav Das Adhikari, +6, and Tuomas P. J. Knowles Authors Info

The onset and development of Alzheimer's disease is linked to the accumulation of pathological aggregates formed from the normally monomeric amyloid-β peptide within the central nervous system. These Aβ aggregates are increasingly successfully targeted with clinical therapies at later stages of the disease, but the fundamental molecular steps in early stage disease that trigger the initial nucleation event leading to the conversion of monomeric Aβ peptide into pathological aggregates remain unknown. Here, we show that the Aβ peptide can form biomolecular condensates on lipid bilayers both in molecular assays and in living cells. Our results reveal that these Aβ condensates can significantly accelerate the primary nucleation step in the amyloid conversion cascade that leads to the formation of amyloid aggregates. We show that Aβ condensates contain phospholipids, are intrinsically heterogeneous, and are prone to undergo a liquid-to-solid transition leading to the formation of amyloid fibrils. These findings uncover the liquid–liquid phase separation behavior of the Aβ peptide and reveal a molecular step very early in the amyloid-β aggregation process.

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CONFERENCE ABSTRACT

BPS2025 - Nanoplastic promotes the amyloid aggregation of amyloid-beta and alpha-synuclein

Gangtong Huang [1] · Pu Chun Ke [2] · Feng Ding [1]

Plastics discharged into the ecosphere can transform through radiation, abrasion, and microbial activities into micro- and nano-particles to instigate interactions with biosystems. While particulate plastics have been shown to bind proteins and peptides in vitro, propagate across the blood-brain barrier and elicit toxicity in vivo, the molecular details of nanoplastic-peptide interactions and its neuronal pathogenesis remain largely unknown. Here, we investigated the polystyrene PS nanoplastic-exacerbated amyloid aggregation and toxicity of amyloid-beta (Aβ) and alpha-synuclein (αS), in association with Alzheimer's disease (AD) and Parkinson's disease (PD), respectively. Driven by hydrophobic interactions, H-bonding, and π-π stacking, the N-terminus of Aβ exhibited strong PS binding affinity, leading to local enrichment of Aβ on the PS surface. The C-terminal region subsequently initiated amyloid fibril nucleation by forming parallel in-register β sheets. Similarly, through electrostatic attraction between the KTKEGV repeat motif with PS surface carboxyl modifications and auxiliary π-π stacking, the amyloidogenicity of locally enriched A53T αS was significantly promoted. The synergistic toxicity of amyloidogenic peptides and PS were confirmed by elevated in vitro expression of proinflammatory mediators and reactive oxygen species (ROS), coupled with other complications resembling AD or PD. Furthermore, PS-exacerbated AD- or PD-like symptoms in mice models were demonstrated by progressive physical, cognitive and motor deficits. Together, our study provides new insights into the molecular mechanisms of nanoplastic-protein interactions and implicated nanoplastics as an external trigger for increasing cerebral amyloidogenesis and accelerating neuropathology.

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PREPRINT

Indigenous gut microbes modulate neural cell state and neurodegenerative disease susceptibility

Lisa Blackmer-Raynolds, Maureen M. Sampson, Anna Kozlov, Aimee Yang, Lyndsey Lipson, Adam M. Hamilton, Sean D. Kelly, Pankaj Chopra, Jianjun Chang, Steven A. Sloan, Timothy R. Sampson

The native microbiome influences a plethora of host processes, including neurological function. However, its impacts on diverse brain cell types remains poorly understood. Here, we performed single nucleus RNA sequencing on hippocampi from wildtype, germ-free mice and reveal the microbiome-dependent transcriptional landscape across all major neural cell types. We found conserved impacts on key adaptive immune and neurodegenerative transcriptional pathways, underscoring the microbiome's contributions to disease-relevant processes. Mono-colonization with select indigenous microbes identified species-specific effects on the transcriptional state of brain myeloid cells. Colonization by *Escherichia coli* induced a distinct adaptive immune and neurogenerative disease-associated cell state, suggesting increased disease susceptibility. Indeed, *E. coli* exposure in the 5xFAD mouse model resulted in exacerbated cognitive decline and amyloid pathology, demonstrating its sufficiency to worsen Alzheimer's disease-relevant outcomes. Together, these results emphasize the broad, species-specific, microbiome-dependent consequences on neurological transcriptional state and highlight the capacity of specific microbes to modulate disease susceptibility.

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PREPRINT

Therapeutic assessment of a novel mitochondrial complex I inhibitor in *in vitro* and *in vivo* models of Alzheimer's disease

Despite recent approval of monoclonal antibodies that reduce amyloid (Aβ) accumulation, the development of disease-modifying strategies targeting the underlying mechanisms of Alzheimer's disease (AD) is urgently needed. We demonstrate that mitochondrial complex I (mtCI) represents a druggable target, where its weak inhibition activates neuroprotective signaling, benefiting AD mouse models with Aβ and p-Tau pathologies. Rational design and structure–activity relationship studies yielded novel mtCI inhibitors profiled in a drug discovery funnel designed to address their safety, selectivity, and efficacy. The new lead compound C458 is highly protective against Aβ toxicity, has favorable pharmacokinetics, and has minimal off-target effects. C458 exhibited excellent brain penetrance, activating neuroprotective pathways with a single dose. Preclinical studies in APP/PS1 mice were conducted via functional tests, metabolic assessment, *in vivo* ^{31}P- NMR spectroscopy, blood cytokine panels, *ex vivo* electrophysiology, and Western blotting. Chronic oral administration improved long-term potentiation, reduced oxidative stress and inflammation, and enhanced mitochondrial biogenesis, antioxidant signaling, and cellular energetics. These studies provide further evidence that the restoration of mitochondrial function and brain energetics in response to mild energetic stress represents a promising disease- modifying strategy for AD.

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PREPRINT

DARG: a Database of Alzheimer Related Genes in Model Organisms

Julia Y. Song, Eric Zhou, Yanhui Hu

Alzheimer disease is affecting a significant portion of the aging population worldwide. Despite extensive research over the years, a comprehensive understanding of its underlying mechanisms and effective treatments remains elusive. Meanwhile, animal models, such as mouse, zebrafish, Drosophila, and C. elegans, have proven invaluable in studying human diseases. In response, we have developed DARG, a Database of Alzheimer disease-related genes in model organisms, designed to bridge the gap between human geneticists investigating the molecular mechanisms of the disease and the model organisms that can be used to explore the functions of disease-associated genes. DARG allows users to search and browse Alzheimer-related human genes from various resources and datasets, identify orthologs in model organisms, and access data on their gene expression and related phenotypes in *Drosophila*.

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PREPRINT

Cerebellar Purkinje cell stripe patterns reveal a differential vulnerability and resistance to cell loss during normal aging in mice

Sarah G. Donofrio, Cheryl Brandenburg, Amanda M. Brown, Tao Lin, Hsiang-Chih Lu, Roy V. Sillitoe

Age-related neurodegenerative diseases involve reduced cell numbers and impaired behavioral capacity. Neurodegeneration and behavioral deficits also occur during aging, and notably in the absence of disease. The cerebellum, which modulates movement and cognition, is susceptible to cell loss in both aging and disease. Here, we demonstrate that cerebellar Purkinje cell loss in aged mice is not spatially random but rather occurs in a pattern of parasagittal stripes. We also find that aged mice exhibit impaired motor coordination and more severe tremor compared to younger mice. However, the relationship between patterned Purkinje cell loss and motor dysfunction is not straightforward. Examination of postmortem samples of human cerebella from neurologically typical individuals supports the presence of selective loss of Purkinje cells during aging. These data reveal a spatiotemporal cellular substrate for aging in the cerebellum that may inform about how neuronal vulnerability leads to neurodegeneration and the ensuing deterioration of behavior.

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Iron deposition is associated with motor and non-motor network breakdown in parkinsonism

Background: Iron deposition has been observed in Parkinsonism and is emerging as a diagnostic marker for movement disorders. Brain functional network disruption has also been detected in parkinsonism, and is believed to be accountable for specific symptoms in parkinsonism. However, how iron deposition influences brain network remains to be elucidated.

Methods: We recruited 16 Parkinson's disease (PD), 8 multiple system atrophy (MSA) and 7 progressive supranuclear palsy (PSP) patients. T1-weighted, susceptibility weighted images and resting-state functional MRI (rs-fMRI) were acquired. Quantitative susceptibility mapping (QSM) analysis was performed to quantify iron deposition in substantia nigra, putamen and dentate nucleus. Cerebellar network, sensorimotor network, default mode network and language networks were segregated using independent analysis. Network and iron deposition status were evaluated in relation to diagnostic groups, motor and non-motor symptoms. The relationship between quantitative iron deposition and brain network status was further interrogated. To further validate the findings, 13 healthy controls and 37 PD patients who had available T1 and rs-fMRI scans were selected from Parkinson's progression markers initiative (PPMI) database, and network analysis was performed.

