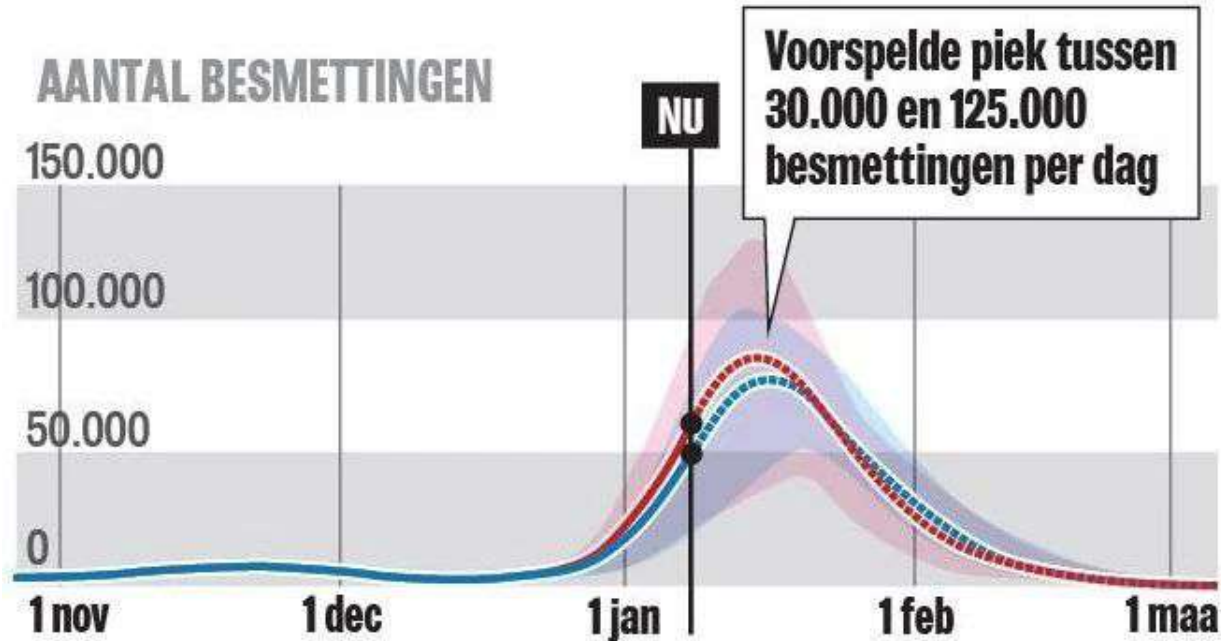
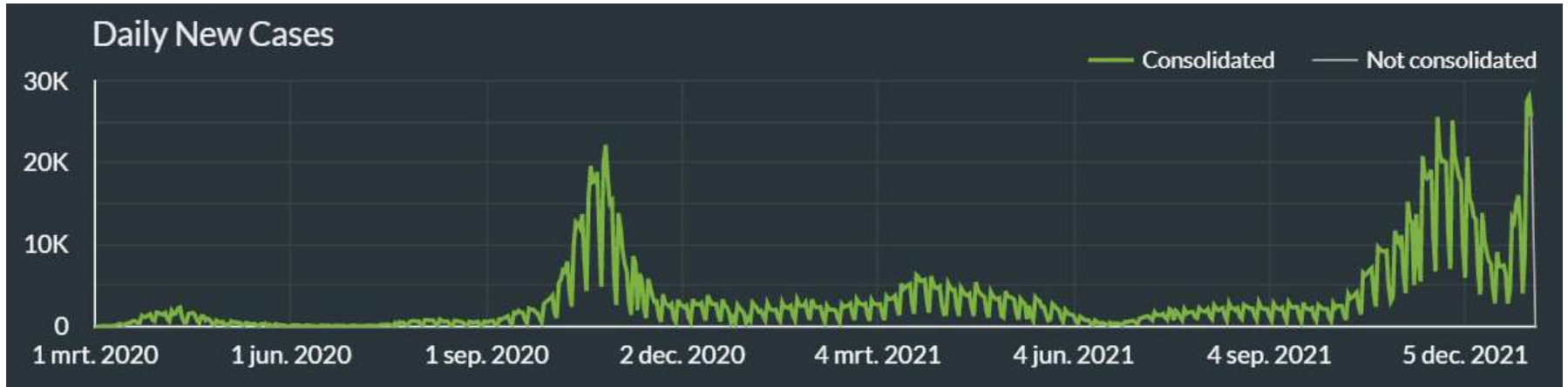




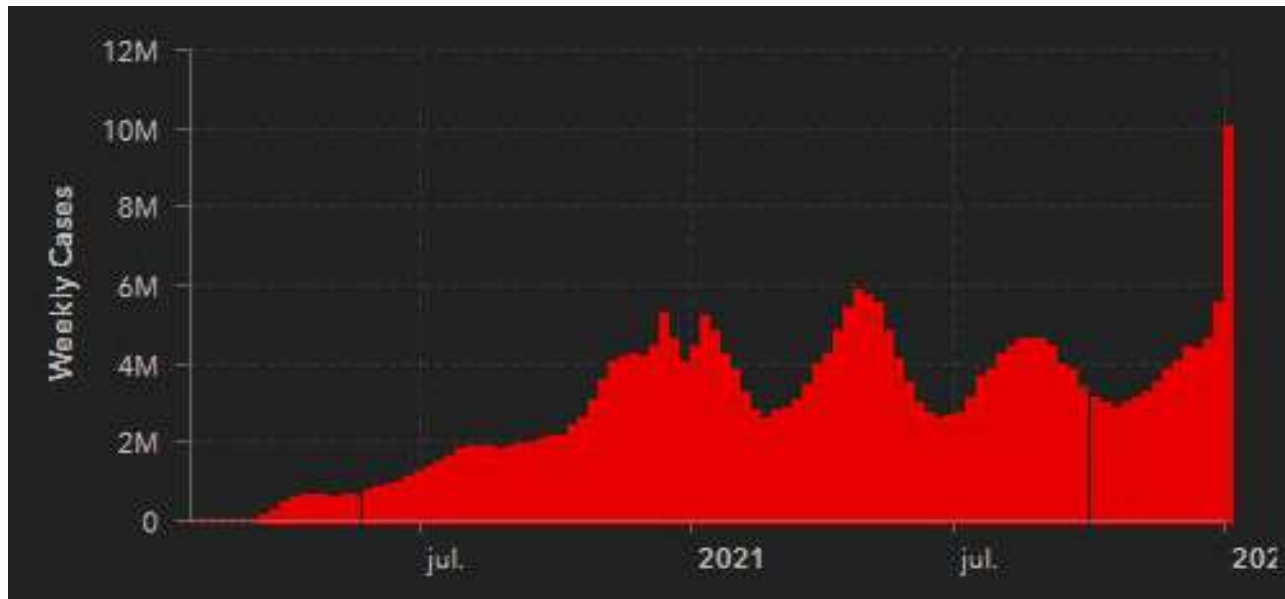
**Heales**  
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**Scientific News**  
**9<sup>th</sup> of January 2022**  
**Sven Bulterijs**

Business/Conferences/  
General news



|                    |                  |                                   |
|--------------------|------------------|-----------------------------------|
| Total Cases        | Total Deaths     | Total Vaccine Doses Administered  |
| <b>305.280.913</b> | <b>5.485.832</b> | <b>9.403.156.265</b>              |
| 28-Day Cases       | 28-Day Deaths    | 28-Day Vaccine Doses Administered |
| <b>35.428.964</b>  | <b>180.909</b>   | <b>943.603.098</b>                |



