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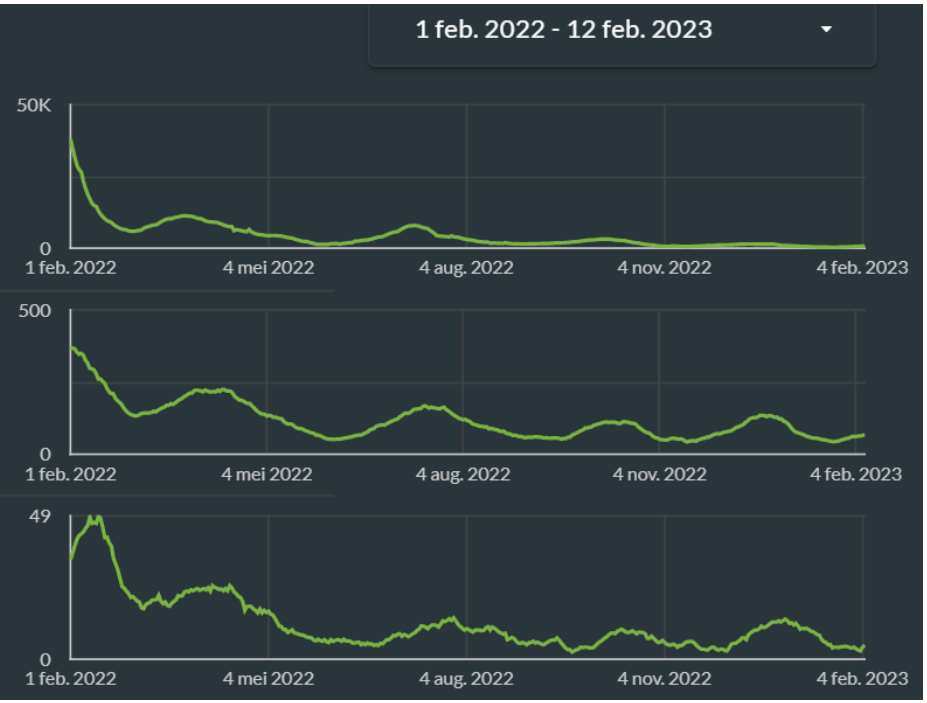
Scientific News
12th of February 2023
Sven Bulterijs

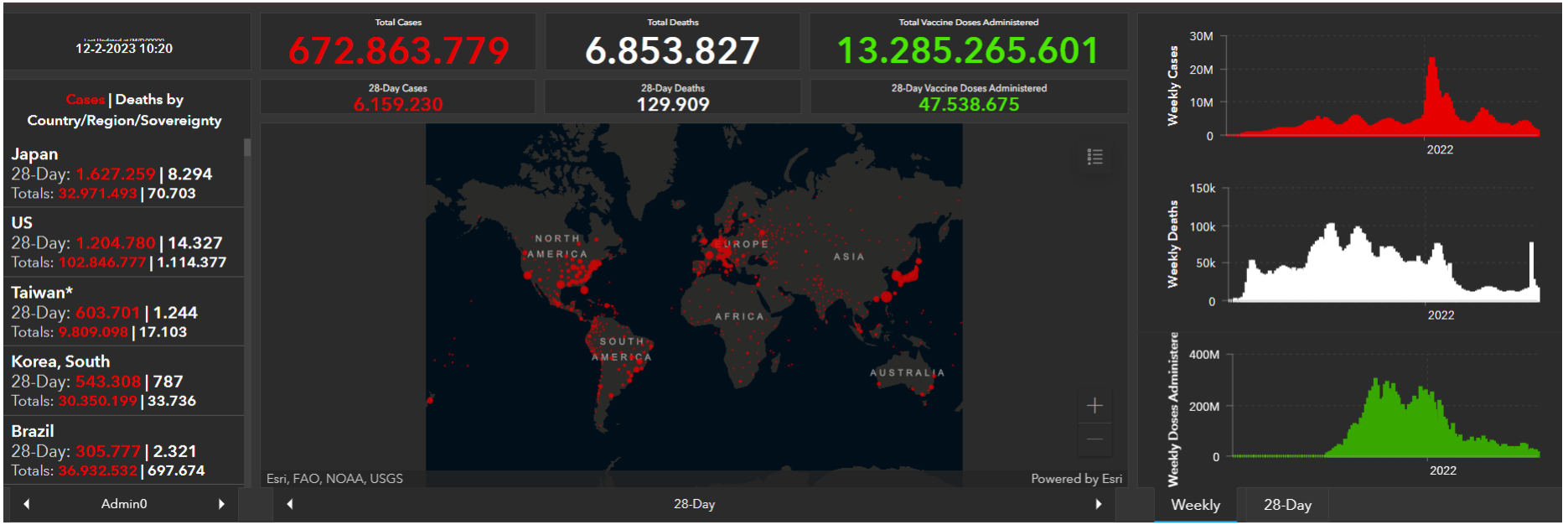
Business/Conferences/ General news

Belgium

	Total	Last 7 days Daily Average
Cases	4,7 mln.	707 * +48%
Hospital Admissions for COVID-19	147,5K	67,3 +18%
Deaths	33,6K	4,9 * +21%



World



Frailty impacts immune responses to Moderna COVID-19 mRNA vaccine in older adults

Charles T Semelka [1], Michael E DeWitt [2], Maria W Blevins [2], Beth C Holbrook [3], John W Sanders [2], Martha A Alexander-Miller [3]

Background: Immune responses to COVID-19 mRNA vaccines have not been well characterized in frail older adults. We postulated that frailty is associated with impaired antibody and cellular mRNA vaccine responses.

Methods: We followed older adults in a retirement facility with longitudinal clinical and serological samples from the first Moderna mRNA-1273 vaccine dose starting in February 2021 through their 3rd (booster) vaccine dose. Outcomes were antibody titers, antibody avidity, and AIM+ T cell function and phenotype. Statistical analysis used linear regression with clustered error for antibody titers over multiple timepoints with clinical predictors including, age, sex, prior infection status, and clinical frailty scale (CFS) score. T cell function analysis used linear regression models with clinical predictors and cellular memory phenotype variables.

Results: Participants (n = 15) had median age of 90 years and mild, moderate, or severe frailty scores (n = 3, 7, or 5 respectively). Over the study time course, anti-spike antibody titers were 10-fold higher in individuals with lower frailty status ($p = 0.001$ and $p = 0.005$, unadjusted and adjusted for prior COVID-19 infection). Following the booster, titers to spike protein improved regardless of COVID-19 infection or degree of frailty ($p = 0.82$ and $p = 0.29$, respectively). Antibody avidity significantly declined over 6 months in all participants following 2 vaccine doses ($p < 0.001$), which was further impaired with higher frailty ($p = 0.001$). Notably, avidity increased to peak levels after the booster ($p < 0.001$). Overall antibody response was inversely correlated with a phenotype of immune-senescent T cells, CD8 + CD28- TEMRA cells ($p = 0.036$, adjusted for COVID-19 infection). Furthermore, there was increased detection of CD8 + CD28- TEMRA cells in individuals with greater frailty ($p = 0.056$, adjusted for COVID-19).

Conclusions: We evaluated the immune responses to the Moderna COVID-19 mRNA vaccine in frail older adults in a retirement community. A higher degree of frailty was associated with diminished antibody quantity and quality. However, a booster vaccine dose at 6 months overcame these effects. Frailty was associated with an increased immune-senescence phenotype that may contribute to the observed changes in the vaccine response. While the strength of our conclusions was limited by a small cohort, these results are important for guiding further investigation of vaccine responses in frail older adults.

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PREPRINT

Senolytic therapy alleviates physiological human brain aging and COVID-19 neuropathology

Aging is the primary risk factor for most neurodegenerative diseases, and recently coronavirus disease 2019 (COVID-19) has been associated with severe neurological manifestations that can eventually impact neurodegenerative conditions in the long-term. The progressive accumulation of senescent cells *in vivo* strongly contributes to brain aging and neurodegenerative co-morbidities but the impact of virus-induced senescence in the aetiology of neuropathologies is unknown. Here, we show that senescent cells accumulate in physiologically aged brain organoids of human origin and that senolytic treatment reduces inflammation and cellular senescence; for which we found that combined treatment with the senolytic drugs dasatinib and quercetin rejuvenates transcriptomic human brain aging clocks. We further interrogated brain frontal cortex regions in postmortem patients who succumbed to severe COVID-19 and observed increased accumulation of senescent cells as compared to age-matched control brains from non-COVID-affected individuals. Moreover, we show that exposure of human brain organoids to SARS-CoV-2 evoked cellular senescence, and that spatial transcriptomic sequencing of virus-induced senescent cells identified a unique SARS-CoV-2 variant-specific inflammatory signature that is different from endogenous naturally-emerging senescent cells. Importantly, following SARS-CoV-2 infection of human brain organoids, treatment with senolytics blocked viral retention and prevented the emergence of senescent corticothalamic and GABAergic neurons. Furthermore, we demonstrate in human ACE2 overexpressing mice that senolytic treatment ameliorates COVID-19 brain pathology following infection with SARS-CoV-2. *In vivo* treatment with senolytics improved SARS-CoV-2 clinical phenotype and survival, alleviated brain senescence and reactive astrogliosis, promoted survival of dopaminergic neurons, and reduced viral and senescence-associated secretory phenotype gene expression in the brain. Collectively, our findings demonstrate SARS-CoV-2 can trigger cellular senescence in the brain, and that senolytic therapy mitigates senescence-driven brain aging and multiple neuropathological sequelae caused by neurotropic viruses, including SARS-CoV-2.