Results: In local cohort, compared to PD, MSA patients showed greater iron deposition in putamen, while PSP patients had greater iron deposition in caudate nucleus and thalamus. Cerebellar and language networks showed significant difference across diagnostic groups, while default mode network and sensorimotor network did not. MSA patients had significantly impaired cerebellar network and language networks compared to PD patients. Cerebellar network was positively associated with motor symptom scores while language network was positively associated with MoCA scores in the patients. Iron deposition was negatively associated with both networks' activity in the patients. In PPMI cohort, impairment was found in both cerebellar and language networks in PD. Cerebellar and language networks correlated with motor and cognitive impairment, respectively.

Conclusion: Cerebellar network and language networks are differently influenced in MSA, PD and PSP, which can serve as potential diagnostic marker. Impairment of cerebellar network and language network are associated with motor symptoms and cognitive impairment, respectively. Moreover, dysfunction of the networks is associated with iron deposition in deep nuclei (SN, DN, Putamen).

G6PD deficiency triggers dopamine loss and the initiation of Parkinson's disease pathogenesis

Morgan G. Stykel [1] · Shehani V. Siripala [1,2,9] · Eric Soubeyrand [1,9] · … · Tariq A. Akhtar [1] · Joel C. Watts [3,4] · Scott D. Ryan [1,2,10] … Show more

Loss of dopaminergic neurons in Parkinson's disease (PD) is preceded by loss of synaptic dopamine (DA) and accumulation of proteinaceous aggregates. Linking these deficits is critical to restoring DA signaling in PD. Using murine and human pluripotent stem cell (hPSC) models of PD coupled with human postmortem tissue, we show that accumulation of α-syn micro-aggregates impairs metabolic flux through the pentose phosphate pathway (PPP). This leads to decreased nicotinamide adenine dinucleotide phosphate (NADP/H) and glutathione (GSH) levels, resulting in DA oxidation and decreased total DA levels. We find that α-syn anchors the PPP enzyme G6PD to synaptic vesicles via the α-syn C terminus and that this interaction is lost in PD. Furthermore, G6PD clinical mutations are associated with PD diagnosis, and G6PD deletion phenocopies PD pathology. Finally, we show that restoring NADPH or GSH levels through genetic and pharmacological intervention blocks DA oxidation and rescues steady-state DA levels, identifying G6PD as a pharmacological target against PD.

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PREPRINT

Severe Osteoarthritis in Aged PANX3 Knockout Mice: Implications for a Novel Primary Osteoarthritis Model

Osteoarthritis (OA) is a multi-factorial disease associated with aging. As the molecular mechanisms underpinning the pathogenesis of this disease are unclear, there are no disease-modifying drugs to combat OA. Pannexin 3 (PANX3) has been shown to promote cartilage loss during posttraumatic OA. In contrast, the ablation of *Panx3* in male mice results in spontaneous full-thickness cartilage lesions at 24 months of age. While protected from traumatic intervertebral disc (IVD) degeneration, *Panx3* knockout (KO) mice show signs of IVD disease with altered disc mechanics. Whether the deleterious effects of ablating *Panx3* in aging is the result from accumulated mechanical damage is unknown. We used male and female wildtype (WT) and global *Panx3* KO C57Bl6 mice aged to 18 months of age. Mice were then randomized to sedentary (SED) or forced treadmill running (FEX) for 6 weeks. Knee joint tissues including patellar tendon, quadriceps and distal patellar enthesis, and synovium were analyzed histologically and through micro-CT, along with lumbar spine IVDs. Half of male and female sedentary *Panx3* KO mice developed full-thickness cartilage lesions, severe synovitis, and ectopic fibrocartilage deposition and calcification of the knee joints in comparison to all other conditions. *Panx3* KO mice with severe OA show signs of quadriceps and patellar enthesitis, characterized by bone and marrow formation. Forced treadmill running did not seem to exacerbate these phenotypes in male or female *Panx3* KO mice; however, it may have contributed to the development of lateral compartment OA. The IVDs of aged *Panx3* KO mice displayed no apparent differences to control mice, and forced treadmill running had no further effects in either genotype. We conclude that aged *Panx3* KO mice show features of late-stage primary OA including full-thickness cartilage erosion, severe synovitis, and enthesitis. These data suggest that the deletion of *Panx3* is deleterious to synovial joint health in aging.

Anti-Graying Effects of External and Internal Treatments with Luteolin on Hair in Model Mice

by Machiko Iida [1,2], Takumi Kagawa [1], Ichiro Yajima [1,2], Akihito Harusato [1], Akira Tazaki [1,3], Delgama A. S. M. Nishadhi [1], Nobuhiko Taguchi [2,4] and Masashi Kato [1,2,3,*]

Little is known about the anti-graying effects of antioxidants on hair. The anti-graying effects of three antioxidants (luteolin, hesperetin, and diosmetin) on hair were investigated according to the sequential processes of hair graying that were previously clarified in model mice [Ednrb(+/−);RET-mice]. External treatment with luteolin, but not that with hesperetin or diosmetin, alleviated hair graying in Ednrb(+/−);RET-mice. Internal treatment with luteolin also mitigated hair graying in the mice. Although both luteolin treatments had very limited effects on hair cycles, the treatments suppressed the increase in $p16^{ink4a}$-positive cells in bulges [senescent keratinocyte stem cells (KSCs)]. Both of the treatments also suppressed decreases in the expression levels of endothelins in KSCs and their receptor (Ednrb) in melanocyte stem cells (MSCs) and alleviated hair graying in the mice. Luteolin is a special antioxidant with an anti-graying potency through improvement of age-related dysfunction in signaling between endothelins in KSCs and their receptor in MSCs. Luteolin for topical and oral use is commercially available to people in the form of supplements. Similar processes of hair graying in Ednrb(+/−);RET-mice and humans have been reported. These results are encouraging for the practical application of luteolin as a medicine with an anti-graying effect on hair in humans.

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A broad assessment of forty-one skin phenotypes reveals complex dimensions of skin ageing

Background: Skin ageing takes on many different forms. Despite this diversity in skin ageing phenotypes, literature published to date is limited in scope, as many research studies either focus on one single phenotype or just a few specific phenotypes. Presently, phenotypes such as wrinkles, pigment spots, and photo-ageing are receiving most of the research attention. We therefore wonder whether the current discourse on skin ageing places a disproportionate amount of focus on a few selected phenotypes, leaving other skin ageing phenotypes underexplored.

Methods: In this cross-sectional study, we performed a broad assessment of forty-one signs of skin ageing and characterised the phenotypes that constituted key components of skin ageing. We also explored the interrelationship among forty-one skin ageing phenotypes using Spearman's Correlation and Principal Component Analysis.

Results: We analysed our study population, which is composed of 3281 ethnic Chinese participants from the Singapore/Malaysia Cross-sectional Genetics Epidemiology Study (SMCGES). The first ten principal components cumulatively explain 46.88% of the variance of skin ageing phenotypes in our study population. We discovered that the commonly discussed forms of skin ageing (i.e., wrinkles, pigmentation, and photo-ageing) only accounted for a small portion (24.39%) of the variance of all skin ageing phenotypes in our study population. Telangiectasia, a poor lip fullness, a lighter skin colour, xerosis, ephelides (freckles), ptosis of eyelids (droopy eyelids), eyebags, and a low eyebrow positioning were other key components of skin ageing, accounting for a further 22.49% of the variance of skin ageing phenotypes in our study population. We found that each of these ten skin ageing phenotypes characterises a key and important aspect of skin ageing. In this broad assessment of skin ageing, we first described the prevalence of forty-one signs of skin ageing and then characterised in detail both the prevalence and severity distribution of ten key skin ageing phenotypes.

Conclusions: We presented clear evidence that skin ageing is much more than just wrinkles, pigmentation and photo-ageing. The addition of telangiectasia, poor lip fullness, a lighter skin colour, xerosis, ephelides, ptosis of eyelids, eyebags, and a low eyebrow positioning added more dimensions to skin ageing phenotype presentations.

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Genetic determinants of skin ageing: a systematic review and meta-analysis of genome-wide association studies and candidate genes

Background: Skin ageing is influenced by complex genetic factors. Various phenotypes such as wrinkling, pigmentation changes, and skin cancers have been linked to specific genetic loci. However, the underlying genetic mechanisms and pathways remain poorly understood. This systematic review and meta-analysis aims to summarise the genetic loci found to be associated with skin ageing phenotypes by published genome-wide association studies (GWAS) and candidate gene studies. We also evaluated the overall association of loci via meta-analysis and identified the association patterns to explore potential biological pathways contributing to skin ageing. The Web of Science, Embase, and PubMed databases were searched on January 2024 using specific exclusion criteria (e.g., study of non-human subjects, focus on skin diseases, or treatments) to identify relevant articles. There did not appear to be any significant publication bias observed across the all phenotypes.