# Vaccination of children has started

Rondje langs de velden

## Deel van Europa vaccineert jonge kinderen al, maar Nederland is nog niet begonnen

08 januari 2022 21:21



In Germany already 8.5% of 5-11 year olds have been vaccinated

# In the US ~25% of 5 to 11 year olds have been vaccinated

## COVID-19 Vaccinations for US Children Ages 5-11

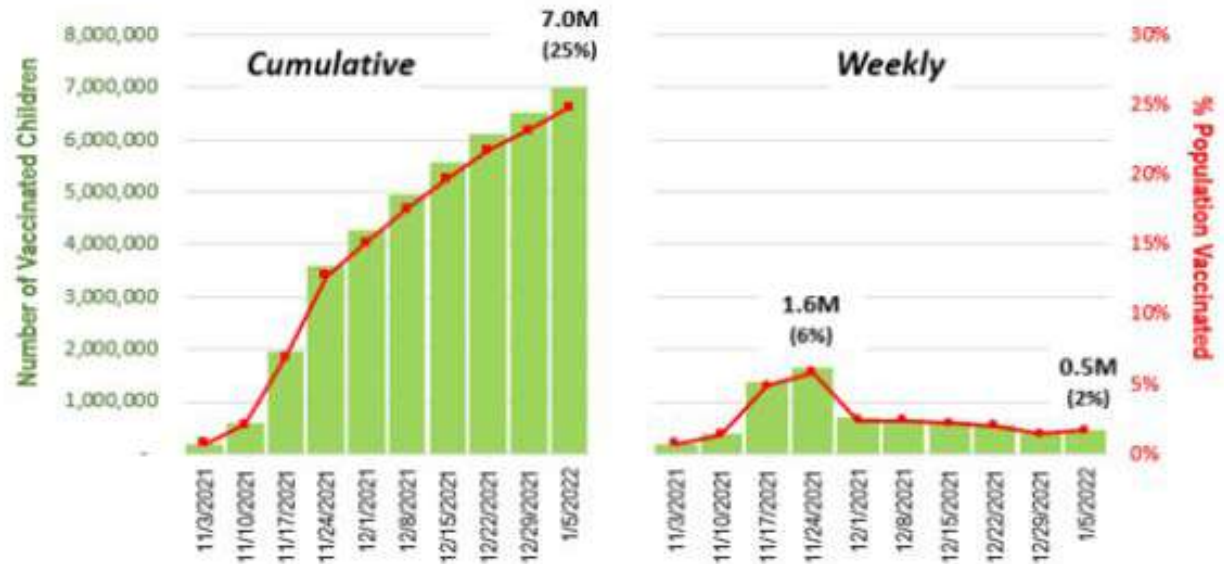
11.3.21 to 1.5.2022

US Children Ages 5-11 Receiving Their Initial COVID-19 Vaccination

As of January 5:

**7.0 million (25%)**  
US children ages 5-11 had received at least **one dose** of COVID-19 vaccine

Per public-use data from the CDC



# Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization

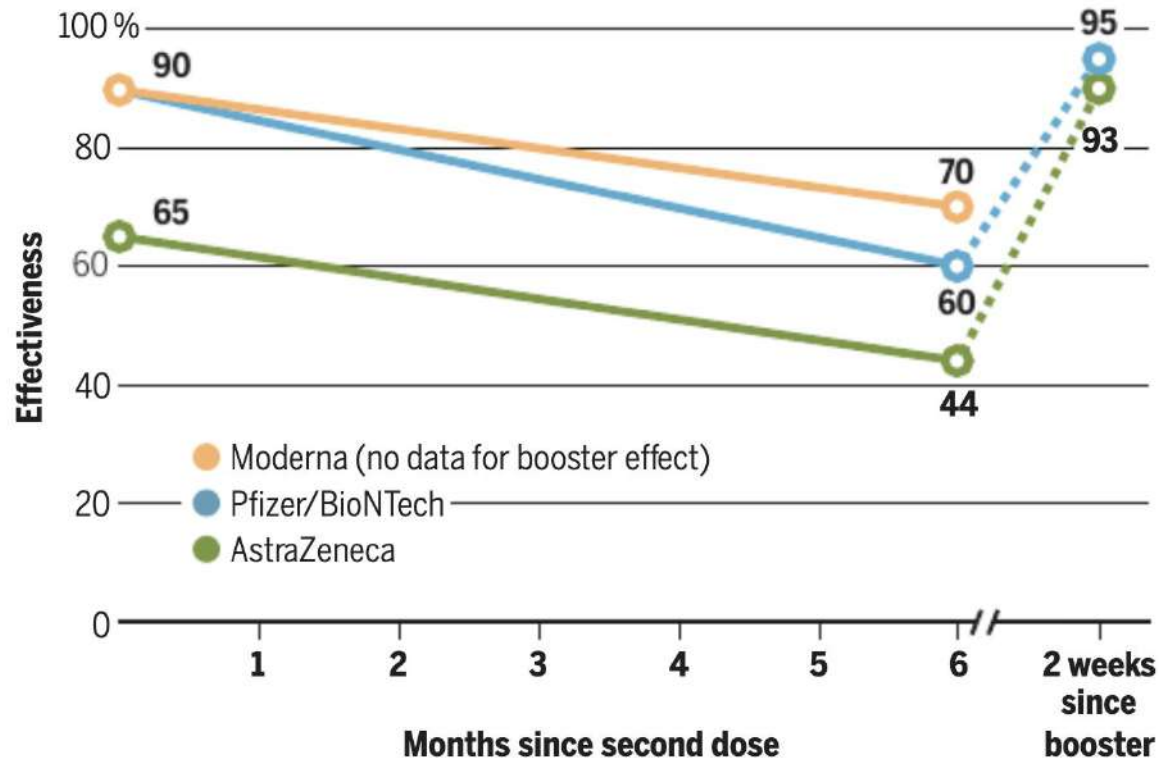
The emergence of Omicron (Pango lineage B.1.1.529), first identified in Botswana and South Africa, may compromise vaccine effectiveness and lead to re-infections<sup>1</sup>. We investigated whether Omicron escapes antibody neutralization in South Africans vaccinated with Pfizer BNT162b2. We also investigated if Omicron requires the ACE2 receptor to infect cells. We isolated and sequence confirmed live Omicron virus from an infected person in South Africa and compared plasma neutralization of Omicron relative to an ancestral SARS-CoV-2 strain, observing that Omicron still required ACE2 to infect. For neutralization, blood samples were taken soon after vaccination from participants who were vaccinated and previously infected or vaccinated with no evidence of previous infection. Neutralization of ancestral virus was much higher in infected and vaccinated versus vaccinated only participants but both groups showed a 22-fold escape from vaccine elicited neutralization by the Omicron variant. However, in the previously infected and vaccinated group, the level of residual neutralization of Omicron was similar to the level of neutralization of ancestral virus observed in the vaccination only group. These data support the notion that, provided high neutralization capacity is elicited by vaccination/boosting approaches, reasonable effectiveness against Omicron may be maintained.