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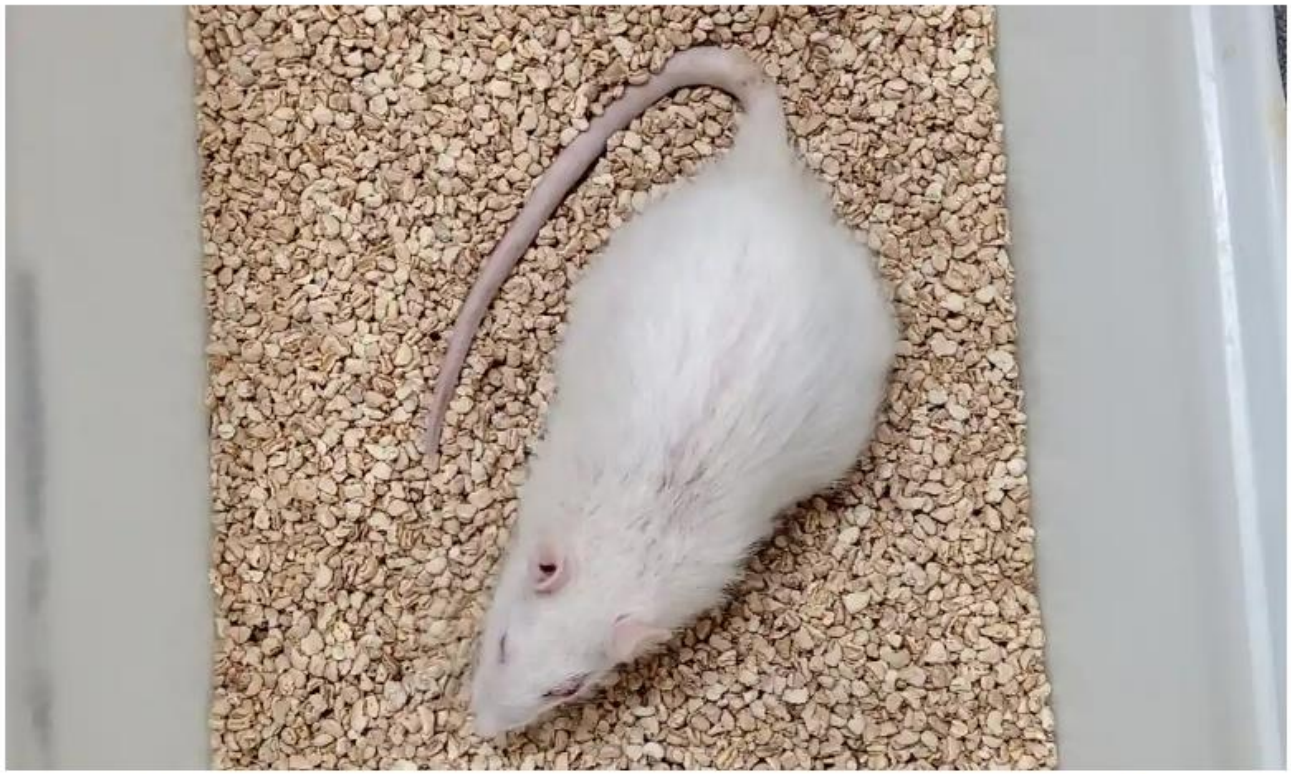
Anti-ageing scientists extend lifespan of oldest living lab rat

Research teases hopes that 'rejuvenation of the body may become commonplace within our lifetimes'



Sima, at 47 months old the oldest living Spague-Dawley rat, was the beneficiary of blood plasma treatments scientists believe have extended her life. Photograph: handout

1. WO2022150818 - ANTI-AGING COMPOSITIONS AND USES THEREOF

[0008] As detailed herein, the present applicants have discovered methods and compositions comprising a concentrated, purified plasma fraction. The plasma fraction may provide an effective treatment for aging and age-related diseases, without causing an immune reaction in the intended recipient. For example, the present composition may be able to reset gene expression, the epigenome, the transcriptome and/or proteome in the recipient to more closely resemble that of a younger individual, thus resulting in a reduction of any of a number of anti-aging phenotypes. The donor of the plasma may be a member of a different species (e.g., livestock) than the recipient (e.g., human), thus crucially circumventing the need for human donor plasma. Also provided herein are novel methods of preparing such compositions that comprise incubating a crude plasma fraction with PEG, sedimenting the fraction, and applying the resuspended sediment to a size exclusion chromatography column.

[0009] Provided herein is a method of preparing a composition comprising a concentrated, purified plasma fraction, wherein the method comprises the following steps in order a) isolating a crude plasma fraction from a composition comprising plasma and platelets; b) incubating a solution comprising the crude plasma fraction of step a) with polyethylene glycol (PEG); c) centrifuging the plasma fraction and polyethylene glycol solution of step b) to generate a sediment; d) resuspending the sediment in a buffer and applying the resuspended sediment to a size exclusion chromatography matrix; e) eluting fractions from the size exclusion chromatography matrix; and f) concentrating the eluted fractions to provide the concentrated, purified plasma fraction.

[0010] In some embodiments, the composition comprising plasma and platelets is obtained from a mammal. In some embodiments, the mammal is a pig, a cow, a goat, a sheep, or a human. In some embodiments, the mammal is selected such that its plasma will not cause an immune reaction with an intended recipient. In some embodiments, the mammal is a healthy juvenile or adolescent mammal. In some embodiments, the intended recipient is a human.

[0011] In some embodiments, isolating the crude plasma fraction from a composition comprising plasma and platelets in step a) comprises centrifugation of the composition comprising plasma and platelets. In some embodiments, the composition comprising plasma and platelets is centrifuged at room temperature.

[0012] In some embodiments, the PEG has an average molecular weight of between 15 kD to 30 kD.

[0013] In some embodiments, the solution comprising the crude plasma fraction and PEG is incubated for about 7 to about 14 hours in step b). In some embodiments, in step c), the crude plasma fraction and polyethylene glycol solution is centrifuged at about 1000xg for at least five minutes at about 4° C.

[0014] In some embodiments, the size exclusion chromatography matrix is a Sephadex G100® column. In some embodiments, the size exclusion chromatography matrix comprises repeating glucose units attached by a- 1,6 glucosidic bonds with a filtration range of 4 kD to 150 kD for globular proteins and 1 kD to 100 kD for dextrans. In some embodiments, the size exclusion chromatography matrix comprises a bead size of 40-120 pm. In some embodiments, the size exclusion chromatography matrix is a Sephacryl S-300 column. In some embodiments, the size exclusion chromatography matrix comprises allyldextran crosslinked with N,N'-methylenebisacrylamide with a filtration range of 100 kD to 1,500 kD for globular proteins. In some embodiments, the size exclusion chromatography matrix comprises a bead size of about 25 pm to about 75 pm.

[0015] In some embodiments, the eluted fractions are concentrated in step f) by dialyzing the eluted fractions with a membrane with a molecular weight cut off of from 12 kD to 14 kD.

[0016] In some embodiments, the method further comprises resuspending the concentrated, purified plasma fraction in step f) in saline to produce a pharmaceutical composition.

[0017] In some embodiments, the method further comprises lyophilizing the pharmaceutical composition.

[0023] In some embodiments, the composition comprises one or more of extracellular vesicles, exosomes, exomeres, nonmembrane bound proteins, exogenous proteins, and other molecules and molecular complexes such as protein associated with extracellular vesicles, exosomes, exomeres, or combinations thereof. In some embodiments, a composition

comprising a concentrated, purified plasma fraction or pharmaceutical composition thereof comprises CD63, CD81, and/or CD9.

New whitepaper

Geriater, Prof. dr. Nele Van Den Noortgate - Inzetten op meer en eerder screenen op kwetsbaarheid bij ouderen.