Main body: A total of 48 studies were included, revealing 30 loci that were confirmed to be associated with skin ageing by multiple studies (e.g., AFG3L1P: odds ratio 1.133 95% confidence interval [1.044, 1.222]; BPIFA3: 1.859 [1.567, 2.151]; CLPTML1: 1.164 [1.0.99, 1.229]; CPNE7: 0.905 [0.852-0.958]; DEF8: 1.186 [1.042, 1.331]; IRF4: 1.260 [1.025, 1.495]; MYO16: 2.303 [1.697, 2.908]; PRDM16: 1.105 [1.084, 1.127]; RORA: 1.391 [1.206, 1.577]; SPG7: 0.922 [0.897, 0.947]; SPON1: 2.214 [1.204, 3.225]; SPTLC1: 1.464 [1.432, 1.495]; TYR: 1.175 [1.007, 1.343]). The lack of significance for many loci may be due to studies analysing different SNPs within the same locus, weakening the overall associations. Several loci were associated with specific phenotypic categories (e.g., skin colour related, skin cancer related, wrinkling and sagging related), suggesting shared biological pathways are involved in the pathogenesis of different skin ageing phenotypes. This pattern was also observed in several of the loci that do not have a significant overall association with skin ageing.

Conclusion: Despite significant heterogeneity among the included studies and the use of subjective visual methods for phenotype assessment, our review highlights the critical role of fundamental biological processes, such as development and cellular organisation, in skin ageing. Future research that targets the same SNP across multiple populations could strengthen the association of additional loci with skin ageing. Further investigation into these underlying biological processes would significantly advance our understanding of the pathogenesis of skin ageing phenotypes.

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Topical ABT-263 treatment reduces aged skin senescence and improves subsequent wound healing

Senescent cells accumulate in aging tissues, impairing their ability to undergo repair and regeneration following injury. Previous research has demonstrated that targeting tissue senescence with senolytics can enhance tissue regeneration and repair by selectively eliminating SnCs in specific aged tissues. In this study, we focused on eliminating senescent skin cells in aged mice to assess the effects on subsequent wound healing. We applied ABT-263 directly to the skin of 24-month-old mice over a 5-day period. Following topical ABT-263, aged skin demonstrated decreased gene expression of senescence markers p16 and p21, accompanied by reductions in SA-β-gal- and p21-positive cells compared to DMSO controls. However, ABT-263 also triggered a temporary inflammatory response and macrophage infiltration in the skin. Bulk RNA sequencing of ABT-263-treated skin revealed prompt upregulation of genes associated with wound healing pathways, including hemostasis, inflammation, cell proliferation, angiogenesis, collagen synthesis, and extracellular matrix organization. Aged mice skin pre-treated with topical ABT-263 exhibited accelerated wound closure. In conclusion, topical ABT-263 effectively reduced several senescence markers in aged skin, thereby priming the skin for improved subsequent wound healing. This enhancement may be attributed to ABT-263-induced senolysis which in turn stimulates the expression of genes involved in extracellular matrix remodeling and wound repair pathways.

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Test of Rapamycin in Aging Dogs (TRIAD): study design and rationale for a prospective, parallel-group, double-masked, randomized, placebo-controlled, multicenter trial of rapamycin in healthy middle-aged dogs from the Dog Aging Project

Companion dogs are a powerful model for aging research given their morphologic and genetic variability, risk for age-related disease, and habitation of the human environment. In addition, the shorter life expectancy of dogs compared to human beings provides a unique opportunity for an accelerated timeline to test interventions that might extend healthy lifespan. The Test of Rapamycin In Aging Dogs (TRIAD) randomized clinical trial is a parallel-group, double-masked, randomized, placebo-controlled, multicenter trial that will test the ability of rapamycin to prolong lifespan and improve several healthspan metrics in healthy, middle-aged dogs recruited from Dog Aging Project participants. Here, we describe the rationale, design, and goals of the TRIAD randomized clinical trial, the first rigorous test of a pharmacologic intervention against biological aging with lifespan and healthspan metrics as endpoints to be performed outside of the laboratory in any species.

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Ginkgolide B increases healthspan and lifespan of female mice

Various anti-aging interventions show promise in extending lifespan, but many are ineffective or even harmful to healthspan. Ginkgolide B (GB), derived from Ginkgo biloba, reduces aging-related morbidities such as osteoporosis, yet its effects on healthspan and longevity have not been fully understood. In this study, we found that continuous oral administration of GB to female mice beginning at 20 months of age extended median survival and median lifespan by 30% and 8.5%, respectively. GB treatment also decreased tumor incidence; enhanced muscle quality, physical performance and metabolism; and reduced systemic inflammation and senescence. Single-nucleus RNA sequencing of skeletal muscle tissue showed that GB ameliorated aging-associated changes in cell type composition, signaling pathways and intercellular communication. GB reduced aging-induced Runx1^{+} type 2B myonuclei through the upregulation of miR-27b-3p, which suppresses Runx1 expression. Using functional analyses, we found that Runx1 promoted senescence and cell death in muscle cells. Collectively, these findings suggest the translational potential of GB to extend healthspan and lifespan and to promote healthy aging.

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Multi-omic profiling of sarcopenia identifies disrupted branched-chain amino acid catabolism as a causal mechanism and therapeutic target

Xinrong Zuo, Rui Zhao, Minming Wu, Yanyan Wang, Shisheng Wang, Kuo Tang, Yang Wang, Jie Chen, Xiaoxiang Yan ✉, Yang Cao ✉ & Tao Li ✉

Sarcopenia is a geriatric disorder characterized by a gradual loss of muscle mass and function. Despite its prevalence, the underlying mechanisms remain unclear, and there are currently no approved treatments. In this study, we conducted a comprehensive analysis of the molecular and metabolic signatures of skeletal muscle in patients with impaired muscle strength and sarcopenia using multi-omics approaches. Across discovery and replication cohorts, we found that disrupted branched-chain amino acid (BCAA) catabolism is a prominent pathway in sarcopenia, which leads to BCAA accumulation and decreased muscle health. Machine learning analysis further supported the causal role of BCAA catabolic dysfunction in sarcopenia. Using mouse models, we validated that defective BCAA catabolism impairs muscle mass and strength through dysregulated mTOR signaling, and enhancing BCAA catabolism by BT2 protects against sarcopenia in aged mice and in mice lacking *Ppm1k*, a positive regulator of BCAA catabolism in skeletal muscle. This study highlights improving BCAA catabolism as a potential treatment of sarcopenia.

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PREPRINT

Avid lysosomal acidification in fibroblasts of the Mediterranean mouse *Mus spretus*

Melissa Sui, Joanne Teh, Kayleigh Fort, Daniel Shaw, Peter Sudmant, Tsuyoshi Koide, Jeffrey M. Good, Juan M. Vazquez, Rachel B. Brem

Failures of the lysosome-autophagy system are a hallmark of aging and many disease states. As a consequence, interventions that enhance lysosome function are of keen interest in the context of drug development. Throughout the biomedical literature, evolutionary biologists have discovered that challenges faced by humans in clinical settings have been resolved by non-model organisms adapting to wild environments. Here, we used a primary cell culture approach to survey lysosomal characteristics in selected species of the genus *Mus*. We found that cells from *M. musculus*, mice adapted to human environments, had weak lysosomal acidification and high expression and activity of the lysosomal enzyme β-galactosidase, a classic marker of cellular senescence. Cells of wild relatives, especially the Mediterranean mouse *M. spretus*, had more robustly performing lysosomes and dampened β-galactosidase levels. We propose that classic laboratory models of lysosome function and senescence may reflect characters that diverge from the phenotypes of wild mice. The *M. spretus* phenotype may ultimately provide a blueprint for interventions that ameliorate lysosome breakdown in stress and disease.

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PREPRINT

Repurposing Regulatory Toxicology Safety Data to Identify Potential Pro-Longevity Substances

Satomi Miwa, Olena Kucheryavenko, Kristin Herrmann, Christopher Saunter, Adelaide Raimundo, David Weinkove, Lars Niemann, Thomas von Zglinicki

The repurposing of existing biosafety datasets offers unique opportunities in biomedical research. Here, we demonstrate how pesticide toxicity data, which include long-term survival studies in mammalian models, can be harnessed to uncover potential drug candidates or drug targets that can improve survival. We show that these substances frequently affect mitochondrial bioenergetics and that they can improve animal healthspan.