# COVID-19 vaccine breakthrough infections

RAVINDRA K. GUPTA AND ERIC J. TOPOL

## Vaccine effectiveness over time

Two doses of messenger RNA (mRNA) or adenovirus vectored COVID-19 vaccines elicit high levels of protection from symptomatic disease, but this wanes over time. Emerging studies show that a third dose (booster) of the same type can restore effectiveness to >90%. Data are averages for Delta variant from multiple studies.





## **A Phase 2a clinical trial of Molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus**

There is an urgent need for an effective, oral, direct-acting therapeutic to block transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and to prevent progression to severe coronavirus disease-2019 (COVID-19). In a Phase 2a double-blind, placebo-controlled, randomized, multicenter clinical trial, we evaluated the safety, tolerability, and antiviral efficacy of the nucleoside analog molnupiravir in 202 unvaccinated participants with confirmed SARS-CoV-2 infection and with symptom duration <7 days. Participants were randomized 1:1 to receive 200 mg molnupiravir or placebo, and then 3:1 to receive molnupiravir (400 or 800 mg) or placebo, orally twice daily for 5 days. Antiviral activity was assessed by reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA in nasopharyngeal swabs. Infectious virus was assessed by inoculation of cultured Vero cells with samples from nasopharyngeal swabs and was detected by RT-PCR. Time to viral RNA clearance (primary endpoint) was decreased in the 800 mg molnupiravir group (median 14 days) compared to the placebo group (median 15 days) (log rank p-value=0.013). 92.5% of participants receiving 800 mg molnupiravir achieved viral RNA clearance compared with 80.3% of placebo recipients by study end (4 weeks). Infectious virus (secondary endpoint) was detected in swabs from 1.9% of the 800 mg molnupiravir group compared with 16.7% of placebo group at day 3 of treatment (p =0.016). At day 5 of treatment, infectious virus was not isolated from any participants receiving 400 or 800 mg molnupiravir compared with 11.1% of placebo recipients (p =0.034 and 0.027, respectively). Molnupiravir was well tolerated, with a similar number of adverse events across all doses.

# Half of top cancer studies fail high-profile reproducibility effort

Barriers to reproducing preclinical results included unhelpful author communication, but critics argue that one-time replication attempts don't tell the whole story.

[Asher Mullard](#)



Vague experimental protocols was one barrier to replication that researchers encountered. Credit: Patrick Hertzog/AFP/Getty

## World's oldest person celebrates 119th birthday in Japan nursing home

**Kane Tanaka has set her sights on becoming 120 next year, as figures show the number of young adults in Japan in steep decline**



📷 Kane Tanaka, the world's oldest person, turned 119 on Sunday. Photograph: KYODO/Reuters

The world's oldest person has celebrated her 119th birthday in [Japan](#), saying she is determined to extend the record by another year.

# The Longevity Biotech Association Launches

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Leaders from across the longevity sector came together in London today to announce the formation of the Longevity Biotechnology Association (LBA). The non-profit organisation says it aims to represent those behind the development of "new medicines and therapies to prevent and cure, rather than merely manage, the health conditions of late life." Three of the LBA's founding members announced the launch at today's [Investing in the Age of Longevity event at Longevity Week](#), including [Juvenescence](#) co-founder and chairman [Jim Mellon](#), [Cambrian Biopharma](#) founder [James Peyer](#), and [Mehmood Khan](#), CEO of [Hevolution Foundation](#).

On the academic side, LBA founding members include Harvard's [David Sinclair](#), [Nir Barzilai](#) from the [Albert Einstein College of Medicine](#), and [Brian Kennedy](#) from the [National University of Singapore](#). In addition to [Peyer](#), biotech company CEOs include [BioAge's Kristen Fortney](#), [Joe Betts-Lacroix](#) of [Retro Biosciences](#), and [Matthias Steger](#) of [Rejuveron Life Sciences](#). Beyond [Mellon](#) and [Kahn](#), investors are also represented by [The Longevity Fund's Laura Deming](#), [Nils Regge](#) of [Apollo Health Ventures](#), [Michael Greve](#) of the [Forever Healthy Foundation](#), and [Longevity Vision Fund's Sergey Young](#).

"I think the LBA will be a powerful and necessary force for the coming years... The ambition of the industry over the next 10 years is to completely upend the conception of aging that most people have... and the bottom line is, the industry has come of age." The LBA has several main objectives, the first of which is to "educate governments, the media, the public and the medical field about the promise of emerging therapies with the potential to treat or prevent multiple age-related conditions at once." Other goals include supporting newcomers to the industry and to help foster the creation of industrywide best practices.

## Biography of Dr. Mehmood Khan



*Credit: NIST: Denease Anderson*

(Term expires November 12, 2021)

Mehmood Khan, is the Chief Executive Officer of Hevolution Foundation, a first of its kind non-profit organization that funds research through grants and provides investments in biotech to incentivize healthspan science across disciplines and borders for the benefit of all. Established by a Saudi Royal Decree with its headquarters in Riyadh with additional international hubs to support the expansion and execute the global mission. Its vision is to expand healthy human lifespan for the benefit of all humanity. Hevolution Foundation aims to be positioned as a global leader, catalyst, partner, and convener, to increase the number of scientists entering the field, to increase the investable opportunities in the field of aging, to help shape the regulatory and government environment.

He also currently serves as the Executive Chairman of Life Biosciences Inc. where he joined the company in April 2019 as the Chief Executive Officer and Board Member. Life Biosciences was founded to advance scientific research and develop innovative new therapies to improve and extend healthy lives for everyone.

Dr. Khan previously served as Vice Chairman and Chief Scientific Officer of Global Research and Development at PepsiCo, a Fortune 50 company employing upwards of 250,000 employees across 22 brands. At PepsiCo, Dr. Khan played a pivotal role in the company's global R&D efforts to create breakthrough innovations in food, beverages, and nutrition, including the incorporation of healthier and more nutritious offerings across its portfolio. Dr. Khan also oversaw PepsiCo's global sustainability initiatives based

## Forever Healthy and Buck Institute announce partnership to advance translational research in human rejuvenation

12/14/2021

### **Michael Greve's Forever Healthy Foundation commits \$5 million to fund breakthrough science with strong potential for startup creation at the Buck**



funding aims to advance early-stage research with high translational potential in order to speed up the transition from lab to product.

Karlsruhe, Germany and Novato, CA, USA

The Forever Healthy Foundation and the Buck Institute for Research on Aging today announced a new partnership to advance early-stage discoveries at the Institute that show promise to reverse physiologic aging in humans. The focus will be on cutting-edge research aimed at the repair of age-related damage at the cellular and molecular level, a hallmark of the aging process. Forever Healthy will commit up to \$1 million per year for five years to drive this innovation. The

# 5 European companies pioneering the longevity industry

December 23, 2021



Aging research articles



## **Senolytic vaccination improves normal and pathological age-related phenotypes and increases lifespan in progeroid mice**

Elimination of senescent cells (senolysis) was recently reported to improve normal and pathological changes associated with aging in mice<sup>1,2</sup>. However, most senolytic agents inhibit antiapoptotic pathways<sup>3</sup>, raising the possibility of off-target effects in normal tissues. Identification of alternative senolytic approaches is therefore warranted. Here we identify glycoprotein nonmetastatic melanoma protein B (GPNMB) as a molecular target for senolytic therapy. Analysis of transcriptome data from senescent vascular endothelial cells revealed that GPNMB was a molecule with a transmembrane domain that was enriched in senescent cells (seno-antigen). GPNMB expression was upregulated in vascular endothelial cells and/or leukocytes of patients and mice with atherosclerosis. Genetic ablation of Gpnmb-positive cells attenuated senescence in adipose tissue and improved systemic metabolic abnormalities in mice fed a high-fat diet, and reduced atherosclerotic burden in apolipoprotein E knockout mice on a high-fat diet. We then immunized mice against Gpnmb and found a reduction in Gpnmb-positive cells. Senolytic vaccination also improved normal and pathological phenotypes associated with aging, and extended the male lifespan of progeroid mice. Our results suggest that vaccination targeting seno-antigens could be a potential strategy for new senolytic therapies.