Geriater, Prof. dr. Mirko Petrovic - Inzetten op sensibilisering over oordeelkundig voorschrijven van medicatie bij ouderen.

Verouderingsbioloog, Dr. Sven Bulterijs - Langer gezond door medicatie: fictie of realiteit.

Cardioloog, Prof. dr. Ernst Rietzschel - De grootste bedreiging voor ons gezondheidssysteem is te veel focussen op de mensen die reeds ziek zijn.

Bewegingswetenschapper, Prof. dr. Greet Cardon - Inzetten op meer beweging bij ouderen.

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After pandemic breather, Big Pharma sees drug development costs rise and returns sink: report

By **Gabrielle Masson** • Feb 8, 2023 12:02pm

Specifically, the cost to take a drug candidate from discovery stage all the way to market launch hit $2.3 billion—a $298 million rise from 2021, although still below 2019 and 2020 levels. The figures come from the latest annual report from Deloitte (PDF), which examines the current state of R&D returns by analyzing projected return on investment (ROI) from late-stage pipelines of the 20 biggest pharmas.

While costs began to creep up again, the amount of money an approved drug was expected to bring in dropped. In 2022, average peak sales per asset were projected to be $389 million per year, plunging from $500 million in 2021 and closer to 2020's return rate of $398 million.

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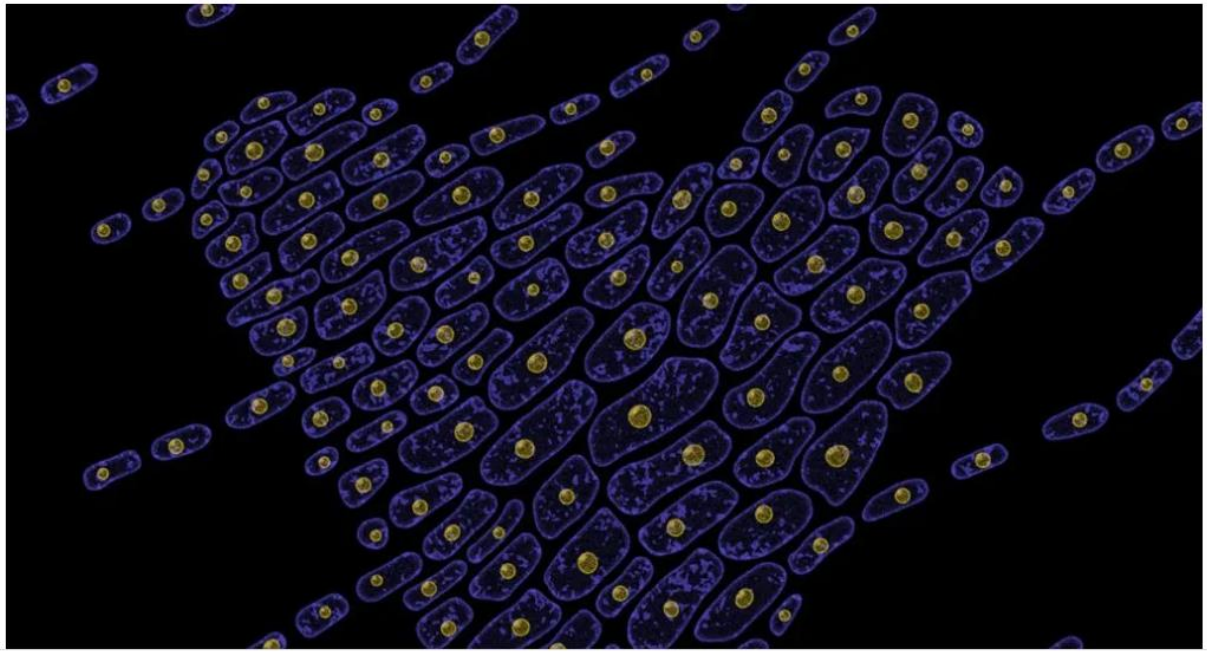
VitaDAO closes $4.1 million fundraising round

Author: **Eleanor Garth** | Published on: **January 30, 2023** | Last updated: **January 30, 2023**



Editor's choice

Empowering cells to boost energy and recovery is a winning move

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Caution with AI-generated content in biomedicine

Generative artificial intelligence tools such as chatGPT have many uses in medicine, but a lack of accuracy poses problems.

Alex Zhavoronkov

Generative artificial intelligence (AI) describes algorithms that can create new content, including text, audio and images, on the basis of patterns learned from large amounts of training data. Large language models that can generate conversational text, such as chatGPT, are not new, but they have recently progressed from proof-of-concept trials to industrial-strength products with applications for consumers. Generative AI systems have many applications in biomedical research and health, including formulating disease hypotheses, discovering novel drug targets, and generating novel small molecules and antibodies.

Aging research articles

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Genome-wide RNA polymerase stalling shapes the transcriptome during aging

Akos Gyenis, Jiang Chang, Joris J. P. G. Demmers, Serena T. Bruens, Sander Barnhoorn, Renata M. C. Brandt, Marjolein P. Baar, Marko Raseta, Kasper W. J. Derks, Jan H. J. Hoeijmakers & Joris Pothof

Gene expression profiling has identified numerous processes altered in aging, but how these changes arise is largely unknown. Here we combined nascent RNA sequencing and RNA polymerase II chromatin immunoprecipitation followed by sequencing to elucidate the underlying mechanisms triggering gene expression changes in wild-type aged mice. We found that in 2-year-old liver, 40% of elongating RNA polymerases are stalled, lowering productive transcription and skewing transcriptional output in a gene-length-dependent fashion. We demonstrate that this transcriptional stress is caused by endogenous DNA damage and explains the majority of gene expression changes in aging in most mainly postmitotic organs, specifically affecting aging hallmark pathways such as nutrient sensing, autophagy, proteostasis, energy metabolism, immune function and cellular stress resilience. Age-related transcriptional stress is evolutionary conserved from nematodes to humans. Thus, accumulation of stochastic endogenous DNA damage during aging deteriorates basal transcription, which establishes the age-related transcriptome and causes dysfunction of key aging hallmark pathways, disclosing how DNA damage functionally underlies major aspects of normal aging.

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Selective ablation of primary and paracrine senescent cells by targeting iron dyshomeostasis

Tesfahun Dessale Admasu,[1,5,*] Kristie Kim,[1] Michael Rae,[1] Roberto Avelar,[2] Ryan L. Gonciarz,[3] Abdelhadi Rebbaa,[1] João Pedro de Magalhães,[2] Adam R. Renslo,[3] Alexandra Stolzing,[4] and Amit Sharma[1,*]

Senescent cells can spread the senescent phenotype to other cells by secreting senescence-associated secretory phenotype factors. The resulting paracrine senescent cells make a significant contribution to the burden of senescent cell accumulation with age. Previous efforts made to characterize paracrine senescence are unreliable due to analyses being based on mixed populations of senescent and non-senescent cells. Here, we use dipeptidyl peptidase-4 (DPP4) as a surface maker to isolate senescent cells from mixed populations. Using this technique, we enrich the percentage of paracrine senescence from 40% to 85%. We then use this enriched culture to characterize DPP4^{+} primary and paracrine senescent cells. We observe ferroptosis dysregulation and ferrous iron accumulation as a common phenomenon in both primary and paracrine senescent cells. Finally, we identify ferroptosis induction and ferrous iron-activatable prodrug as a broad-spectrum senolytic approach to ablate multiple types of primary and paracrine senescent cells.

Resurrection of endogenous retroviruses during aging reinforces senescence

Whether and how certain transposable elements with viral origins, such as endogenous retroviruses (ERVs) dormant in our genomes, can become awakened and contribute to the aging process is largely unknown. In human senescent cells, we found that HERVK (HML-2), the most recently integrated human ERVs, are unlocked to transcribe viral genes and produce retrovirus-like particles (RVLPs). These HERVK RVLPs constitute a transmissible message to elicit senescence phenotypes in young cells, which can be blocked by neutralizing antibodies. The activation of ERVs was also observed in organs of aged primates and mice as well as in human tissues and serum from the elderly. Their repression alleviates cellular senescence and tissue degeneration and, to some extent, organismal aging. These findings indicate that the resurrection of ERVs is a hallmark and driving force of cellular senescence and tissue aging.