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PREPRINT

DoliClock:A Lipid-Based Aging Clock Reveals Accelerated Aging in Neurological Disorders

Djakim Latumalea, Maximilian Unfried, Diogo Goncalves Barardo, Jan Gruber, Brian K. Kennedy

Aging is a multifaceted process influenced by intrinsic and extrinsic factors, with lipid alterations playing a critical role in brain aging and neurological disorders. This study introduces DoliClock, a lipid-based biological aging clock designed to predict the age of the prefrontal cortex using post-mortem lipidomic data. Significant age acceleration was observed in samples with autism, schizophrenia, and Down syndrome, with autism showing the most pronounced effects in aging-rate. An increase in entropy around age 40, suggests dysregulation of the mevalonate pathway and dolichol accumulation. Dolichol, a lipid integral to N-glycosylation and intracellular transport, emerged as a potential aging biomarker, with specific variants such as dolichol-19 and dolichol-20 showing unique age-related associations. These findings suggest that lipidomics can provide valuable insights into the molecular mechanisms of brain aging and neurological disorders. By linking dolichol levels and entropy changes to aging, this study highlights the potential of lipid-based biomarkers for understanding and predicting biological age, especially in conditions associated with premature aging.

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PREPRINT

Exploring the role of transposable elements to sex gap in longevity in Drosophila species

In Drosophila, like in many other animal species, females tend to live longer than males, a phenomenon known as sex gap in longevity (SGL). One of the possible causes underlying this phenomenon could be related to the high content of transposable elements (TE) in the Y chromosome (toxic Y hypothesis). TE activity is normally repressed by epigenetic mechanisms, but this regulation weakens with age. Since the Y chromosome is rich in TEs, age-related TE activity should be more pronounced in old males than in old females, likely affecting longevity patterns. In this work, we studied the natural variation in SGL in wild-type populations of three different Drosophila species that vary in their TE content: *Drosophila melanogaster*, *Drosophila simulans*, and *Drosophila suzukii*. Transcriptomic data revealed increased copy-specific TE expression in *D. melanogaster* and *D. suzukii* older flies. Moreover, we observed a higher number of upregulated TEs in old males compared to old females across all the three species tested. Additionally, we detected an increase in TE-chimeric transcript generation in some aged samples, particularly in *D. suzukii* males. Finally, the replacement of the Y chromosome between strains with different SGL led to a progressive reduction in male lifespan and increased TE transcriptional release over generations, suggesting a Y chromosome important role in male longevity. Our work contributes to a better understanding of the genomic differences that lead to variation in longevity patterns between sexes in several species, and emphasizes the importance of studying the role of TEs in male longevity.

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Nicotinamide Riboside Supplementation Alleviates Testicular Aging Induced by Disruption of Qprt–Dependent NAD^+ De Novo Synthesis in Mice

Recent studies have shown that disruptions in the nicotinamide adenine dinucleotide (NAD^+) de novo synthesis pathway accelerate ovarian aging, yet its role in spermatogenesis remains largely unknown. In this study, we investigated the impact of the NAD^+ de novo synthesis pathway on spermatogenesis by generating Qprt-deficient mice using CRISPR-Cas9 to target quinolinate phosphoribosyl transferase (Qprt), a key enzyme predominantly expressed in spermatocytes. Our results revealed that the deletion of Qprt did not affect NAD^+ levels or spermatogenesis in the testes of 3-month-old mice. However, from 6 months of age onward, Qprt-deficient mice exhibited significantly reduced NAD^+ levels in the testes compared to wild-type (WT) controls, along with a notable decrease in germ cell numbers and increased apoptosis. Additionally, these mice demonstrated mitochondrial dysfunction in spermatocytes, impaired progression through prophase I of meiosis, defective double-strand break (DSB) repair, and abnormal meiotic sex chromosome inactivation. Importantly, supplementation with the NAD^+ precursor nicotinamide riboside (NR) in Qprt-deficient mice restored NAD^+ levels and rescued the spermatogenic defects. These findings underscore the critical role of NAD^+ de novo synthesis in maintaining NAD^+ homeostasis and highlight its importance in meiotic recombination and meiotic sex chromosome inactivation in spermatogenesis.

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Mitochondrial NAD^+ deficiency in vascular smooth muscle impairs collagen III turnover to trigger thoracic and abdominal aortic aneurysm

Thoracic and abdominal aortic aneurysm poses a substantial mortality risk in adults, yet many of its underlying factors remain unidentified. Here, we identify mitochondrial nicotinamide adenine dinucleotide $(NAD)^+$ deficiency as a causal factor for the development of aortic aneurysm. Multiomics analysis of 150 surgical aortic specimens indicated impaired NAD^+ salvage and mitochondrial transport in human thoracic aortic aneurysm, with expression of the NAD^+ transporter SLC25A51 inversely correlating with disease severity and postoperative progression. Genome-wide gene-based association analysis further linked low *SLC25A51* expression to risk of aortic aneurysm and dissection. In mouse models, smooth muscle-specific knockout of *Nampt*, *Nmnat1*, *Nmnat3*, *Slc25a51*, *Nadk2* and *Aldh18a1*, genes involved in NAD^+ salvage and transport, induced aortic aneurysm, with *Slc25a51* deletion producing the most severe effects. Using these models, we suggest a mechanism that may explain the disease pathogenesis: the production of type III procollagen during aortic medial matrix turnover imposes a high demand for proline, an essential amino acid component of collagen. Deficiency in the mitochondrial NAD^+ pool, regulated by NAD^+ salvage and transport, hinders proline biosynthesis in mitochondria, contributing to thoracic and abdominal aortic aneurysm.

Salt Substitution and Recurrent Stroke and Death
A Randomized Clinical Trial

Xiong Ding, MPH[1,2]; Xinyi Zhang, MPH[3]; Liping Huang, PhD[4]; et al

Design, Setting, and Participants The Salt Substitute and Stroke Study (SSaSS), an open-label, cluster randomized clinical trial, was conducted in 600 northern Chinese villages (clusters). Patients who self-reported a hospital diagnosis of stroke were included in this prespecified subgroup analysis. Data were analyzed from November 2023 to August 2024.

Interventions Participants were assigned to use either a salt substitute, consisting of 75% sodium chloride and 25% potassium chloride by mass, or regular salt.

Main Outcomes and Measures The primary outcome was recurrent stroke.

Results After excluding 5746 persons without a baseline history of stroke, 15 249 patients with stroke (mean [SD] age, 64.1 [8.8] years; 6999 [45.9%] female; 8250 male [54.1%]) were included. Over a median (IQR) follow-up of 61.2 (60.9-61.6) months, the mean difference in systolic blood pressure was −2.05 mm Hg (95% CI, −3.03 to −1.08 mm Hg). A total of 2735 recurrent stroke events (691 fatal and 2044 nonfatal) and 3242 deaths were recorded. Recurrent stroke was significantly lower in the salt substitute vs regular salt group (rate ratio [RR], 0.86; 95% CI, 0.77-0.95; *P* = .005), with larger effects on hemorrhagic stroke (relative reduction, 30%; *P* = .002). Death rates were also significantly lower (RR, 0.88; 95% CI, 0.82-0.96; *P* = .003), with larger effects on stroke-related deaths (relative reduction 21%; *P* = .01). No significant difference was observed for hyperkalemia (RR, 1.01; 95% CI, 0.74-1.38; *P* = .96).

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Heterogeneity of Primary Outcomes in Large Atherosclerotic Cardiovascular Disease Trials Published in Prominent Medical Journals

Daniel Shepshelovich, MD[1]; Dafna Yahav, MD[2,3]; Danielle R. Rome, MD, MPH[1]; et al

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The extent of heterogeneity in end points reported by randomized clinical trials (RCTs) of atherosclerotic cardiovascular disease (ASCVD) is unknown. We aimed to describe the heterogeneity of primary end points reported in contemporary ASCVD RCT publications and to compare them with the original end points at RCT initiation.

This cohort study was considered nonhuman participants research by the Columbia University institutional review board and did not require informed consent. The study followed the STROBE reporting guideline.

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PREPRINT

Epigenomic insights into extreme longevity in the world's oldest terrestrial animal, Jonathan

Benjamin Vaisvil, Daniel P. Schmitt, Angela Jones, Vinayak Kapatral, James M. Ford, Madison L. Taylor, Mathia Colwell, Jonathan Hollins, Sam Pascucci, Konstantin Weissenow, Burkhard Rost, Pascal Notin, Justin Gerlach, Thomas C. Terwilliger, Li-Wei Hung, Lars Juhl Jensen, Steve Horvath, Christopher Faulk, Yanjun Ma, Stephen W. Clark

Giant tortoises exhibit exceptional longevity, often exceeding the human lifespan. To understand the genomic and epigenomic basis of their longevity, awe analyzed the DNA sequence and methylome of Jonathan, an Aldabra giant tortoise (Aldabrachelys gigantea), estimated to be 192 years old. Relative to other giant tortoises (Aldabrachelys gigantea and Chelonoidis abingdonii), we found Jonathan has gene variants in pathways associated with aging, including DNA repair and telomere regulation. Consistent with his advanced age, Jonathan has significant age-related changes in DNA methylation and methylation entropy, compared with a 5-year-old Aldabra individual. Notably, we found that low entropy regions in Jonathan's methylome were enriched for genes involved in the electron transport chain. This suggests that high-fidelity transcription of these genes may be crucial for extreme longevity. With this data, we propose a model for aging, that links efficient mitochondrial energy production with nuclear maintenance of low methylation entropy.