# Deletion of SA $\beta$ -Gal<sup>+</sup> cells using senolytics improves muscle regeneration in old mice

Cory M. Dungan, Kevin A. Murach, Christopher J. Zdunek, Zuo Jian Tang, Georgia L. VonLehmden, Camille R. Brightwell, Zachary Hettinger, Davis A. Englund, Zheng Liu, Christopher S. Fry ... [See all authors](#) ▾

First published: 13 December 2021 | <https://doi.org/10.1111/accel.13528>

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## Abstract

Systemic deletion of senescent cells leads to robust improvements in cognitive, cardiovascular, and whole-body metabolism, but their role in tissue reparative processes is incompletely understood. We hypothesized that senolytic drugs would enhance regeneration in aged skeletal muscle. Young (3 months) and old (20 months) male C57Bl/6j mice were administered the senolytics dasatinib (5 mg/kg) and quercetin (50 mg/kg) or vehicle bi-weekly for 4 months. Tibialis anterior (TA) was then injected with 1.2% BaCl<sub>2</sub> or PBS 7- or 28 days prior to euthanization. Senescence-associated  $\beta$ -Galactosidase positive (SA  $\beta$ -Gal<sup>+</sup>) cell abundance was low in muscle from both young and old mice and increased similarly 7 days following injury in both age groups, with no effect of D+Q. Most SA  $\beta$ -Gal<sup>+</sup> cells were also CD11b<sup>+</sup> in young and old mice 7- and 14 days following injury, suggesting they are infiltrating immune cells. By 14 days, SA  $\beta$ -Gal<sup>+</sup>/CD11b<sup>+</sup> cells from old mice expressed senescence genes, whereas those from young mice expressed higher levels of genes characteristic of anti-inflammatory macrophages. SA  $\beta$ -Gal<sup>+</sup> cells remained elevated in old compared to young mice 28 days following injury, which were reduced by D+Q only in the old mice. In D+Q-treated old mice, muscle regenerated following injury to a greater extent compared to vehicle-treated old mice, having larger fiber cross-sectional area after 28 days. Conversely, D+Q blunted regeneration in young mice. *In vitro* experiments suggested D+Q directly improve myogenic progenitor cell proliferation. Enhanced physical function and improved muscle regeneration demonstrate that senolytics have beneficial effects only in old mice.

# Chemically induced senescence in human stem cell-derived neurons promotes phenotypic presentation of neurodegeneration

Ali Fathi, Sakthikumar Mathivanan, Linghai Kong, Andrew J. Petersen, Cole R. K. Harder, Jasper Block, Julia Marie Miller, Anita Bhattacharyya, Daifeng Wang, Su-Chun Zhang 

First published: 24 December 2021 | <https://doi.org/10.1111/accel.13541>

Ali Fathi and Sakthikumar Mathivanan are contribute equally.

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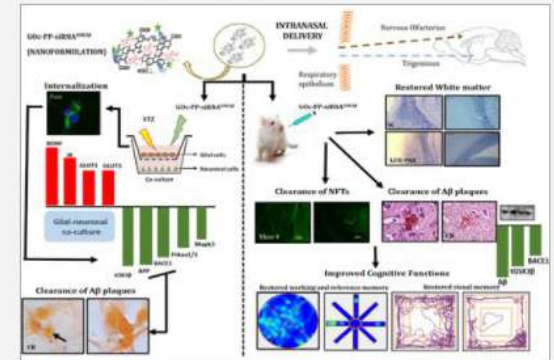
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## Abstract

Modeling age-related neurodegenerative disorders with human stem cells are difficult due to the embryonic nature of stem cell-derived neurons. We developed a chemical cocktail to induce senescence of iPSC-derived neurons to address this challenge. We first screened small molecules that induce embryonic fibroblasts to exhibit features characteristic of aged fibroblasts. We then optimized a cocktail of small molecules that induced senescence in fibroblasts and cortical neurons without causing DNA damage. The utility of the “senescence cocktail” was validated in motor neurons derived from ALS patient iPSCs which exhibited protein aggregation and axonal degeneration substantially earlier than those without cocktail treatment. Our “senescence cocktail” will likely enhance the manifestation of disease-related phenotypes in neurons derived from iPSCs, enabling the generation of reliable drug discovery platforms.

Sporadic Alzheimer's disease (sAD) is a progressive neurodegenerative disorder with dysfunctional insulin signaling and energy metabolism. Emerging evidence suggests impairments in brain insulin responsiveness, glucose utilization, and energy metabolism may be major causes of amyloid precursor protein mishandling. The support for this notion comes from the studies wherein streptozotocin (STZ) induced brain insulin resistance in rodent model resulted in sAD-like neuropathology with cognitive decline. Our previous study showed a compromised insulin signaling pathway, glucose uptake, glucose metabolism, and energy homeostasis in STZ-induced glial-neuronal coculture and *in vivo* model of sAD. Various components of insulin signaling pathway were examined to understand the metabolic correlation, and GSK3 $\beta$  was selected for gene knockdown strategy to reverse sAD pathology based on the data. In the present study, we have synthesized carboxylated graphene oxide (GO) nanosheets functionalized with PEG and subsequently with polyethylenimine (PEI) to provide attachment sites for GSK3 $\beta$  siRNA. Our results showed that siRNA mediated knockdown of the GSK3 $\beta$  gene reduced expression of amyloid pathway genes (APP and BACE1), which was further confirmed by reduced amyloid beta (A $\beta$ ) levels in the *in vitro* STZ-induced sAD model. GSK3 $\beta$  knockdown also restored insulin signaling, AMPK and Mapk3 pathway by restoring the expression of corresponding candidate genes in these pathways (IR, Glut1/3, Prkaa1/2, Mapk3, BDNF) that reflected improved cellular energy homeostasis, neuronal proliferation, differentiation, maturation, and repair. Behavioral data from Morris water maze (MWM), open field (OF), novel object recognition (NOR), Y maze, and radial arm maze (RAM) tests showed that 0.5  $\mu$ g nanoformulation (GOc-PP-siRNA<sup>GSK3 $\beta$</sup> ) intranasally for 7 days improved spatial memory, rescued anxiety like behavior, improved visual and working memory, and rescued exploratory behavior in STZ-induced sAD rats. GSK3 $\beta$  silencing resulted in decreased BACE1 expression and prevented accumulation of A $\beta$  in the cortex and hippocampus. These molecular findings with improved behavioral performances were further correlated with reduced amyloid beta (A $\beta$ ) and neurofibrillary tangle (NFTs) formation in the cortex and hippocampus of GOc-PP-siRNA<sup>GSK3 $\beta$</sup>  administered sAD rats. Therefore, it is conceivable from the present study that nanoparticle-mediated targeting of GSK3 $\beta$  in the sAD appears to be a promising strategy to reverse sAD pathology.