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PREPRINT

Somatic nuclear mitochondrial DNA insertions are prevalent in the human brain and accumulate in aging fibroblasts

Weichen Zhou, Kalpita Karan, Hans-Ulrich Klein, Gabriel Sturm, Phillip De Jager, David A Bennett, Michio Hirano, Martin Picard, Ryan Mills

The transfer of mitochondrial DNA into the nuclear genomes of eukaryotes (Numts) has been linked to lifespan in some non-human species. We investigated their association with human aging in two ways. First, we quantified Numts in 1,187 post-mortem brain and blood samples. Human brains exhibited a 5.5-fold enrichment of somatic Numt insertions in the dorsolateral prefrontal cortex compared to the cerebellum, suggesting that they arose spontaneously during development or with aging. Moreover, more brain Numts was linked to earlier mortality. The brains of individuals with no cognitive impairment who died at younger ages carried approximately 2 more Numts per decade of life lost than those who lived longer. Second, we tested the dynamic transfer of Numts in a repeated-measures WGS study in a human fibroblast model that recapitulates several molecular features of human aging. These longitudinal experiments revealed a gradual accumulation of one Numt every ~9 days, independent of large-scale genomic instability. Targeted genetic and pharmacological perturbations of mitochondrial oxidative phosphorylation did not affect numtogenesis, whereas chronic glucocorticoid stress increased the Numts transfer rate by 39.8%. Combined, our data document spontaneous numtogenesis in aging human cells and demonstrate an association between brain cortical somatic Numts and human lifespan.

Senescence atlas reveals an aged-like inflamed niche that blunts muscle regeneration

Victoria Moiseeva, Andrés Cisneros, Valentina Sica, Oleg Deryagin, Yiwei Lai, Sascha Jung, Eva Andrés, Juan An, Jessica Segalés, Laura Ortet, Vera Lukesova, Giacomo Volpe, Alberto Benguria, Ana Dopazo, Salvador Aznar-Benitah, Yasuteru Urano, Antonio del Sol, Miguel A. Esteban, Yasuyuki Ohkawa, Antonio L. Serrano, Eusebio Perdiguero & Pura Muñoz-Cánoves

Tissue regeneration requires coordination between resident stem cells and local niche cells[1,2]. Here we identify that senescent cells are integral components of the skeletal muscle regenerative niche that repress regeneration at all stages of life. The technical limitation of senescent-cell scarcity[3] was overcome by combining single-cell transcriptomics and a senescent-cell enrichment sorting protocol. We identified and isolated different senescent cell types from damaged muscles of young and old mice. Deeper transcriptome, chromatin and pathway analyses revealed conservation of cell identity traits as well as two universal senescence hallmarks (inflammation and fibrosis) across cell type, regeneration time and ageing. Senescent cells create an aged-like inflamed niche that mirrors inflammation associated with ageing (inflammageing[4]) and arrests stem cell proliferation and regeneration. Reducing the burden of senescent cells, or reducing their inflammatory secretome through CD36 neutralization, accelerates regeneration in young and old mice. By contrast, transplantation of senescent cells delays regeneration. Our results provide a technique for isolating in vivo senescent cells, define a senescence blueprint for muscle, and uncover unproductive functional interactions between senescent cells and stem cells in regenerative niches that can be overcome. As senescent cells also accumulate in human muscles, our findings open potential paths for improving muscle repair throughout life.

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PREPRINT

Fusion of dysfunction muscle stem cells with myofibers induces sarcopenia in mice

Xun Wang, Prashant Mishra

Sarcopenia, or age-associated muscle atrophy, is a progressive condition which affects ~10-30% of the human geriatric population (*1, 2*). A number of contributors to sarcopenia have been proposed, including the progressive loss of muscle stem cells (MuSCs) with age. However, studies in mice have provided evidence that MuSC depletion is not sufficient to induce sarcopenia (*3, 4*). We recently showed that in response to age-associated mitochondrial damage, MuSCs self-remove by fusing with neighboring myofibers, which depletes the stem cell population of damaged progenitors (*5*). Here, we show that MuSC-myofiber fusion is sufficient to initiate myofiber atrophy in mice, which limits their motor function and lifespan. Conversely, inhibition of MuSC-myofiber fusion blocks myofiber atrophy with age, with a concomitant increase in the maximum lifespan of animals. These findings suggest a model where the accumulation fusion of damaged MuSCs with adult myofibers is a key driving feature of sarcopenia, and resolves the findings that MuSC depletion on its own does not initiate myofiber atrophy.

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PREPRINT

Premature Aging and Reduced Cancer Incidence Associated with Body-Wide Loss of *Myc*

Huabo Wang, Jie Lu, Taylor Stevens, Alexander Roberts, Jordan Mandel, Raghunandan Avula, Yijen Wu, Jinglin Wang, Clinton Van't Land, Toren Finkel, Jerry E. Vockley, Merlin Airik, Rannar Airik, Radhika Muzumdar, Zhenwei Gong, Michel S. Torbenson, Edward V. Prochownik

MYC proto-oncogene dysregulation alters metabolic, translational, cell cycle and other functions in ways that support tumor induction and maintenance. Myc+/- mice are healthier and longer-lived than control mice but the long-term ramifications of more complete Myc loss remain unknown. We now describe the life-long consequences of body-wide Myc inactivation initiated post-natally. "MycKO" mice rapidly acquire numerous features of premature aging including altered body composition and habitus, metabolic dysfunction, hepatic steatosis and the dysregulation of numerous gene sets involved in functions that normally deteriorate with aging. Yet, MycKO mice have an extended life span that correlates with a 4-5-fold lower lifetime cancer incidence. Aging tissues from normal mice and humans deregulate many of the same gene sets as do young MycKO mice while also down-regulating Myc and many of its target genes. Normal aging and its associated cancer predisposition are thus highly linked via Myc and its target genes and can be genetically separated.

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The antitumour effects of caloric restriction are mediated by the gut microbiome

Yu-Qin Mao, Jia-Ting Huang, Shi-Long Zhang, Chao Kong, Zhan-Ming Li, Hui Jing, Hui-Ling Chen, Chao-Yue Kong, Sheng-Hui Huang, Pei-Ran Cai, Bing Han ✉ & Li-Shun Wang ✉

Calorie restriction (CR) and intermittent fasting (IF) without malnutrition reduce the risk of cancer development. Separately, CR and IF can also lead to gut microbiota remodelling. However, whether the gut microbiota has a role in the antitumour effect related to CR or IF is still unknown. Here we show that CR, but not IF, protects against subcutaneous MC38 tumour formation through a mechanism that is dependent on the gut microbiota in female mice. After CR, we identify enrichment of *Bifidobacterium* through 16S rRNA sequencing of the gut microbiome. Moreover, *Bifidobacterium bifidum* administration is sufficient to rescue the antitumour effect of CR in microbiota-depleted mice. Mechanistically, *B. bifidum* mediates the CR-induced antitumour effect through acetate production and this effect is also dependent on the accumulation of interferon-$\gamma^{+}CD8^{+}$ T cells in the tumour microenvironment. Our results demonstrate that CR can modulate the gut taxonomic composition, which should be of oncological significance in tumour growth kinetics and cancer immunosurveillance.

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Comprehensive longitudinal non-invasive quantification of healthspan and frailty in a large cohort (n = 546) of geriatric C57BL/6 J mice

Serena Marcozzi [1 2], Giorgia Bigossi [1], Maria Elisa Giuliani [1], Robertina Giacconi [1], Maurizio Cardelli [1], Francesco Piacenza [1], Fiorenza Orlando [3], Agnese Segala [4], Alessandra Valerio [4], Enzo Nisoli [5], Dario Brunetti [6 7], Annibale Puca [8 9], Federico Boschi [10], Carlo Gaetano [11], Alessia Mongelli [11], Fabrizia Lattanzio [2], Mauro Provinciali [1], Marco Malavolta [12]

Frailty is an age-related condition characterized by a multisystem functional decline, increased vulnerability to stressors, and adverse health outcomes. Quantifying the degree of frailty in humans and animals is a health measure useful for translational geroscience research. Two frailty measurements, namely the frailty phenotype (FP) and the clinical frailty index (CFI), have been validated in mice and are frequently applied in preclinical research. However, these two tools are based on different concepts and do not necessarily identify the same mice as frail. In particular, the FP is based on a dichotomous classification that suffers from high sample size requirements and misclassification problems. Based on the monthly longitudinal non-invasive assessment of frailty in a large cohort of mice, here we develop an alternative scoring method, which we called physical function score (PFS), proposed as a continuous variable that resumes into a unique function, the five criteria included in the FP. This score would not only reduce misclassification of frailty but it also makes the two tools, PFS and CFI, integrable to provide an overall measurement of health, named vitality score (VS) in aging mice. VS displays a higher association with mortality than PFS or CFI and correlates with biomarkers related to the accumulation of senescent cells and the epigenetic clock. This longitudinal non-invasive assessment strategy and the VS may help to overcome the different sensitivity in frailty identification, reduce the sample size in longitudinal experiments, and establish the effectiveness of therapeutic/preventive interventions for frailty or other age-related diseases in geriatric animals.