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PREPRINT

Multi-tissue transcriptomic aging atlas reveals predictive aging biomarkers in the killifish

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Aging is associated with progressive tissue dysfunction, leading to frailty and mortality. Characterizing aging features, such as changes in gene expression and dynamics, shared across tissues or specific to each tissue, is crucial for understanding systemic and local factors contributing to the aging process. We performed RNA-sequencing on 13 tissues at 6 different ages in the African turquoise killifish, the shortest-lived vertebrate that can be raised in captivity. This comprehensive, sex-balanced 'atlas' dataset reveals the varying strength of sex-age interactions across killifish tissues and identifies age-altered biological pathways that are evolutionarily conserved. Demonstrating the utility of this resource, we discovered that the killifish head kidney exhibits a myeloid bias during aging, a phenomenon more pronounced in females than in males. In addition, we developed tissue-specific 'transcriptomic clocks' and identified biomarkers predictive of chronological age. We show the importance of sex-specific clocks for selected tissues and use the tissue clocks to evaluate a dietary intervention in the killifish. Our work provides a comprehensive resource for studying aging dynamics across tissues in the killifish, a powerful vertebrate aging model.

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Enhancing epigenetic aging clocks in cetaceans: accurate age estimations in small endangered delphinids, killer whales, pilot whales, belugas, humpbacks, and bowhead whales

This study presents refined epigenetic clocks for cetaceans, building on previous research that estimated ages in several species from bottlenose dolphins to bowhead and humpback whales using cytosine methylation levels. We combined publicly available data (generated on the HorvathMammalMethylChip40 platform) from skin (n = 805) and blood (n = 286) samples across 13 cetacean species, aged 0 to 139 years. By combining methylation data from different sources, we enhanced our sample size, thereby strengthening the statistical validity of our clocks. We used elastic net regression with leave one sample out (LOO) and leave one species out (LOSO) cross validation to produce highly accurate blood only (Median Absolute Error [MAE] = 1.64 years, r = 0.96), skin only (MAE = 2.32 years, r = 0.94) and blood and skin multi-tissue (MAE = 2.24 years, r = 0.94) clocks. In addition, the LOSO blood and skin (MAE = 5.6 years, repeated measures r = 0.83), skin only (MAE = 6.22 years, repeated measures r = 0.81), and blood only (MAE = 4.11 years, repeated measures r = 0.95) clock analysis demonstrated relatively high correlation toward cetacean species not included within this current data set and provide evidence for a broader application of this model. Our results introduce a multi-species, two-tissue clock for broader applicability across cetaceans, alongside single-tissue multi-species clocks for blood and skin, which allow for more detailed aging analysis depending on the availability of samples. In addition, we developed species-specific clocks for enhanced precision, resulting in four blood-specific clocks and eight skin-specific clocks for individual species; all improving upon existing accuracy estimates for previously published species-specific clocks. By pooling methylation data from various studies, we increased our sample size, significantly enhancing the statistical power for building accurate clocks. These new epigenetic age estimators for cetaceans provide more accurate tools for aiding in conservation efforts of endangered cetaceans.

C. elegans aging research

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PREPRINT

Negative Effect of Gst-35 on the Health Span of Caenorhabditis elegans Through Lysosomal Dysfunction via the Pmk-1 and Skr Genes

As global life expectancy increases, the focus has shifted from merely extending lifespan to promoting healthy aging. GSTA1, GSTA2, and GSTA3 (GSTA1-3), members of the alpha class of glutathione S-transferases, are involved in diverse biological processes, including metabolism and immune regulation, highlighting their potential influence on human health span and lifespan. In this study, we employed Caenorhabditis elegans as a model organism to investigate the role of gst-35, an ortholog of mammalian GSTA1-3, in healthy aging. Our results demonstrated that gst-35 overexpression has detrimental effects on multiple physiological functions in nematodes. Specifically, gst-35 overexpression significantly reduced lifespan, impaired development and growth, and substantially diminished reproductive capacity, physical fitness, and stress resistance. In contrast, gst-35 knockout partially enhanced physical fitness and stress resistance. Comprehensive RNA-sequencing transcriptome analysis revealed that gst-35 overexpression disrupted metabolic homeostasis and induced lysosomal dysfunction. These effects were mediated through the activation of the pmk-1 signaling pathway and suppression of skr genes, which collectively impaired healthy aging processes. These findings illuminate the complex role of gst-35 in aging and provide valuable insights into the molecular mechanisms underlying healthy aging, offering potential targets for interventions aimed at promoting health span.

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PREPRINT

Functional Specialization of S-Adenosylmethionine Synthases Links Phosphatidylcholine to Mitochondrial Function and Stress Survival

S-adenosylmethionine (SAM), produced by SAM synthases, is critical for various cellular regulatory pathways and the synthesis of diverse metabolites. Studies have often equated the effects of knocking down one synthase with broader SAM-dependent outcomes such as histone methylation or phosphatidylcholine (PC) production. Humans and many other organisms express multiple SAM synthases. Evidence in *Caenorhabditis elegans*, which possesses four SAM synthase genes, suggest that the enzymatic source of SAM impacts its function. For instance, loss of *sams-1* leads to enhanced heat shock survival and increased lifespan, whereas reducing *sams-4* adversely affects heat stress survival. Here, we show that SAMS-1 contributes to a variety of intermediary metabolic pathways, whereas SAMS-4 is more important to generate SAM for methylation reactions. We demonstrate that loss of *sams-1* exerts age-dependent effects on nuclear-encoded mitochondrial gene expression, mitochondrial metabolites, and may induce mitophagy. We propose a mechanistic model where reduced SAM from SAMS-1 acts through PC to impact mitochondria, thereby enhancing survival during heat stress.

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Intestine-specific disruption of mitochondrial superoxide dismutase extends longevity

Reactive oxygen species (ROS) are highly reactive oxygen containing molecules that are generated by normal metabolism. While ROS can cause damage to the building blocks that make up cells, these molecules can also act as intracellular signals that promote longevity. The levels of ROS within the cell can be regulated by antioxidant enzymes, such as superoxide dismutase (SOD), which converts superoxide to hydrogen peroxide. Interestingly, our previous work has shown that disruption of the mitochondrial SOD gene *sod-2* results in increased lifespan, suggesting that elevating levels of mitochondrial superoxide can promote longevity. To explore the molecular mechanisms involved, we determined the tissues in which disruption of *sod-2* is necessary for lifespan extension and the tissues in which disruption of *sod-2* is sufficient to extend lifespan. We found that tissue-specific restoration of SOD-2 expression in worms lacking SOD-2 could partially revert changes in fertility, embryonic lethality and resistance to stress, but did not inhibit the effects of *sod-2* deletion on lifespan. Knocking down *sod-2* expression using RNA interference specifically in the intestine, but not other tissues, was sufficient to extend longevity. Intestine-specific knockdown of *sod-2* also increased resistance to heat stress while decreasing resistance to oxidative stress. Combined, these results indicate that disruption of *sod-2* in neurons, intestine, germline, or muscle is not required for lifespan extension, but that decreasing *sod-2* expression in just the intestine extends lifespan. This work defines the conditions required for disruption of mitochondrial superoxide dismutase to increase longevity.

Complex I superoxide anion production is necessary and sufficient for complex I inhibitor–induced dopaminergic neurodegeneration in Caenorhabditis elegans

Parkinson's Disease (PD) is the 2nd most prevalent neurodegenerative disease, but there is currently no cure and limited understanding of the pathogenesis resulting in dopaminergic neurodegeneration. Inhibitors of electron transport chain Complex I (CI) have long been associated with and are now used to model PD, but CI inhibition results in multiple effects including ATP depletion and reactive oxygen species (ROS) generation. The lack of tools to isolate effects of CI inhibition have rendered it difficult to determine which mechanistic step is critical for CI inhibitor-induced dopaminergic neurodegeneration. Here we report that CI-derived superoxide anion, not ATP depletion, is the critical driver of CI inhibitor-induced dopaminergic neurodegeneration in the model organism Caenorhabditis elegans. We first use SuperNova, a light-activated ROS-generating protein, fused to CI to demonstrate that in absence of enzymatic inhibition CI-localized ROS production is sufficient to drive morphological damage and loss of function of the dopaminergic neurons. Second, we prevented superoxide anion production during exposure to the CI inhibitors rotenone and pyridaben and report a full rescue of CI inhibitor-induced degeneration and functional loss, without rescue of inhibitor-induced ATP depletion. We highlight the importance of mitochondrial superoxide anion generation in the pathogenesis of PD and build a foundation for further definition of the pathways activated by mitochondrial ROS that led to neuronal dysfunction and death. Identification of these underlying mechanisms allows for future prevention of toxicant exposure-induced PD based on mechanistic knowledge.