# Cancer risk across mammals

[Orsolya Vincze](#) , [Fernando Colchero](#), [Jean-Francois Lemaître](#), [Dalia A. Conde](#), [Samuel Pavard](#), [Margaux Bieuville](#), [Araxi O. Urrutia](#), [Beata Ujvari](#), [Amy M. Boddy](#), [Carlo C. Maley](#), [Frédéric Thomas](#) & [Mathieu Giraudeau](#)

[Nature](#) (2021) | [Cite this article](#)

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## Abstract

Cancer is a ubiquitous disease of metazoans, predicted to disproportionately affect larger, long-lived organisms owing to their greater number of cell divisions, and thus increased probability of somatic mutations<sup>1,2</sup>. While elevated cancer risk with larger body size and/or longevity has been documented within species<sup>3,4,5</sup>, Peto's paradox indicates the apparent lack of such an association among taxa<sup>6</sup>. Yet, unequivocal empirical evidence for Peto's paradox is lacking, stemming from the difficulty of estimating cancer risk in non-model species. Here we build and analyse a database on cancer-related mortality using data on adult zoo mammals (110,148 individuals, 191 species) and map age-controlled cancer mortality to the mammalian tree of life. We demonstrate the universality and high frequency of oncogenic phenomena in mammals and reveal substantial differences in cancer mortality across major mammalian orders. We show that the phylogenetic distribution of cancer mortality is associated with diet, with carnivorous mammals (especially mammal-consuming ones) facing the highest cancer-related mortality. Moreover, we provide unequivocal evidence for the body size and longevity components of Peto's paradox by showing that cancer mortality risk is largely independent of both body mass and adult life expectancy across species. These results highlight the key role of life-history evolution in shaping cancer resistance and provide major advancements in the quest for natural anticancer defences.

# Pan-cancer analysis reveals molecular patterns associated with age

[Yajas Shah](#) <sup>5</sup> • [Akanksha Verma](#) <sup>5</sup> • [Andrew R. Marderstein](#) • ... [Bhavneet Bhinder](#) •

[J. Sebastian Garcia Medina](#) • [Olivier Elemento](#)  <sup>6</sup>  • [Show all authors](#) • [Show footnotes](#)


Older age is a strong risk factor for several diseases, including cancer. The etiology and biology of age-associated differences among cancers are poorly understood. To address this knowledge gap, we aim to delineate differences in tumor molecular characteristics between younger and older patients across a variety of tumor types from The Cancer Genome Atlas. We show that these groups exhibit widespread molecular differences in select tumor types. Our work shows that tumors in younger individuals exhibit a dysregulated molecular aging phenotype and are associated with hallmarks of premature senescence. Additionally, we find that these tumors are enriched for driver gene mutations, resulting in homologous recombination defects. Lastly, we observe a trend toward decreased immune infiltration and function in older patients and find that, immunologically, young tumor tissue resembles aged healthy tissue. Taken together, we find that tumors from young individuals possess unique characteristics that may be leveraged for therapy.

# Misexpression of genes lacking CpG islands drives degenerative changes during aging

JUN-YEONG LEE , IAN DAVIS, ELLIOT H. H. YOUTH , JONGHWAN KIM , GARY CHURCHILL , JAMES GODWIN , RON KORSTANJE , AND SAMUEL BECK 

[Authors Info & Affiliations](#)

SCIENCE ADVANCES • 15 Dec 2021 • Vol 7, Issue 51 • DOI: 10.1126/sciadv.abj9111

 3,473



## Abstract

Cellular aging is characterized by disruption of the nuclear lamina and its associated heterochromatin. How these structural changes within the nucleus contribute to age-related degeneration of the organism is unclear. Genes lacking CpG islands (CGI<sup>-</sup> genes) generally associate with heterochromatin when they are inactive. Here, we show that the expression of these genes is globally activated in aged cells and tissues. This CGI<sup>-</sup> gene misexpression is a common feature of normal and pathological aging in mice and humans. We report evidence that CGI<sup>-</sup> gene up-regulation is directly responsible for age-related physiological deterioration, notably for increased secretion of inflammatory mediators.



# DNA methylation clocks tick in naked mole rats but queens age more slowly than nonbreeders

[Steve Horvath](#) , [Amin Haghani](#), [Nicholas Macoretta](#), [Julia Ablava](#), [Joseph A. Zoller](#), [Caesar Z. Li](#), [Joshua Zhang](#), [Masaki Takasugi](#), [Yang Zhao](#), [Elena Rydkina](#), [Zhihui Zhang](#), [Stephan Emmrich](#), [Ken Raj](#), [Andrei Seluanov](#), [Chris G. Faulkes](#)  & [Vera Gorbunova](#) 

[Nature Aging](#) (2021) | [Cite this article](#)

5162 Accesses | 103 Altmetric | [Metrics](#)

## Abstract

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Naked mole rats (NMRs) live an exceptionally long life, appear not to exhibit age-related decline in physiological capacity and are resistant to age-related diseases. However, it has been unknown whether NMRs also evade aging according to a primary hallmark of aging: epigenetic changes. To address this question, we profiled  $n = 385$  samples from 11 tissue types at loci that are highly conserved between mammalian species using a custom array (HorvathMammalMethylChip40). We observed strong epigenetic aging effects and developed seven highly accurate epigenetic clocks for several tissues (pan-tissue, blood, kidney, liver, skin clocks) and two dual-species (human–NMR) clocks. The skin clock correctly estimated induced pluripotent stem cells derived from NMR fibroblasts to be of prenatal age. The NMR epigenetic clocks revealed that breeding NMR queens age more slowly than nonbreeders, a feature that is also observed in some eusocial insects. Our results show that despite a phenotype of negligible senescence, the NMR ages epigenetically.



# Clinical course of the longest-lived man in the world: A case report

**Background and objective:** Supercentenarians, people who have reached 110 years of age, represent an ultimate model of human longevity. We have conducted research from both biomedical and psychosocial perspectives to clarify the factors that contribute to healthy longevity. The current study described the clinical course of the oldest lived man in the world.

**Methods:** Kimura Jiroemon, who is the verified oldest man in recorded history, lived for more than 116 years. We conducted a longitudinal investigation including physical and psychological assessments, blood data, and electrocardiogram (ECG) from the age of 111 and obtained medical data such as computed tomography (CT) images during the course of hospitalizations in the last year of his life.

**Results:** At the age of 111, Jiroemon was almost independent regarding activities of daily living. Additionally, his Philadelphia Geriatric Center Morale Scale score was 15/17, indicating high psychological well-being. His biological data included first-degree atrioventricular (AV) block on ECG; mild decreases of hemoglobin (11.6 g/dL), hematocrit (36.2%), and albumin levels (3.5 g/dL); and elevated serum cystatin C levels (1.32 mg/L), indicating potential dysfunction of the renal and electrical conduction systems. He then lived without fatal illness until the age of 115 years. At this age, he lost consciousness, and his ECG revealed complete AV block. At the first hospitalization for intensive examination, his doctor recommended implanting a cardiac pacemaker, but he and his family declined. On December 12, 2012, his condition rapidly worsened, and he was hospitalized twice for heart failure because of AV block. On May 11, 2013, he lost consciousness after breakfast, and he was hospitalized for the fourth time. He was diagnosed with pneumonia and heart failure based on his chest CT findings and elevated brain natriuretic peptide levels (160 pg/mL), and died on June 12, 2013 at the age of 116.