Heritability of the glycan clock of biological age

Anika Mijakovac [1], Azra Frkatović [2], Maja Hanić [2], Jelena Ivok [2], Marina Martinić Kavur [2], Maja Pučić-Baković [2], Tim Spector [3], Vlatka Zoldoš [1], Massimo Mangino [3 4], Gordan Lauc [2 5]

Immunoglobulin G is posttranslationally modified by the addition of complex N-glycans affecting its function and mediating inflammation at multiple levels. IgG glycome composition changes with age and health in a predictive pattern, presumably due to inflammaging. As a result, a novel biological aging biomarker, glycan clock of age, was developed. Glycan clock of age is the first of biological aging clocks for which multiple studies showed a possibility of clock reversal even with simple lifestyle interventions. However, none of the previous studies determined to which extent the glycan clock can be turned, and how much is fixed by genetic predisposition. To determine the contribution of genetic and environmental factors to phenotypic variation of the glycan clock, we performed heritability analysis on two TwinsUK female cohorts. IgG glycans from monozygotic and dizygotic twin pairs were analyzed by UHPLC and glycan age was calculated using the glycan clock. In order to determine additive genetic, shared, and unique environmental contributions, a classical twin design was applied. Heritability of the glycan clock was calculated for participants of one cross-sectional and one longitudinal cohort with three time points to assess the reliability of measurements. Heritability estimate for the glycan clock was 39% on average, suggesting a moderate contribution of additive genetic factors (A) to glycan clock variation. Remarkably, heritability estimates remained approximately the same in all time points of the longitudinal study, even though IgG glycome composition changed substantially. Most environmental contributions came from shared environmental factors (C), with unique environmental factors (E) having a minor role. Interestingly, heritability estimates nearly doubled, to an average of 71%, when we included age as a covariant. This intervention also inflated the estimates of unique environmental factors contributing to glycan clock variation. A complex interplay between genetic and environmental factors defines alternative IgG glycosylation during aging and, consequently, dictates the glycan clock's ticking. Apparently, environmental factors (including lifestyle choices) have a strong impact on the biological age measured with the glycan clock, which additionally clarifies why this aging clock is one of the most potent biomarkers of biological aging.

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PREPRINT

Evolutionary transcriptomics reveals longevity mostly driven by polygenic and indirect selection in mammals

Weiqiang Liu, Pingfen Zhu, Meng Li, Zihao Li, Yang Yu, Gaoming Liu, Juan Du, Xiao Wang, Jing Yang, Ran Tian, Inge Seim, Alaattin Kaya, Mingzhou Li, Ming Li, Vadim N. Gladyshev, Xuming Zhou

The maximum lifespan varies more than 100-fold in mammals. This experiment of nature may uncover of the evolutionary forces and molecular features that define longevity. To understand the relationship between gene expression variation and maximum lifespan, we carried out a comparative transcriptomics analysis of liver, kidney, and brain tissues of 106 mammalian species. We found that expression is largely conserved and very limited genes exhibit common expression patterns with longevity in all the three organs analyzed. However, many pathways, e.g., “Insulin signaling pathway”, and “FoxO signaling pathway”, show accumulated correlations with maximum lifespan across mammals. Analyses of selection features further reveal that methionine restriction related genes whose expressions associated with longevity, are under strong selection in long-lived mammals, suggesting that a common approach could be utilized by natural selection and artificial intervention to control lifespan. These results suggest that natural lifespan regulation via gene expression is likely to be driven through polygenic model and indirect selection.

Methionine Metabolism Is Down-Regulated in Heart of Long-Lived Mammals

by Natalia Mota-Martorell [1], Mariona Jové [1], Rebeca Berdún [1], Èlia Òbis [1], Gustavo Barja [2] and Reinald Pamplona [1,*]

Methionine constitutes a central hub of intracellular metabolic adaptations leading to an extended longevity (maximum lifespan). The present study follows a comparative approach analyzing methionine and related metabolite and amino acid profiles using an LC-MS/MS platform in the hearts of seven mammalian species with a longevity ranging from 3.8 to 57 years. Our findings demonstrate the existence of species-specific heart phenotypes associated with high longevity characterized by: (i) low concentration of methionine and its related sulphur-containing metabolites; (ii) low amino acid pool; and (iii) low choline concentration. Our results support the existence of heart metabotypes characterized by a down-regulation in long-lived species, supporting the idea that in longevity, less is more.

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Lithium treatment extends human lifespan: findings from the UK Biobank

Elisa Araldi[1,2] , Catherine R. Jutzeler[3] , Michael Ristow[1,4]

Lithium is a nutritional trace element that is also used pharmacologically for the management of bipolar and related psychiatric disorders. Recent studies have shown that lithium supplementation can extend health and lifespan in different animal models. Moreover, nutritional lithium uptake from drinking water was repeatedly found to be positively correlated with human longevity. By analyzing a large observational aging cohort (UK Biobank, n = 501,461 individuals) along with prescription data derived from the National Health Services (NHS), we here find therapeutic supplementation of lithium linked to decreased mortality (p = 0.0017) of individuals diagnosed with affective disorders. Subsequent multivariate survival analyses reveal lithium to be the strongest factor in regards to increased survival effects (hazard ratio = 0.274 [0.119–0.634 CI 95%, p = 0.0023]), corresponding to 3.641 times lower (95% CI 1.577–8.407) chances of dying at a given age for lithium users compared to users of other anti-psychotic drugs. While these results may further support the use of lithium as a geroprotective supplement, it should be noted that doses applied within the UK Biobank/NHS setting require close supervision by qualified medical professionals.

Metformin use history and genome-wide DNA methylation profile: potential molecular mechanism for aging and longevity

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Background: Metformin, a commonly prescribed anti-diabetic medication, has repeatedly been shown to hinder aging in pre-clinical models and to be associated with lower mortality for humans. It is, however, not well understood how metformin can potentially prolong lifespan from a biological standpoint. We hypothesized that metformin's potential mechanism of action for longevity is through its epigenetic modifications.

Methods: To test our hypothesis, we conducted a post-hoc analysis of available genome-wide DNA methylation (DNAm) data obtained from whole blood collected from inpatients with and without a history of metformin use. We assessed the methylation profile of 171 patients (first run) and only among 63 diabetic patients (second run) and compared the DNAm rates between metformin users and nonusers.

Results: Enrichment analysis from the Kyoto Encyclopedia of Genes and Genome (KEGG) showed pathways relevant to metformin's mechanism of action, such as longevity, AMPK, and inflammatory pathways. We also identified several pathways related to delirium whose risk factor is aging. Moreover, top hits from the Gene Ontology (GO) included HIF-1α pathways. However, no individual CpG site showed genome-wide statistical significance (p < 5E-08).

Conclusion: This study may elucidate metformin's potential role in longevity through epigenetic modifications and other possible mechanisms of action.

Structure of the lysosomal mTORC1–TFEB–Rag–Ragulator megacomplex

Zhicheng Cui, Gennaro Napolitano, Mariana E. G. de Araujo, Alessandra Esposito, Jlenia Monfregola, Lukas A. Huber, Andrea Ballabio & James H. Hurley

The transcription factor TFEB is a master regulator of lysosomal biogenesis and autophagy[1]. The phosphorylation of TFEB by the mechanistic target of rapamycin complex 1 (mTORC1)[2,3,4,5] is unique in its mTORC1 substrate recruitment mechanism, which is strictly dependent on the amino acid-mediated activation of the RagC GTPase activating protein FLCN[6,7]. TFEB lacks the TOR signalling motif responsible for the recruitment of other mTORC1 substrates. We used cryogenic-electron microscopy to determine the structure of TFEB as presented to mTORC1 for phosphorylation, which we refer to as the 'megacomplex'. Two full Rag–Ragulator complexes present each molecule of TFEB to the mTOR active site. One Rag–Ragulator complex is bound to Raptor in the canonical mode seen previously in the absence of TFEB. A second Rag–Ragulator complex (non-canonical) docks onto the first through a RagC GDP-dependent contact with the second Ragulator complex. The non-canonical Rag dimer binds the first helix of TFEB with a $RagC^{GDP}$-dependent aspartate clamp in the cleft between the Rag G domains. In cellulo mutation of the clamp drives TFEB constitutively into the nucleus while having no effect on mTORC1 localization. The remainder of the 108-amino acid TFEB docking domain winds around Raptor and then back to RagA. The double use of RagC GDP contacts in both Rag dimers explains the strong dependence of TFEB phosphorylation on FLCN and the RagC GDP state.