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Iron-deplete diet enhances *Caenorhabditis elegans* lifespan via oxidative stress response pathways

Priyanka Das, Ravi, Jogender Singh

Gut microbes play a crucial role in modulating host lifespan. However, the microbial factors that influence host longevity and their mechanisms of action remain poorly understood. Using the expression of *Caenorhabditis elegans* FAT-7, a stearoyl-CoA 9-desaturase, as a proxy for lifespan modulation, we conduct a genome-wide bacterial mutant screen and identify 26 *Escherichia coli* mutants that enhance host lifespan. Transcriptomic and biochemical analyses reveal that these mutant diets induce oxidative stress and activate the mitochondrial unfolded protein response (UPRmt). Lifespan extension requires the oxidative stress response regulators SKN-1, SEK-1, and HLH-30. Mechanistically, these effects are linked to reduced iron availability, as iron supplementation restores FAT-7 expression, suppresses UPRmt activation, and abolishes lifespan extension. Iron chelation mimics the pro-longevity effects of the mutant diets, highlighting dietary iron as a key modulator of aging. Our findings reveal a bacterial-host metabolic axis that links iron homeostasis, oxidative stress, and longevity in *C. elegans*.

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PREPRINT

WormAI:Artificial Intelligence of Networks for Nematode Phenotyping

Maggie Lieu, Qi Cao, Ruoqing Meng, Dong Zhang, Veeren M. Chauhan

The nematode *Caenorhabditis elegans* is a key model organism in biological research due to its genetic similarity to humans and its utility in studying complex processes. Traditional image analysis methods, such as those using ImageJ, are labour-intensive, which has led to the integration of AI. This study introduces an AI framework with three machine learning models: WormGAN, a Generative Adversarial Network for generating synthetic nematode images to enhance training data; WormDET, for precise movement tracking; and WormREG, for accurate anatomical measurements. Together, these tools significantly improve the efficiency and accuracy of phenotypic analysis. WormAI demonstrates substantial potential for high-throughput dataset analysis, advancing research in systems biology, drug discovery, and aging. This framework streamlines workflows, enabling faster and more precise discoveries in *C. elegans* studies.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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International Consortium to Classify Ageing-related Pathologies (ICCARP) senescence definitions: achieving international consensus

ORIGINAL ARTICLE | Open access | Published: 21 February 2025

Senescence definitions: ICCARP consensus

With the global increase in ageing populations, a clear understanding of the physiological and pathological changes associated with ageing is vital for advancing research and clinical practice. Following the World Health Organization's decision to classify age-related aetiologies [1], the International Consortium to Classify Ageing-related Pathologies (ICCARP) was established in 2023, led by Cardiff Metropolitan University [2].

The aim of the ICCARP is to develop a systematic and comprehensive classification system for ageing-related changes including pathologies, diseases, and syndromes. Currently, the ICCARP is in the process of identifying all phenomena that meet the criteria for ageing-related pathologies, to develop proposals for grouping and naming them within a comprehensive classification system. However, during the course of this project, it became evident that certain terms, specifically relating to 'senescence', were interpreted and understood in multiple ways, often dependent upon the professional background of an expert and the context in which the term was being used. To achieve our goals, it is vital that we use a universal language when naming and proposing ageing-related changes to provide a clear, unambiguous understanding of the changes and their underlying contribution to maintaining or degrading organismal integrity (physiology versus pathology). Furthermore, establishing clear nomenclature will be advantageous in the wider efforts to unify the study of ageing, and to better align research and clinical practice.

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What makes biological age epigenetic clocks tick

Mahdi Moqri, Jesse R. Poganik, Steve Horvath & Vadim N. Gladyshev

Nature Aging (2025) | Cite this article

Epigenetic clocks are increasingly used to study aging[1]. However, confusion persists regarding the specific signals that clocks capture, as these encompass intrinsic, extrinsic, stochastic and programmatic changes. As such, it is important to understand the factors that drive potentially discordant results between clocks and how such complexities may be reconciled. Here, we highlight five important signals that are captured to different extents by epigenetic clocks and suggest additional standard analyses to more specifically represent these factors. These steps will ultimately improve our understanding of the various factors that make different clocks tick.

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Hallmarks of aging: A user's guide for comparative biologists

Since the first description of a set of characteristics of aging as so-called hallmarks or pillars in 2013/2014, these characteristics have served as guideposts for the research in aging biology. They have been examined in a range of contexts, across tissues, in response to disease conditions or environmental factors, and served as a benchmark for various anti-aging interventions. While the hallmarks of aging were intended to capture generalizable characteristics of aging, they are derived mostly from studies of rodents and humans. Comparative studies of aging including species from across the animal tree of life have great promise to reveal new insights into the mechanistic foundations of aging, as there is a great diversity in lifespan and age-associated physiological changes. However, it is unclear how well the defined hallmarks of aging apply across diverse species. Here, we review each of the twelve hallmarks of aging defined by Lopez-Otin in 2023 with respect to the availability of data from diverse species. We evaluate the current methods used to assess these hallmarks for their potential to be adapted for comparative studies. Not unexpectedly, we find that the data supporting the described hallmarks of aging are restricted mostly to humans and a few model systems and that no data are available for many animal clades. Similarly, not all hallmarks can be easily assessed in diverse species. However, for at least half of the hallmarks, there are methods available today that can be employed to fill this gap in knowledge, suggesting that these studies can be prioritized while methods are developed for comparative study of the remaining hallmarks.

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Mesenchymal stem cell exosome therapy: current research status in the treatment of neurodegenerative diseases and the possibility of reversing normal brain aging

With the exacerbation of the aging population trend, a series of neurodegenerative diseases caused by brain aging have become increasingly common, significantly impacting the daily lives of the elderly and imposing heavier burdens on nations and societies. Brain aging is a complex process involving multiple mechanisms, including oxidative stress, apoptosis of damaged neuronal cells, chronic inflammation, and mitochondrial dysfunction, and research into new therapeutic strategies to delay brain aging has gradually become a research focus in recent years. Mesenchymal stem cells (MSCs) have been widely used in cell therapy due to their functions such as antioxidative stress, anti-inflammation, and tissue regeneration. However, accompanying safety issues such as immune rejection, tumor development, and pulmonary embolism cannot be avoided. Studies have shown that using exosome derived from mesenchymal stem cells (MSC-Exo) for the treatment of neurodegenerative diseases is a safe and effective method. It not only has the therapeutic effects of stem cells but also avoids the risks associated with cell therapy. Therefore, exploring new therapeutic strategies to delay normal brain aging from the mechanism of MSC-Exo in the treatment of neurodegenerative diseases is feasible. This review summarizes the characteristics of MSC-Exo and their clinical progress in the treatment of neurodegenerative diseases, aiming to explore the possibility and potential mechanisms of MSC-Exo in reversing brain aging.

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Regulatory Roles of Exosomes in Aging and Aging-Related Diseases

Exosomes are small vesicles with diameters ranging from 30 to 150 nm. They originate from cellular endocytic systems. These vesicles contain a rich payload of biomolecules, including proteins, nucleic acids, lipids, and metabolic products. Exosomes mediate intercellular communication and are key regulators of a diverse array of biological processes, such as oxidative stress and chronic inflammation. Furthermore, exosomes have been implicated in the pathogenesis of infectious diseases, autoimmune disorders, and cancer. Aging is closely associated with the onset and progression of numerous diseases and is significantly influenced by exosomes. Recent studies have consistently highlighted the important functions of exosomes in the regulation of cellular senescence. Additionally, research has explored their potential to delay aging, such as the alleviatory effects of stem cell-derived exosomes on the aging process, which offers broad potential for the development and application of exosomes as anti-aging therapeutic strategies. This review aims to comprehensively investigate the multifaceted impact of exosomes while concurrently evaluating their potential applications and underscoring their strategic significance in advancing anti-aging strategies.

Validation requirements for AI-based intervention-evaluation in aging and longevity research and practice

The field of aging and longevity research is overwhelmed by vast amounts of data, calling for the use of Artificial Intelligence (AI), including Large Language Models (LLMs), for the evaluation of geroprotective interventions. Such evaluations should be correct, useful, comprehensive, explainable, and they should consider causality, interdisciplinarity, adherence to standards, longitudinal data and known aging biology. In particular, comprehensive analyses should go beyond comparing data based on canonical biomedical databases, suggesting the use of AI to interpret changes in biomarkers and outcomes. Our requirements motivate the use of LLMs with Knowledge Graphs and dedicated workflows employing, e.g., Retrieval-Augmented Generation. While naive trust in the responses of AI tools can cause harm, adding our requirements to LLM queries can improve response quality, calling for benchmarking efforts and justifying the informed use of LLMs for advice on longevity interventions.