**Conclusions:** Despite having no cardiovascular risk factors throughout his life, Jiroemon developed heart failure from potential heart and kidney dysfunction, suggesting that aging of the cardiorenal system was the ultimate pathology of the oldest man in the world. His clinical course represents a model of both suppression of morbidity and extreme longevity. Comprehensive health and longevity research studies from physical and psychological aspects are required.

**Keywords:** Cardiorenal syndrome; Case report; Centenarian; Gerontology; Longevity; Supercentenarian.

## ***In Vivo* Transcriptomic Profiling using Cell Encapsulation Identifies Effector Pathways of Systemic Aging**

Omid Mashinchian, Xiaotong Hong, Joris Michaud, Eugenia Migliavacca, Gregory Lefebvre, Christophe Boss, Filippo De Franceschi, Emmeran Le Moal, Jasmin Colletette-Tremblay, Joan Isern, Sylviane Metairon, Frederic Raymond, Patrick Descombes, Nicolas Bouche, Pura Muñoz-Cánoves, Jerome N. Feige, C. Florian Bentzinger

**doi:** <https://doi.org/10.1101/2020.03.09.979054>

This article is a preprint and has not been certified by peer review [what does this mean?].



**Abstract**

Full Text

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### **Abstract**



Sustained exposure to a young systemic environment rejuvenates aged organisms and promotes cellular function. However, due to the intrinsic complexity of tissues it remains challenging to pinpoint niche-independent effects of circulating factors on specific cell populations. Here we describe a method for the encapsulation of human and mouse skeletal muscle progenitors in diffusible polyethersulfone hollow fiber capsules that can be used to profile systemic aging *in vivo* independent of heterogeneous short-range tissue interactions. We observed that circulating long-range signaling factors in the old systemic environment lead to an activation of Myc and E2F transcription factors, induce senescence and suppress myogenic differentiation. Importantly, *in vitro* profiling using young and old serum in 2D culture does not capture all pathways deregulated in encapsulated cells in aged mice. Thus, *in vivo* transcriptomic profiling using cell encapsulation allows for the characterization of effector pathways of systemic aging with unparalleled accuracy.

# Protective Effects of Familial Longevity Decrease with Age and Become Negligible for Centenarians

Natalia S Gavrilova, Ph.D , Leonid A Gavrilov, Ph.D

*The Journals of Gerontology: Series A*, glab380, <https://doi.org/10.1093/gerona/glab380>

**Published:** 20 December 2021 **Article history** ▼

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## Abstract

It is known that biological relatives of long-lived individuals demonstrate lower mortality and longer lifespan compared to relatives of shorter-lived individuals, and at least part of this advantage is likely to be genetic. Less information, however, is available about effects of familial longevity on age-specific mortality trajectories. We compared mortality patterns after age 50 years for 10,045 siblings of U.S. centenarians and 12,308 siblings of shorter-lived individuals (died at age 65 years). Similar comparisons were made for sons and daughters of longer-lived parents (both parents lived 80 years and more) and shorter-lived parents (both parents lived less than 80 years) within each group of siblings. Although relatives of longer-lived individuals have lower mortality at younger ages compared to relatives of shorter lived individuals, this mortality advantage practically disappears by age 100 years. To validate this observation further, we analyzed survival of 3,408 U.S. centenarians born in 1890–97 with known information on maternal and paternal lifespan. We found using the Cox proportional hazards model that both maternal and paternal longevity (lifespan 80+ years) is not significantly associated with survival after age 100 years. The results are compatible with the predictions of reliability theory of aging suggesting higher initial levels of system redundancy (reserves) in individuals with protective familial/genetic background and hence lower initial mortality. Heterogeneity hypothesis is another possible explanation for the observed phenomena.

## Sex-related differences in aging rate are associated with sex chromosome system in amphibians

Hugo Cayuela , Jean-François Lemaître, Jean-Paul Léna, Víctor Ronget, Iñigo Martínez-Solano, Erin Muths, David S. Pilliod, Benedikt R. Schmidt, Gregorio Sánchez-Montes ... [See all authors](#) 

First published: 08 December 2021 | <https://doi.org/10.1111/evo.14410>

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### Abstract

Sex-related differences in mortality are widespread in the animal kingdom. Although studies have shown that sex determination systems might drive lifespan evolution, sex chromosome influence on aging rates have not been investigated so far, likely due to an apparent lack of demographic data from clades including both XY (with heterogametic males) and ZW (heterogametic females) systems. Taking advantage of a unique collection of capture–recapture datasets in amphibians, a vertebrate group where XY and ZW systems have repeatedly evolved over the past 200 million years, we examined whether sex heterogamy can predict sex differences in aging rates and lifespans. We showed that the strength and direction of sex differences in aging rates (and not lifespan) differ between XY and ZW systems. Sex-specific variation in aging rates was moderate within each system, but aging rates tended to be consistently higher in the heterogametic sex. This led to small but detectable effects of sex chromosome system on sex differences in aging rates in our models. Although preliminary, our results suggest that exposed recessive deleterious mutations on the X/Z chromosome (the “unguarded X/Z effect”) or repeat-rich Y/W chromosome (the “toxic Y/W effect”) could accelerate aging in the heterogametic sex in some vertebrate clades.

## Antecedent Metabolic Health and Metformin (ANTHEM) Aging study: Rationale and study design for a randomized controlled trial

Santosh Kumari <sup>1 2</sup>, Matthew Bubak <sup>3</sup>, Hayden M Schoenberg <sup>1 2</sup>, Arik Davidyan <sup>3</sup>,  
Christian J Elliehausen <sup>1 2</sup>, Katrin G Kuhn <sup>4</sup>, Timothy M VanWagoner <sup>5</sup>, Rowan Karaman <sup>6 7</sup>,  
Robert Hal Scofield <sup>8 9 10 11</sup>, Benjamin F Miller <sup>3 11 12</sup>, Adam R Konopka <sup>1 2</sup>

Affiliations + expand

PMID: 34865016 DOI: 10.1093/gerona/glab358

### Abstract

The antidiabetic medication metformin has been proposed to be the first drug tested to target aging and extend healthspan in humans. While there is extensive epidemiological support for the health benefits of metformin in patient populations, it is not clear if these protective effects apply to those free of age-related disease. Our previous data in older adults without diabetes suggest a dichotomous change in insulin sensitivity and skeletal muscle mitochondrial adaptations after metformin treatment when co-prescribed with exercise. Those who entered the study as insulin sensitive had no change to detrimental effects while those who were insulin resistant had positive changes. The objective of this clinical trial is to determine if 1) antecedent metabolic health and 2) skeletal muscle mitochondrial remodeling and function mediate the positive or detrimental effects of metformin monotherapy, independent of exercise, on the metabolism and biology of aging. In a randomized, double blind clinical trial, adults free of chronic disease (n=148, 40-75 years old) are stratified as either insulin sensitive or resistant based on HOMA-IR ( $\leq 2.2$  or  $\geq 2.5$ ) and take 1500 mg/day of metformin or placebo for 12 weeks. Hyperinsulinemic-euglycemic clamps and skeletal muscle biopsies are performed before and after 12 weeks to assess primary outcomes of peripheral insulin sensitivity and mitochondrial remodeling and function. Findings from this trial will identify clinical characteristics and cellular mechanisms involved in modulating the effectiveness of metformin treatment to target aging that could inform larger phase 3 clinical trials aimed at testing aging as a treatment indication for metformin.