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PREPRINT

All-optical spatiotemporal mapping of ROS dynamics across mitochondrial microdomains *in situ*

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Hydrogen peroxide (H_2O_2) functions as a second messenger to signal metabolic distress through highly compartmentalized production in mitochondria. The dynamics of ROS generation and diffusion between mitochondrial compartments and into the cytosol govern oxidative stress responses and pathology, though our understanding of these processes remains limited. Here, we couple the H_2O_2 biosensor, HyPer7, with optogenetic stimulation of the ROS-generating protein KillerRed targeted into multiple mitochondrial microdomains. Single mitochondrial photogeneration of H_2O_2 demonstrates the spatiotemporal dynamics of ROS diffusion and transient hyperfusion of mitochondria due to ROS. Measurement of microdomain-specific H_2O_2 diffusion kinetics reveals directionally selective diffusion through mitochondrial microdomains. All-optical generation and detection of physiologically-relevant concentrations of H_2O_2 between mitochondrial compartments provide a map of mitochondrial H_2O_2 diffusion dynamics *in situ*. These kinetic details of spatiotemporal ROS dynamics and inter-mitochondrial spreading forms a framework to understand the role of ROS in health and disease.

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Loss of epigenetic information as a cause of mammalian aging

Jae-Hyun Yang [29] • Motoshi Hayano [29] • Patrick T. Griffin • ... Andreas R. Pfenning • Luis A. Rajman • David A. Sinclair [30] • Show all authors • Show footnotes

All living things experience an increase in entropy, manifested as a loss of genetic and epigenetic information. In yeast, epigenetic information is lost over time due to the relocalization of chromatin-modifying proteins to DNA breaks, causing cells to lose their identity, a hallmark of yeast aging. Using a system called “ICE” (inducible changes to the epigenome), we find that the act of faithful DNA repair advances aging at physiological, cognitive, and molecular levels, including erosion of the epigenetic landscape, cellular exdifferentiation, senescence, and advancement of the DNA methylation clock, which can be reversed by OSK-mediated rejuvenation. These data are consistent with the information theory of aging, which states that a loss of epigenetic information is a reversible cause of aging.

Epigenetic profile of Japanese supercentenarians: a cross-sectional study

Background: Centenarians and supercentenarians with exceptional longevity are excellent models for research towards improvements of healthy life expectancy. Extensive research regarding the maintenance and reduction of epigenetic age has provided insights into increasing healthy longevity. To this end, we explored the epigenetic signatures reflecting hallmarks of exceptional healthy longevity, including avoidance of age-related diseases and cognitive functional decline.

Methods: In this cross-sectional study, we enrolled Japanese non-centenarians (eligible participants aged 20-80 years) from the Tohoku Medical Megabank Community-Based Cohort Study and centenarians and supercentenarians (aged 101-115 years) from the Tokyo Centenarian Study and the Japanese Semi-supercentenarian Study. We assessed participants' whole-blood DNA methylation profiles and then developed sex-specific and non-specific first-generation epigenetic clocks by elastic net regression, calculated individuals' epigenetic ages, and assessed their age acceleration. We also screened for age-related CpG sites in non-centenarians by epigenome-wide linear regression analyses and ANOVA. We subsequently investigated which CpG sites in centenarians and supercentenarians had DNA methylation patterns following the age-related findings obtained from non-centenarians and which did not. We further characterised CpG sites with hypermethylation or hypomethylation in the centenarians and supercentenarians using enrichment and protein-protein interaction network analyses.

Findings: We enrolled 421 non-centenarians (231 [55%] women and 190 [45%] men; age range 20-78 years), recruited between May 20, 2013, and March 31, 2016, and 94 centenarians and supercentenarians (66 women [70%] and 28 [30%] men; age range 101-115 years), recruited between Jan 20, 2001, and April 17, 2018. Non-sex-specific epigenetic clock showed the highest accuracy (r=0·96) based on which centenarians and supercentenarians had negative epigenetic age acceleration. Epigenome-wide association analyses further showed that centenarians and supercentenarians had younger-than-expected epigenetic states (DNA methylation profiles similar to those of non-centenarians) for 557 CpG sites enriched in cancer-related and neuropsychiatric-related genes, whereas these individuals had advanced (or older) epigenetic states for 163 CpG sites represented by genes related to TGF-β signalling, which is involved in anti-inflammatory responses and known to contribute to healthy ageing.

Interpretation: These results indicate that exceptionally healthy longevity depends not only on maintaining young epigenetic states but also on advanced states of specific epigenetic regions.

SIRT6 is a key regulator of mitochondrial function in the brain

Dmitrii Smirnov, Ekaterina Eremenko, Daniel Stein, Shai Kaluski, Weronika Jasinska, Claudia Cosentino, Barbara Martinez-Pastor, Yariv Brotman, Raul Mostoslavsky, Ekaterina Khrameeva & Debra Toiber

The SIRT6 deacetylase has been implicated in DNA repair, telomere maintenance, glucose and lipid metabolism and, importantly, it has critical roles in the brain ranging from its development to neurodegeneration. Here, we combined transcriptomics and metabolomics approaches to characterize the functions of SIRT6 in mouse brains. Our analysis reveals that SIRT6 is a central regulator of mitochondrial activity in the brain. SIRT6 deficiency in the brain leads to mitochondrial deficiency with a global downregulation of mitochondria-related genes and pronounced changes in metabolite content. We suggest that SIRT6 affects mitochondrial functions through its interaction with the transcription factor YY1 that, together, regulate mitochondrial gene expression. Moreover, SIRT6 target genes include SIRT3 and SIRT4, which are significantly downregulated in SIRT6-deficient brains. Our results demonstrate that the lack of SIRT6 leads to decreased mitochondrial gene expression and metabolomic changes of TCA cycle byproducts, including increased ROS production, reduced mitochondrial number, and impaired membrane potential that can be partially rescued by restoring SIRT3 and SIRT4 levels. Importantly, the changes we observed in SIRT6-deficient brains are also occurring in aging human brains and particularly in patients with Alzheimer's, Parkinson's, Huntington's, and Amyotrophic lateral sclerosis disease. Overall, our results suggest that the reduced levels of SIRT6 in the aging brain and neurodegeneration initiate mitochondrial dysfunction by altering gene expression, ROS production, and mitochondrial decay.

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Leukocyte telomere length in children born following blastocyst-stage embryo transfer

Perinatal and childhood adverse outcomes associated with assisted reproductive technology (ART) has been reported, but it remains unknown whether the initial leukocyte telomere length (LTL), which is an indicator of age-related phenotypes in later life, is affected. Here, we estimated the LTLs of 1,137 individuals from 365 families, including 202 children conceived by ART and 205 children conceived spontaneously from two centers of the China National Birth Cohort, using whole-genome sequencing (WGS) data. One-year-old children conceived by ART had shorter LTLs than those conceived spontaneously (beta, −0.36; $P = 1.29 \times 10^{-3}$) after adjusting for plurality, sex and other potential confounding factors. In particular, blastocyst-stage embryo transfer was associated with shorter LTL (beta, −0.54, $P = 2.69 \times 10^{-3}$) in children conceived by ART. The association was validated in 586 children conceived by ART from five centers using different LTL quantification methods (that is, WGS or qPCR). Blastocyst-stage embryo transfer resulted in shorter telomere lengths in mice at postnatal day 1 ($P = 2.10 \times 10^{-4}$) and mice at 6 months ($P = 0.042$). In vitro culturing of mice embryos did not result in shorter telomere lengths in the late cleavage stage, but it did suppress telomerase activity in the early blastocyst stage. Our findings demonstrate the need to evaluate the long-term consequences of ART, particularly for aging-related phenotypes, in children conceived by ART.

OxPhos defects cause hypermetabolism and reduce lifespan in cells and in patients with mitochondrial diseases

Patients with primary mitochondrial oxidative phosphorylation (OxPhos) defects present with fatigue and multi-system disorders, are often lean, and die prematurely, but the mechanistic basis for this clinical picture remains unclear. By integrating data from 17 cohorts of patients with mitochondrial diseases (n = 690) we find evidence that these disorders increase resting energy expenditure, a state termed *hypermetabolism*. We examine this phenomenon longitudinally in patient-derived fibroblasts from multiple donors. Genetically or pharmacologically disrupting OxPhos approximately doubles cellular energy expenditure. This cell-autonomous state of hypermetabolism occurs despite near-normal OxPhos coupling efficiency, excluding uncoupling as a general mechanism. Instead, hypermetabolism is associated with mitochondrial DNA instability, activation of the integrated stress response (ISR), and increased extracellular secretion of age-related cytokines and metabokines including GDF15. In parallel, OxPhos defects accelerate telomere erosion and epigenetic aging per cell division, consistent with evidence that excess energy expenditure accelerates biological aging. To explore potential mechanisms for these effects, we generate a longitudinal RNASeq and DNA methylation resource dataset, which reveals conserved, energetically demanding, genome-wide recalibrations. Taken together, these findings highlight the need to understand how OxPhos defects influence the energetic cost of living, and the link between hypermetabolism and aging in cells and patients with mitochondrial diseases.