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Deep learning and generative artificial intelligence in aging research and healthy longevity medicine

With the global population aging at an unprecedented rate, there is a need to extend healthy productive life span. This review examines how Deep Learning (DL) and Generative Artificial Intelligence (GenAI) are used in biomarker discovery, deep aging clock development, geroprotector identification and generation of dual-purpose therapeutics targeting aging and disease. The paper explores the emergence of multimodal, multitasking research systems highlighting promising future directions for GenAI in human and animal aging research, as well as clinical application in healthy longevity medicine.

Senescence as a molecular target in skin aging and disease

Skin aging represents a multifactorial process influenced by both intrinsic and extrinsic factors, collectively known as the skin exposome. Cellular senescence, characterized by stable cell cycle arrest and secretion of pro-inflammatory molecules, has been implicated as a key driver of physiological and pathological skin aging. Increasing evidence points towards the role of senescence in a variety of dermatological diseases, where the accumulation of senescent cells in the epidermis and dermis exacerbates disease progression. Emerging therapeutic strategies such as senolytics and senomorphics offer promising avenues to target senescent cells and mitigate their deleterious effects, providing potential treatments for both skin aging and senescence-associated skin diseases. This review explores the molecular mechanisms of cellular senescence and its role in promoting age-related skin changes and pathologies, while compiling the observed effects of senotherapeutics in the skin and discussing the translational relevance.

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Autophagy in Tissue Repair and Regeneration

by Daniel Moreno-Blas, Teresa Adell and Cristina González-Estévez *

Autophagy is a cellular recycling system that, through the sequestration and degradation of intracellular components regulates multiple cellular functions to maintain cellular homeostasis and survival. Dysregulation of autophagy is closely associated with the development of physiological alterations and human diseases, including the loss of regenerative capacity. Tissue regeneration is a highly complex process that relies on the coordinated interplay of several cellular processes, such as injury sensing, defense responses, cell proliferation, differentiation, migration, and cellular senescence. These processes act synergistically to repair or replace damaged tissues and restore their morphology and function. In this review, we examine the evidence supporting the involvement of the autophagy pathway in the different cellular mechanisms comprising the processes of regeneration and repair across different regenerative contexts. Additionally, we explore how modulating autophagy can enhance or accelerate regeneration and repair, highlighting autophagy as a promising therapeutic target in regenerative medicine for the development of autophagy-based treatments for human diseases.

Methylglyoxal Formation—Metabolic Routes and Consequences

by Janka Vašková [1,*], Gabriela Kováčová [2], Jakub Pudelský [2], Drahomír Palenčár [3] and Helena Mičková [1]

Methylglyoxal (MGO), a by-product of glycolysis, plays a significant role in cellular metabolism, particularly under stress conditions. However, MGO is a potent glycotoxin, and its accumulation has been linked to the development of several pathological conditions due to oxidative stress, including diabetes mellitus and neurodegenerative diseases. This paper focuses on the biochemical mechanisms by which MGO contributes to oxidative stress, particularly through the formation of advanced glycation end products (AGEs), its interactions with antioxidant systems, and its involvement in chronic diseases like diabetes, neurodegeneration, and cardiovascular disorders. MGO exerts its effects through multiple signaling pathways, including NF-κB, MAPK, and Nrf2, which induce oxidative stress. Additionally, MGO triggers apoptosis primarily via intrinsic and extrinsic pathways, while endoplasmic reticulum (ER) stress is mediated through PERK-eIF2α and IRE1-JNK signaling. Moreover, the activation of inflammatory pathways, particularly through RAGE and NF-κB, plays a crucial role in the pathogenesis of these conditions. This study points out the connection between oxidative and carbonyl stress due to increased MGO formation, and it should be an incentive to search for a marker that could have prognostic significance or could be a targeted therapeutic intervention in various diseases.

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Cancer treatments accelerate ageing

Marco Demaria

Nature Reviews Cancer (2025) | Cite this article

Advancements in cancer treatment have led to a growing population of cancer survivors worldwide, who often experience premature onset of age-related conditions. Understanding the molecular and cellular basis of the long-term consequences of cancer treatment is essential for developing interventions to mitigate their adverse effects.

Dietary Restrictions and Cancer Prevention: State of the Art

Greta Caprara [1], Rani Pallavi [1 2 3], Shalini Sanyal [2 3], Pier Giuseppe Pelicci [1]

Worldwide, almost 10 million cancer deaths occurred in 2022, a number that is expected to rise to 16.3 million by 2040. Primary prevention has long been acknowledged as a crucial approach to reducing cancer incidence. In fact, between 30 and 50 percent of all tumors are known to be preventable by eating a healthy diet, staying active, avoiding alcohol, smoking, and being overweight. Accordingly, many international organizations have created tumor prevention guidelines, which underlie the importance of following a diet that emphasizes eating plant-based foods while minimizing the consumption of red/processed meat, sugars, processed foods, and alcohol. However, further research is needed to define the relationship between the effect of specific diets or nutritional components on cancer prevention. Interestingly, reductions in food intake and dietetic restrictions can extend the lifespan of yeast, nematodes, flies, and rodents. Despite controversial results in humans, those approaches have the potential to ameliorate health via direct and indirect effects on specific signaling pathways involved in cancer onset. Here, we describe the latest knowledge on the cancer-preventive potential of dietary restrictions and the biochemical processes involved. Molecular, preclinical, and clinical studies evaluating the effects of different fasting strategies will also be reviewed.

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Awareness, knowledge, and motivations about lifespan, healthspan, and Healthy Longevity Medicine in the general population: the HEalthy LOngevity (HELO) conceptual framework

The global population is ageing and the gap between lifespan (total years lived) and healthspan (years lived free of diseases) is increasing. Healthy Longevity Medicine (HLM) is an approach to optimise health and healthspan, and it has substantial public health implications. Despite those implications, the understanding of public perspectives on this field is lacking. The HEalthy LOngevity (HELO) framework was developed through a literature review guided by expert discussions across disciplines to include evidence-based concepts of health-related decision-making, ageing, and HLM. The framework organises concepts into three components. The first two components, awareness and knowledge, explore public perception and understanding of the healthy longevity field, respectively. The third component, motivations, reflects factors underlying motivations towards healthy longevity. These include personality, current behaviours, personal values and beliefs, and health-related perceptions. The framework outlines the theoretical foundation to explore public knowledge and interest in healthy longevity. The framework will be refined based on findings from qualitative focus groups in Singapore and then applied to quantitative population surveys globally. These HELO initiatives aim to inform strategies for integrating HLM into public healthcare, promoting health and healthspan.

Human stem cell–based cell replacement therapy for Parkinson's disease: enhancing the survival of postmitotic dopamine neuron grafts