*C. elegans* aging research

## High-Content *C. elegans* Screen Identifies Natural Compounds Impacting Mitochondria-Lipid Homeostasis and Promoting Healthspan

by  Silvia Maglioni <sup>1</sup> ,  Nayna Arsalan <sup>1</sup> ,  Anna Hamacher <sup>2,3</sup> ,  Shiwa Afshar <sup>1</sup> ,  
 Alfonso Schiavi <sup>1</sup> ,  Mathias Beller <sup>2,3</sup>  and  Natascia Ventura <sup>1,4,\*</sup> 

The aging process is concurrently shaped by genetic and extrinsic factors. In this work, we screened a small library of natural compounds, many of marine origin, to identify novel possible anti-aging interventions in *Caenorhabditis elegans*, a powerful model organism for aging studies. To this aim, we exploited a high-content microscopy platform to search for interventions able to induce phenotypes associated with mild mitochondrial stress, which is known to promote animal's health- and lifespan. Worms were initially exposed to three different concentrations of the drugs in liquid culture, in search of those affecting animal size and expression of mitochondrial stress response genes. This was followed by a validation step with nine compounds on solid media to refine compounds concentration, which led to the identification of four compounds (namely isobavachalcone, manzamine A, kahalalide F and lutein) consistently affecting development, fertility, size and lipid content of the nematodes. Treatment of *Drosophila* cells with the four hits confirmed their effects on mitochondria activity and lipid content. Out of these four, two were specifically chosen for analysis of age-related parameters, kahalalide F and lutein, which conferred increased resistance to heat and oxidative stress and extended animals' healthspan. We also found that, out of different mitochondrial stress response genes, only the *C. elegans* ortholog of the synaptic regulatory proteins neuroligins, *nlg-1*, was consistently induced by the two compounds and mediated lutein healthspan effects.

**Keywords:** *C. elegans*; HCS; mitochondria; natural compounds; kahalalide F; lutein; neuroligin

REVIEWS/COMMENTS/  
METHODS/EDITORIALS



# Advanced pathological ageing should be represented in the ICD

Evelyne Bischof<sup>a, b</sup>, Andrea B Maier<sup>c, d, e, f</sup>, Kai-Fu Lee<sup>g, h</sup>, Alex Zhavoronkov<sup>i, j, k</sup>, David Sinclair<sup>l</sup>  


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# Advanced pathological ageing should be represented in the ICD

Iliia Stambler<sup>a, b, c</sup> , Aleksey Alekseev<sup>d</sup>, Yuri Matveyev<sup>e</sup>, Daria Khaltourina<sup>a, f</sup>

Review Article | [Published: 20 December 2021](#)

## Molecular damage in aging

[Vadim N. Gladyshev](#), [Stephen B. Kritchevsky](#), [Steven G. Clarke](#), [Ana Maria Cuervo](#), [Oliver Fiehn](#), [João Pedro de Magalhães](#), [Theresa Mau](#), [Michal Maes](#), [Robert L. Moritz](#), [Laura J. Niedernhofer](#), [Emile Van Schaftingen](#), [Gregory J. Tranah](#), [Kenneth Walsh](#), [Yoshimitsu Yura](#), [Bohan Zhang](#) & [Steven R. Cummings](#) 

*Nature Aging* **1**, 1096–1106 (2021) | [Cite this article](#)

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### Abstract

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Cellular metabolism and environmental interactions generate molecular damage affecting all levels of biological organization. Accumulation of this damage over time is thought to have a central role in the aging process. Insufficient attention has been paid to the role of molecular damage in aging-related phenotypes, particularly in humans, in part because of the difficulty in measuring its various forms. Recently, omics approaches have been developed that begin to address this challenge, because they can assess a sizable proportion of age-related damage at the level of small molecules, proteins, RNA, DNA, organelles and cells. This Review describes the concept of molecular damage in aging and discusses its diverse aspects from theoretical models to experimental approaches. Measurement of multiple types of damage enables studies of the role of damage in aging and lays a foundation for testing interventions that reduce the burden of molecular damage, thereby targeting aging.

## Translational control in cell ageing: an update

Katrina Woodward ; Nikolay E. Shirokikh  



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Cellular ageing is one of the main drivers of organismal ageing and holds keys towards improving the longevity and quality of the extended life. Elucidating mechanisms underlying the emergence of the aged cells as well as their altered responses to the environment will help understanding the evolutionarily defined longevity preferences across species with different strategies of survival. Much is understood about the role of alterations in the DNA, including many epigenetic modifications such as methylation, in relation to the aged cell phenotype. While transcriptomes of the aged cells are beginning to be better-characterised, their translational responses remain under active investigation. Many of the translationally controlled homeostatic pathways are centred around mitigation of DNA damage, cell stress response and regulation of the proliferative potential of the cells, and thus are critical for the aged cell function. Translation profiling-type studies have boosted the opportunities in discovering the function of protein biosynthesis control and are starting to be applied to the aged cells. Here, we provide a summary of the current knowledge about translational mechanisms considered to be commonly altered in the aged cells, including the integrated stress response-, mechanistic target of Rapamycin- and elongation factor 2 kinase-mediated pathways. We enlist and discuss findings of the recent works that use broad profiling-type approaches to investigate the age-related translational pathways. We outline the limitations of the methods and the remaining unknowns in the established ageing-associated translation mechanisms, and flag translational mechanisms with high prospective importance in ageing, for future studies.

# Alpha-Ketoglutarate dietary supplementation to improve health in humans

Bibek Gyanwali • Zi Xiang Lim • Janjira Soh • ... Jorming Goh • Andrea B. Maier • Brian K. Kennedy  

Alpha-ketoglutarate (AKG) is an intermediate in the Krebs cycle involved in various metabolic and cellular pathways. As an antioxidant, AKG interferes in nitrogen and ammonia balance, and affects epigenetic and immune regulation. These pleiotropic functions of AKG suggest it may also extend human healthspan. Recent studies in worms and mice support this concept. A few studies published in the 1980s and 1990s in humans suggested the potential benefits of AKG in muscle growth, wound healing, and in promoting faster recovery after surgery. So far there are no recently published studies demonstrating the role of AKG in treating aging and age-related diseases; hence, further clinical studies are required to better understand the role of AKG in humans. This review will discuss the regulatory role of AKG in aging, as well as its potential therapeutic use in humans to treat age-related diseases.

# From Model Organisms to Humans, the Opportunity for More Rigor in Methodologic and Statistical Analysis, Design, and Interpretation of Aging and Senescence Research

Daniella E Chusyd, Steven N Austad, Andrew W Brown, Xiwei Chen, Stephanie L Dickinson, Keisuke Ejima, David Fluharty, Lilian Golzarri-Arroyo, Richard Holden, Jasmine Jamshidi-Naeini ... [Show more](#)

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## Abstract

This review identifies frequent design and analysis errors in aging and senescence research and discusses best practices in study design, statistical methods, analyses, and interpretation. Recommendations are offered for how to avoid these problems. The following issues are addressed: 1) errors in randomization, 2) errors related to testing within-group instead of between-group differences, 3) failing to account for clustering, 4) failing to consider interference effects, 5) standardizing metrics of effect size, 6) maximum lifespan testing, 7) testing for effects beyond the mean, 8) tests for power and sample size, 9) compression of morbidity versus survival curve-squaring, and 10) other hot topics, including modeling high-dimensional data and complex relationships and assessing model assumptions and biases. We hope that bringing increased awareness of these topics to the scientific community will emphasize the importance of employing sound statistical practices in all aspects of aging and senescence research.