C. elegans aging research

A meta-analysis of RNA-Seq studies to identify novel genes that regulate aging

Mohamad D Bairakdar [1], Ambuj Tewari [2], Matthias C Truttmann [3]

Aging is a ubiquitous biological process that limits the maximal lifespan of most organisms. Significant efforts by many groups have identified mechanisms that, when triggered by natural or artificial stimuli, are sufficient to either enhance or decrease maximal lifespan. Previous aging studies using the nematode Caenorhabditis elegans (C. elegans) generated a wealth of publicly available transcriptomics datasets linking changes in gene expression to lifespan regulation. However, a comprehensive comparison of these datasets across studies in the context of aging biology is missing. Here, we carry out a systematic meta-analysis of over 1200 bulk RNA sequencing (RNASeq) samples obtained from 74 peer-reviewed publications on aging-related transcriptomic changes in C. elegans. Using both differential expression analyses and machine learning approaches, we mine the pooled data for novel pro-longevity genes. We find that both approaches identify known and propose novel pro-longevity genes. Further, we find that inter-lab experimental variance complicates the application of machine learning algorithms, a limitation that was not solved using bulk RNA-Seq batch correction and normalization techniques. Taken as a whole, our results indicate that machine learning approaches may hold promise for the identification of genes that regulate aging but will require more sophisticated batch correction strategies or standardized input data to reliably identify novel pro-longevity genes.

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Adult-restricted gene knock-down reveals candidates that affect locomotive healthspan in C. elegans

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Affiliations + expand

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Abstract

Understanding how we can age healthily is a challenge at the heart of biogerontological interest. Whereas myriad genes are known to affect the lifespan of model organisms, effects of such interventions on healthspan-the period of life where an animal is considered healthy, rather than merely alive-are less clear. To understand relationships between life- and healthspan, in recent years several platforms were developed with the purpose of assessing both readouts simultaneously. We here relied on one such platform, the WorMotel, to study effects of adulthood-restricted knock-down of 130 Caenorhabditis elegans genes on the locomotive health of the animals along their lifespans. We found that knock-down of six genes affected healthspan while lifespan remained unchanged. For two of these, F26A3.4 and chn-1, knock-down resulted in an improvement of healthspan. In follow-up experiments we showed that knockdown of F26A3.4 indeed improves locomotive health and muscle structure at old age.

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PREPRINT

*Ce*Lab, a Microfluidic Platform for the Study of Life History Traits, reveals Metformin and SGK-1 regulation of Longevity and Reproductive Span

Salman Sohrabi, Vanessa Cota, Coleen T. Murphy

The potential to carry out high-throughput assays in a whole organism in a small space is one of the benefits of *C. elegans*, but worm assays often require a large sample size with frequent physical manipulations, rendering them highly labor-intensive. Microfluidic assays have been designed with specific questions in mind, such as analysis of behavior, embryonic development, lifespan, and motility. While these devices have many advantages, current technologies to automate worm experiments have several limitations that prevent widespread adoption, and most do not allow analyses of reproduction-linked traits. We developed a miniature *C. elegans* lab-on-a-chip device, *Ce*Lab, a reusable, multi-layer device with 200 separate incubation arenas that allows progeny removal, to automate a variety of worm assays on both individual and population levels. *Ce*Lab enables high-throughput simultaneous analysis of lifespan, reproductive span, and progeny production, refuting assumptions about the Disposable Soma hypothesis. Because *Ce*Lab chambers require small volumes, the chip is ideal for drug screens; we found that drugs previously shown to increase lifespan also increase reproductive span, and we discovered that low-dose metformin increases both. *Ce*Lab reduces the limitations of escaping and matricide that typically limit plate assays, revealing that feeding with heat-killed bacteria greatly extends lifespan and reproductive span of mated animals. *Ce*Lab allows tracking of life history traits of individuals, which revealed that the nutrient-sensing mTOR pathway mutant, *sgk-1*, reproduces nearly until its death. These findings would not have been possible to make in standard plate assays, in low-throughput assays, or in normal population assays.

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One-day thermal regime extends the lifespan in Caenorhabditis elegans

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Free PMC article

Abstract

Environmental factors, including temperature, can modulate an animal's lifespan. However, their underlying mechanisms remain largely undefined. We observed a profound effect of temperature on the aging of *Caenorhabditis elegans* (*C. elegans*) by performing proteomic analysis at different time points (young adult, middle age, and old age) and temperature conditions (20 °C and 25 °C). Importantly, although at the higher temperature, animals had short life spans, the shift from 20 °C to 25 °C for one day during early adulthood was beneficial for protein homeostasis since; it decreased protein synthesis and increased degradation. Consistent with our findings, animals who lived longer in the 25 °C shift were also more resistant to high temperatures along with oxidative and UV stresses. Furthermore, the lifespan extension by the 25 °C shift was mediated by three important transcription factors, namely FOXO/DAF-16, HSF-1, and HIF-1. We revealed an unexpected and complicated mechanism underlying the effects of temperature on aging, which could potentially aid in developing strategies to treat age-related diseases. Our data are available in ProteomeXchange with the identifier PXD024916.

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Rilmenidine extends lifespan and healthspan in *Caenorhabditis elegans* via a nischarin I1-imidazoline receptor

Dominic F. Bennett, Anita Goyala, Cyril Statzer, Charles W. Beckett, Alexander Tyshkovskiy, Vadim N. Gladyshev, Collin Y. Ewald ✉, João Pedro de Magalhães ✉

Repurposing drugs capable of extending lifespan and health span has a huge untapped potential in translational geroscience. Here, we searched for known compounds that elicit a similar gene expression signature to caloric restriction and identified rilmenidine, an I1-imidazoline receptor agonist and prescription medication for the treatment of hypertension. We then show that treating *Caenorhabditis elegans* with rilmenidine at young and older ages increases lifespan. We also demonstrate that the stress-resilience, health span, and lifespan benefits of rilmenidine treatment in *C. elegans* are mediated by the I1-imidazoline receptor *nish-1*, implicating this receptor as a potential longevity target. Consistent with the shared caloric-restriction-mimicking gene signature, supplementing rilmenidine to calorically restricted *C. elegans*, genetic reduction of TORC1 function, or rapamycin treatment did not further increase lifespan. The rilmenidine-induced longevity required the transcription factors FOXO/DAF-16 and NRF1,2,3/SKN-1. Furthermore, we find that autophagy, but not AMPK signaling, was needed for rilmenidine-induced longevity. Moreover, transcriptional changes similar to caloric restriction were observed in liver and kidney tissues in mice treated with rilmenidine. Together, these results reveal a geroprotective and potential caloric restriction mimetic effect by rilmenidine that warrant fresh lines of inquiry into this compound.

Anti-retroviral treatment with zidovudine alters pyrimidine metabolism, reduces translation, and extends healthy longevity via ATF-4

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The human population is aging, and the need for interventions to slow progression of age-related diseases (geroprotective interventions) is growing. Repurposing compounds already used clinically, usually at modified doses, allows rapid implementation of geroprotective pharmaceuticals. Here we find the anti-retroviral nucleoside reverse transcriptase inhibitor (NRTI) zidovudine robustly extends lifespan and health span in C. elegans, independent of electron transport chain impairment or ROS accumulation. Rather, zidovudine treatment modifies pyrimidine metabolism and transcripts related to proteostasis. Testing regulators of mitochondrial stress and proteostasis shows that lifespan extension is dependent on activating transcription factor 4 (ATF-4). ATF-4 regulates longevity induced by mitochondrial stress, specifically communication between mitochondrial and cytosolic translation. Translation is reduced in zidovudine-treated worms, also dependent on ATF-4. Finally, we show ATF-4-dependent lifespan extension induced by didanosine, another NRTI. Altogether, our work elucidates the geroprotective effects of NRTIs such as zidovudine in vivo, via reduction of translation and ATF-4.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Testing the evidence that lifespan-extending compound interventions are conserved across laboratory animal model species

Michael Bene & Adam B. Salmon

A growing number of pharmaceutical and small molecule interventions are reported to extend the lifespan of laboratory animals including *Caenorhabditis*, *Drosophila*, and mouse. However, the degree to which these pro-longevity interventions are conserved across species is unclear. Here, we took two approaches to ask the question: to what extent do longevity intervention studies in *Caenorhabditis* and *Drosophila* recapitulate effects on mouse lifespan? The first approach analyzes all published reports on longevity in the literature collated by the DrugAge database, and the second approach focused on results designed for reproducibility as reported from the NIA-supported Interventions Testing Program (ITP) and the *Caenorhabditis* Interventions Testing Program (CITP). Using published data sources, we identify only modest sensitivity and specificity of *Drosophila* interventional studies for identifying pro-longevity compounds in mouse lifespan studies. Surprisingly, reported studies in *C. elegans* show little predictive value for identifying drugs that extend lifespan in mice. The results therefore suggest caution should be used when making assumptions about the translatability of lifespan-extending compounds across species, including human intervention.