Kim, Tae Wan*

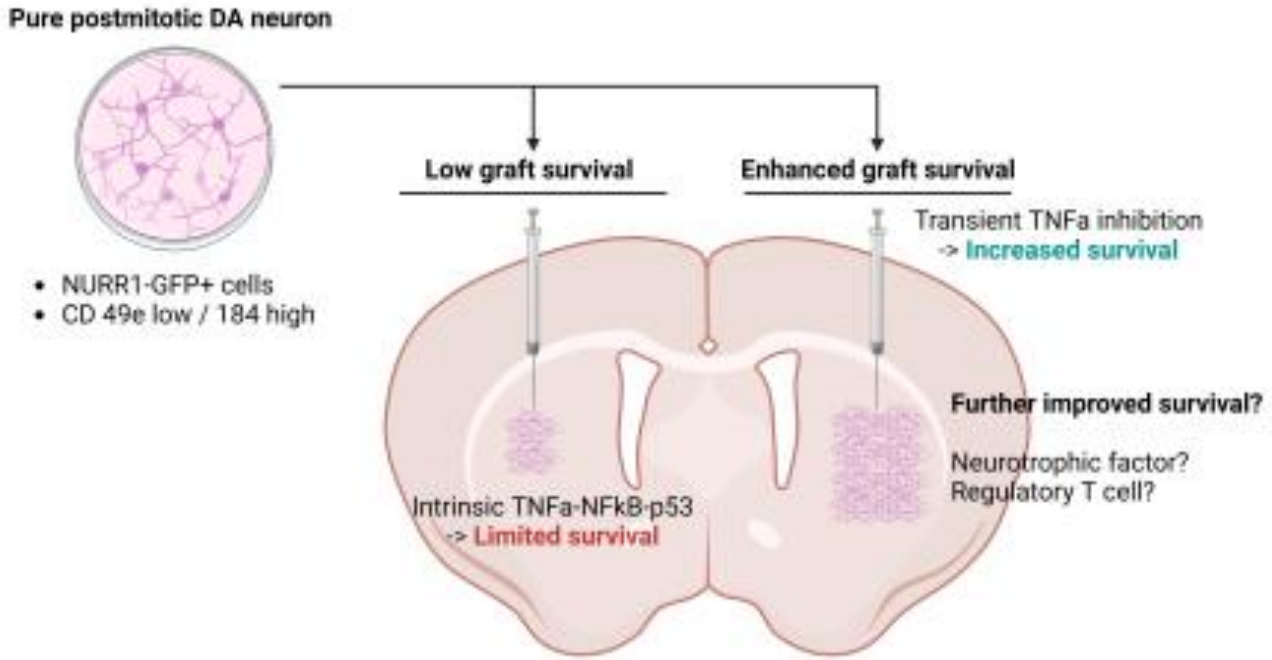
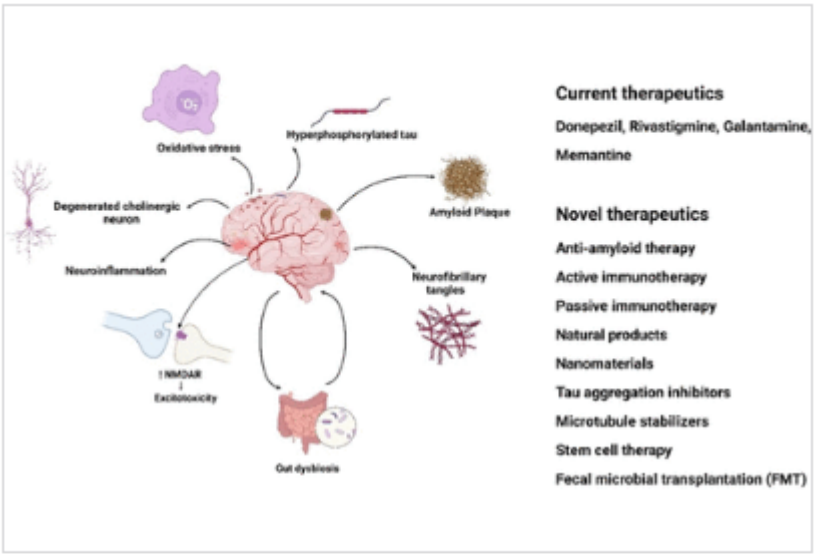


Figure 1 | Strategies to improve the *in vivo* survival of postmitotic DA neurons, purified through NURR1-driven GFP expression or CD marker-based isolation with CD 49e and 184, following implantations.
The intrinsic TNFα-NFκB-p53 axis triggers graft death. Transient administration of a TNFα inhibitor enhancers graft survival. Potential strategies to further improve in vivo graft survival beyond intrinsic factors would involve manipulating extrinsic host environmental factors, including co-treatment TNFα inhibitor with neurotrophic factors, such as GDNF, and/or regulatory T cells. Created with BioRegend.com. CD: Cell surface marker; DA: dopamine; GDNF: glia-cell-line-derived neurotrophic factor; GFP: green fluorescent protein; NFκB: nuclear factor kappa B; TNFα: tumor necrosis factor-alpha.

Newer Therapeutic Approaches in Treating Alzheimer's Disease: A Comprehensive Review

Radhakrishna Reddi Sree, Manjunath Kalyan, Nikhilesh Anand, Sangeetha Mani, Vasavi Rakesh Gorantla, Meena Kishore Sakharkar, Byoung-Joon Song, and Saravana Babu Chidambaram*

Alzheimer's disease (AD) is an aging-related irreversible neurodegenerative disease affecting mostly the elderly population. The main pathological features of AD are the extracellular Aβ plaques generated by APP cleavage through the amyloidogenic pathway, the intracellular neurofibrillary tangles (NFT) resulting from the hyperphosphorylated tau proteins, and cholinergic neurodegeneration. However, the actual causes of AD are unknown, but several studies suggest hereditary mutations in *PSEN1* and *-2*, *APOE4*, *APP*, and the *TAU* genes are the major perpetrators. In order to understand the etiology and pathogenesis of AD, various hypotheses are proposed. These include the following hypotheses: amyloid accumulation, tauopathy, inflammation, oxidative stress, mitochondrial dysfunction, glutamate/excitotoxicity, cholinergic deficiency, and gut dysbiosis. Currently approved therapeutic interventions are donepezil, galantamine, and rivastigmine, which are cholinesterase inhibitors (ChEIs), and memantine, which is an *N*-methyl-D-aspartate (NMDA) antagonist. These treatment strategies focus on only symptomatic management of AD by attenuating symptoms but not regeneration of neurons or clearance of Aβ plaques and hyperphosphorylated Tau. This review focuses on the pathophysiology, novel therapeutic targets, and disease-altering treatments such as α-secretase modulators, active immunotherapy, passive immunotherapy, natural antioxidant products, nanomaterials, antiamyloid therapy, tau aggregation inhibitors, transplantation of fecal microbiota or stem cells, and microtubule stabilizers that are in clinical trials or still under investigation.



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Protocols for the application of human embryonic stem cell-derived neurons for aging modeling and gene manipulation

Hui Zhang [1 10], Shuhui Sun [1 10], Juan Carlos Izpisua Belmonte [9], Guang-Hui Liu [2 3 5 8 11 12] ✉, Si Wang [4 8] ✉, Weiqi Zhang [3 5 6 7 8] ✉, Jing Qu [1 2 3 5 8] ✉

Invitro models of neuronal aging and gene manipulation in human neurons (hNeurons) are valuable tools for investigating human brain aging and diseases. Here, we present a protocol for applying human embryonic stem cell (hESC)-derived neurons to model aging and the further application of small interfering RNA (siRNA)-mediated gene silencing for functional investigations. We describe steps for neuronal differentiation and culture, siRNA transfection, and technical considerations to ensure reproducibility. Our protocol enables investigations ofthe molecular mechanism underlying neuronal aging and facilitates drug evaluation.

OTHER RESEARCH & REVIEWS

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A rapid chemical reprogramming system to generate human pluripotent stem cells

Chemical reprogramming enables the generation of human pluripotent stem (hCiPS) cells from somatic cells using small molecules, providing a promising strategy for regenerative medicine. However, the current method is time consuming, and some cell lines from different donors are resistant to chemical induction, limiting the utility of this approach. Here, we developed a fast reprogramming system capable of generating hCiPS cells in as few as 10 days. This accelerated method enables efficient generation of hCiPS cells with a consistent 100% success rate across 15 different donors, increasing efficiency by over 20-fold within 16 days, especially for previously resistant cells. Mechanistically, we identified KAT3A/KAT3B and KAT6A as key epigenetic obstacles; suppressing these factors facilitated the transition of somatic cells to a poised state by triggering switches in the epigenome. These results highlight the superiority of this system for generating hCiPS cells, which represents a next-generation approach for manufacturing cells for further applications.

COVID-19 Vaccination and Odds of Post–COVID-19 Condition Symptoms in Children Aged 5 to 17 Years

Exposures COVID-19 mRNA vaccination status at time of infection was the exposure of interest; participants were categorized as vaccinated (≥2-dose series completed ≥14 days before infection) or unvaccinated. Vaccination status was verified through vaccination cards or vaccine registry and/or medical records when available.

Main Outcome and Measures Main outcomes were estimates of the odds of PCC symptoms. Multivariate logistic regression was performed to estimate the odds of PCC among vaccinated children compared with odds of PCC among unvaccinated children.

Results A total of 622 participants were included, with 28 (5%) case participants and 594 (95%) control participants. Median (IQR) age was 10.0 (7.0-11.9) years for case participants and 10.3 (7.8-12.7) years for control participants ($P = .37$). Approximately half of both groups reported female sex (13 case participants [46%] and 287 control participants [48%]). Overall, 57% of case participants (16 children) and 77% of control participants (458 children) were vaccinated ($P = .05$). After adjusting for demographic characteristics, number of acute COVID-19 symptoms, and baseline health, COVID-19 vaccination was associated with decreased odds of 1 or more PCC symptom (adjusted odds ratio [aOR], 0.43; 95% CI, 0.19-0.98) and 2 or more PCC symptoms (aOR, 0.27; 95% CI, 0.10-0.69).

Conclusions and Relevance In this study, mRNA COVID-19 vaccination was associated with reduced odds of PCC in children. The aORs correspond to an estimated 57% and 73% reduced likelihood of 1 or more and 2 or more PCC symptoms, respectively, among vaccinated vs unvaccinated children. These findings suggest benefits of COVID-19 vaccination beyond those associated with protection against acute COVID-19 and may encourage increased pediatric uptake.