# Emerging rejuvenation strategies–Reducing the biological age

Bohan Zhang <sup>1</sup>, Alexandre Trapp <sup>1</sup>, Csaba Kerepesi <sup>1</sup>, Vadim N Gladyshev <sup>1</sup>

Affiliations + expand

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**Free article**

## Abstract

Several interventions have recently emerged that were proposed to reverse rather than just attenuate aging, but the criteria for what it takes to achieve rejuvenation remain controversial. Distinguishing potential rejuvenation therapies from other longevity interventions, such as those that slow down aging, is challenging, and these anti-aging strategies are often referred to interchangeably. We suggest that the prerequisite for a rejuvenation intervention is a robust, sustained, and systemic reduction in biological age, which can be assessed by biomarkers of aging, such as epigenetic clocks. We discuss known and putative rejuvenation interventions and comparatively analyze them to explore underlying mechanisms.

**Keywords:** aging; biomarkers; epigenetic clocks; rejuvenation.

# The hyperfunction theory: an emerging paradigm for the biology of aging

David Gems <sup>1</sup>

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## Abstract

The process of senescence (aging) is predominantly determined by the action of wild-type genes. For most organisms, this does not reflect any adaptive function that senescence serves, but rather evolutionary effects of declining selection against genes with deleterious effects later in life. To understand aging requires an account of how evolutionary mechanisms give rise to pathogenic gene action and late-life disease, that integrates evolutionary (ultimate) and mechanistic (proximate) causes into a single explanation. A well-supported evolutionary explanation by G.C. Williams argues that senescence can evolve due to pleiotropic effects of alleles with antagonistic effects on fitness and late-life health (antagonistic pleiotropy, AP). What has remained unclear is how gene action gives rise to late-life disease pathophysiology. One ultimate-proximate account is T.B.L. Kirkwood's disposable soma theory. Based on the hypothesis that stochastic molecular damage causes senescence, this reasons that aging is coupled to reproductive fitness due to preferential investment of resources into reproduction, rather than somatic maintenance. An alternative and more recent ultimate-proximate theory argues that aging is largely caused by programmatic, developmental-type mechanisms. Here ideas about AP and programmatic aging are reviewed, particularly those of M.V. Blagosklonny (the hyperfunction theory) and J.P. de Magalhães (the developmental theory), and their capacity to make sense of diverse experimental findings is assessed.

**Keywords:** antagonistic pleiotropy; hyperfunction; insulin/IGF-1 signalling; mTOR; programmatic aging; quasi-programs; theories of aging.

# Aging-Related Cellular, Structural and Functional Changes in the Lymph Nodes: A Significant Component of Immunosenescence? An Overview

by  Marta Cakala-Jakimowicz <sup>1,\*</sup>   Paulina Kolodziej-Wojnar <sup>1</sup>  and  Monika Puzianowska-Kuznicka <sup>1,2,\*</sup> 

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## Abstract

Aging affects all tissues and organs. Aging of the immune system results in the severe disruption of its functions, leading to an increased susceptibility to infections, an increase in autoimmune disorders and cancer incidence, and a decreased response to vaccines. Lymph nodes are precisely organized structures of the peripheral lymphoid organs and are the key sites coordinating innate and long-term adaptive immune responses to external antigens and vaccines. They are also involved in immune tolerance. The aging of lymph nodes results in decreased cell transport to and within the nodes, a disturbance in the structure and organization of nodal zones, incorrect location of individual immune cell types and impaired intercellular interactions, as well as changes in the production of adequate amounts of chemokines and cytokines necessary for immune cell proliferation, survival and function, impaired naïve T- and B-cell homeostasis, and a diminished long-term humoral response. Understanding the causes of these stromal and lymphoid microenvironment changes in the lymph nodes that cause the aging-related dysfunction of the immune system can help to improve long-term immune responses and the effectiveness of vaccines in the elderly. [View Full-Text](#)



*Keywords:* aging; immunosenescence; lymph nodes; stromal cells; lymphatic endothelial cells; lymphocytes; neutrophils



# The costs and benefits of senotherapeutics for human health

Marco Raffaele PhD <sup>a</sup>, Manlio Vinciguerra PhD <sup>a, b, c</sup>  

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## Summary

Cellular senescence is a major contributor to age-related diseases in humans; however, it also has a beneficial role in physiological and pathological processes, including wound healing, host immunity, and tumour suppression. Reducing the burden of cell senescence in animal models of cardiometabolic disorders, inflammatory conditions, neurodegenerative diseases, and cancer using pharmaceutical approaches that selectively target senescent cells (ie, senolytics) or that suppress senescence-associated secretory phenotype (ie, senomorphics) holds great promise for the management of chronic age-associated conditions. Although studies have provided evidence that senolytics or senomorphics are effective at decreasing the number of senescent cells in humans, the short-term and long-term side-effects of these therapies are largely unknown. In this Review, we systematically discuss the senolytics and senomorphics that have been investigated in clinical trials or have been used off-label, presenting their various adverse effects. Despite the potential of senotherapeutics to transform anti-ageing medicine, a cautionary approach regarding unwanted dose-dependent side-effects should be adopted.

# A new insight into cell biological and biochemical changes through aging

Somayeh Sahabi <sup>b, 1</sup>, Davoud Jafari-Gharabaghlou <sup>c, d, 1</sup>, Nosratollah Zarghami <sup>a, b, d</sup> ✉

After several years of extensive research, the main cause of aging is yet elusive. There are some theories about aging, such as stem cell aging, senescent cells accumulation, and neuro-endocrine theories. None of them is able to explain all changes that happen in cells and body through aging. By finding out the main cause of aging, it will be much easier to control, prevent and even reverse the aging process. Our cells, regardless of their replicative capacity, get old through aging and they have almost the same epigenetic age. Different cell signaling pathways contribute to aging. The most important one is mTORC1 that becomes hyperactive in cells that undergo aging. Other significant changes with age are lysosome accumulation, impaired autophagy, and mitophagy. Immune system undergoes gradual changes through aging including a shift from lymphoid to myeloid lineage production as well as increased IL-6 and TNF- $\alpha$  which lead to age-related weight loss and meta-inflammation. Additionally, our endocrine system also experiences some changes that should be taken into consideration when looking for the main cause of aging in the human body. In this review, we planned to summarize some of the changes that happen in cells and the body through aging.

# The potential of aging rejuvenation

Ana O'Lughlen <sup>1</sup>

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## Abstract

Aging is a process by which basic cellular functions and tissue homeostasis start to decline and organs become progressively dysfunctional. Although aging was once considered irreversible, the concept of the elixir of youth or rejuvenation has been in the history for centuries. In fact, recent scientific studies now show the existence of alternative strategies to delay aging. Here, we discuss how different signaling pathways, a variety of cell types and molecules can contribute to delay aging. In addition, we will define recently described rejuvenation strategies, with an emphasis on the potential for extracellular vesicles (EV).

**Keywords:** SASP; Senescence; aging; extracellular vesicles; intercellular communication; rejuvenation.

# OTHER RESEARCH & REVIEWS