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Why is rapamycin not a rapalog?

Ajla Hodzic Kuerec, Andrea B Maier

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Free article

Abstract

Rapamycin (sirolimus) is an immunosuppressive drug approved by the Food and Drug Administration (FDA). It is also a leading candidate for targeting aging. Rapamycin and its analogs (everolimus, temsirolimus, ridaforolimus) inhibit the mammalian target of rapamycin (mTOR) kinase by binding to FK506-binding proteins (FKBP) and have a similar chemical structure that only differs in the functional group present at carbon-40. Analogs of rapamycin were developed to improve its pharmacological properties, such as low oral bioavailability and a long half-life. The analogs of rapamycin are referred to as 'rapalogs.' Rapamycin is the parent compound and should there with not be called a 'rapalog.'

Compound combinations targeting longevity: Challenges and perspectives ☆

Olga Y. Rybina [a, b], Alexander V. Symonenko [a], Elena G. Pasyukova [a]

Aging is one of the world's greatest concerns, requiring urgent, effective, large-scale interventions to decrease the number of late-life chronic diseases and improve human healthspan. Anti-aging drug therapy is one of the most promising strategies to combat the effects of aging. However, most geroprotective compounds are known to successfully affect only a few aging-related targets. Given this, there is a great biological rationale for the use of combinations of anti-aging interventions. In this review, we characterize the various types of compound combinations used to modulate lifespan, discuss the existing evidence on their role in life extension, and present some key points about current challenges and future prospects for the development of combination drug anti-aging therapy.

Potential Synergistic Supplementation of NAD+ Promoting Compounds as a Strategy for Increasing Healthspan

by Arastu Sharma [1,2], Sophie Chabloz [2], Rebecca A. Lapides [3,4], Elisabeth Roider [3,5,6] and Collin Y. Ewald [1,*]

Disrupted biological function, manifesting through the hallmarks of aging, poses one of the largest threats to healthspan and risk of disease development, such as metabolic disorders, cardiovascular ailments, and neurodegeneration. In recent years, numerous geroprotectors, senolytics, and other nutraceuticals have emerged as potential disruptors of aging and may be viable interventions in the immediate state of human longevity science. In this review, we focus on the decrease in nicotinamide adenine dinucleotide (NAD+) with age and the supplementation of NAD+ precursors, such as nicotinamide mononucleotide (NMN) or nicotinamide riboside (NR), in combination with other geroprotective compounds, to restore NAD+ levels present in youth. Furthermore, these geroprotectors may enhance the efficacy of NMN supplementation while concurrently providing their own numerous health benefits. By analyzing the prevention of NAD+ degradation through the inhibition of CD38 or supporting protective downstream agents of SIRT1, we provide a potential framework of the CD38/NAD+/SIRT1 axis through which geroprotectors may enhance the efficacy of NAD+ precursor supplementation and reduce the risk of age-related diseases, thereby potentiating healthspan in humans.

Biological Age Predictors: The Status Quo and Future Trends

by Veronika V. Erema *, Anna Y. Yakovchik, Daria A. Kashtanova, Zanda V. Bochkaeva, Mikhail V. Ivanov, Dmitry V. Sosin, Lorena R. Matkava, Vladimir S. Yudin, Valentin V. Makarov, Anton A. Keskinov, Sergey A. Kraevoy and Sergey M. Yudin

There is no single universal biomarker yet to estimate overall health status and longevity prospects. Moreover, a consensual approach to the very concept of aging and the means of its assessment are yet to be developed. Markers of aging could facilitate effective health control, more accurate life expectancy estimates, and improved health and quality of life. Clinicians routinely use several indicators that could be biomarkers of aging. Duly validated in a large cohort, models based on a combination of these markers could provide a highly accurate assessment of biological age and the pace of aging. Biological aging is a complex characteristic of chronological age (usually), health-to-age concordance, and medically estimated life expectancy. This study is a review of the most promising techniques that could soon be used in routine clinical practice. Two main selection criteria were applied: a sufficient sample size and reliability based on validation. The selected biological age calculators were grouped according to the type of biomarker used: (1) standard clinical and laboratory markers; (2) molecular markers; and (3) epigenetic markers. The most accurate were the calculators, which factored in a variety of biomarkers. Despite their demonstrated effectiveness, most of them require further improvement and cannot yet be considered for use in standard clinical practice. To illustrate their clinical application, we reviewed their use during the COVID-19 pandemic.

The Role of SOX Transcription Factors in Ageing and Age-Related Diseases

by Milena Stevanovic [1,2,3], Andrijana Lazic [1], Marija Schwirtlich [1] and Danijela Stanisavljevic Ninkovic [1,*]

The quest for eternal youth and immortality is as old as humankind. Ageing is an inevitable physiological process accompanied by many functional declines that are driving factors for age-related diseases. Stem cell exhaustion is one of the major hallmarks of ageing. The SOX transcription factors play well-known roles in self-renewal and differentiation of both embryonic and adult stem cells. As a consequence of ageing, the repertoire of adult stem cells present in various organs steadily declines, and their dysfunction/death could lead to reduced regenerative potential and development of age-related diseases. Thus, restoring the function of aged stem cells, inducing their regenerative potential, and slowing down the ageing process are critical for improving the health span and, consequently, the lifespan of humans. Reprograming factors, including SOX family members, emerge as crucial players in rejuvenation. This review focuses on the roles of SOX transcription factors in stem cell exhaustion and age-related diseases, including neurodegenerative diseases, visual deterioration, chronic obstructive pulmonary disease, osteoporosis, and age-related cancers. A better understanding of the molecular mechanisms of ageing and the roles of SOX transcription factors in this process could open new avenues for developing novel strategies that will delay ageing and prevent age-related diseases.

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Cellular senescence: from mechanisms to current biomarkers and senotherapies

Vasco Lucas [1], Cláudia Cavadas [1], Célia Alexandra Aveleira [2]

An increase in life expectancy in developed countries has led to an insurgency of chronic aging-related diseases. In the last few decades, several studies provided evidence of the prominent role of cellular senescence in many of these pathologies. Key traits of senescent cells include cell cycle arrest, apoptosis resistance, and secretome shift to senescence-associated secretory phenotype (SASP) resulting in increased secretion of various intermediate bioactive factors important for senescence pathophysiology. However, cellular senescence is a highly phenotypically heterogeneous process, hindering the discovery of totally specific and accurate biomarkers. Also, strategies to prevent the pathological effect of senescent cell accumulation during aging by impairing senescence onset or promoting senescent cell clearance have shown great potential during *in vivo* studies and some are already in early stages of clinical translation. The adaptability of these senotherapeutic approaches to human application has been questioned due to the lack of proper senescence targeting and senescence involvement in important physiological functions. In this review, we explore the heterogeneous phenotype of senescent cells and its influence on the expression of biomarkers currently used for senescence detection. We also discuss the current evidence regarding the efficacy, reliability, development stage, and potential for human applicability of the main existing senotherapeutic strategies. **Significance Statement** This manuscript is an extensive review of what is currently known about the complex process of cellular senescence exploring its most defining features. The main body of the discussion focus on how the multi-feature fluctuation of the senescence phenotype and the physiological role of cellular senescence have both caused a limitation in the search for truly reliable senescence biomarkers and the progression in the development of senotherapies.

OTHER RESEARCH & REVIEWS

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Transcriptomic congruence analysis for evaluating model organisms

Wei Zong, Tanbin Rahman, Li Zhu, +10, and George C. Tseng Authors Info & Affiliations

Model organisms are instrumental substitutes for human studies to expedite basic, translational, and clinical research. Despite their indispensable role in mechanistic investigation and drug development, molecular congruence of animal models to humans has long been questioned and debated. Little effort has been made for an objective quantification and mechanistic exploration of a model organism's resemblance to humans in terms of molecular response under disease or drug treatment. We hereby propose a framework, namely Congruence Analysis for Model Organisms (CAMO), for transcriptomic response analysis by developing threshold-free differential expression analysis, quantitative concordance/discordance scores incorporating data variabilities, pathway-centric downstream investigation, knowledge retrieval by text mining, and topological gene module detection for hypothesis generation. Instead of a genome-wide vague and dichotomous answer of "poorly" or "greatly" mimicking humans, CAMO assists researchers to numerically quantify congruence, to dissect true cross-species differences from unwanted biological or cohort variabilities, and to visually identify molecular mechanisms and pathway subnetworks that are best or least mimicked by model organisms, which altogether provides foundations for hypothesis generation and subsequent translational decisions.