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Scientific News
3rd of April 2022
Sven Bulterijs

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Business/Conferences/ General news

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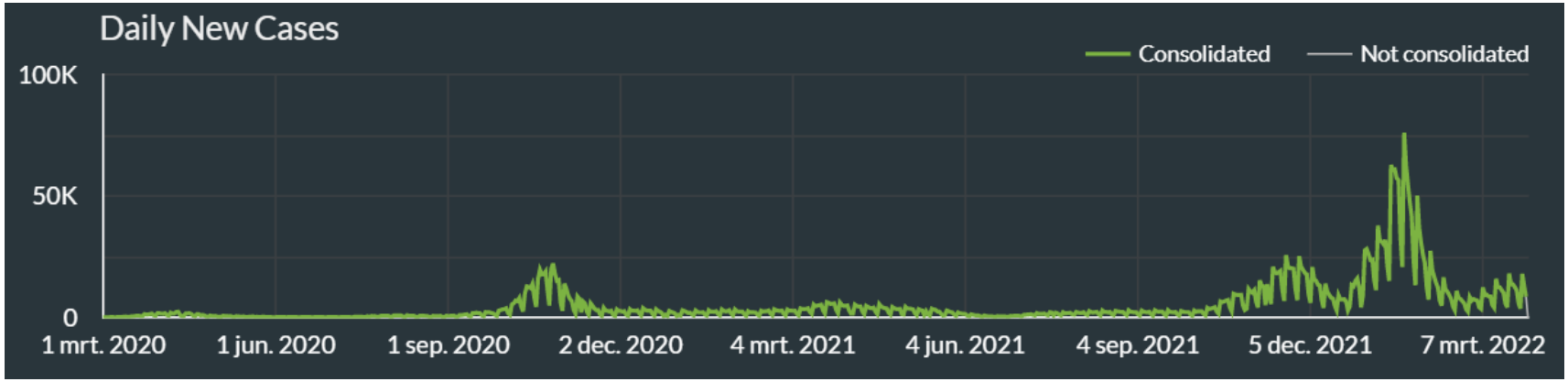

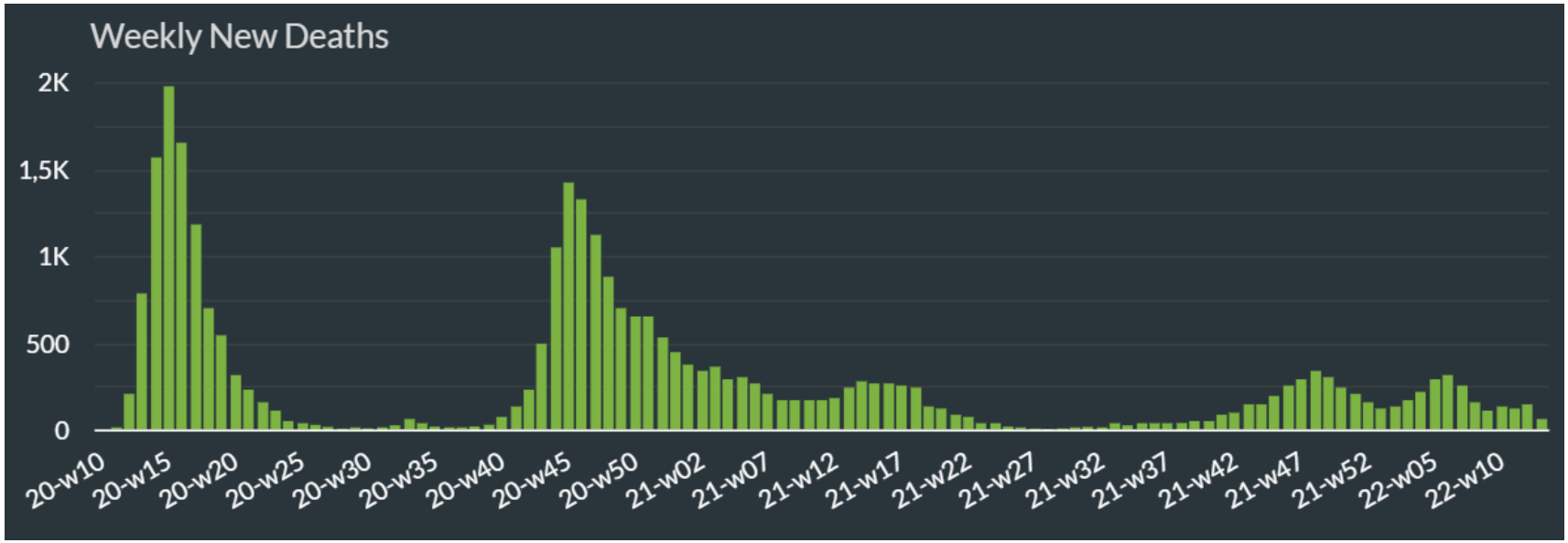

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Vaccinatie jongsten blijft hangen onder veertig procent

De meest omstreden fase van de vaccinatiecampagne, die voor vijf- tot elfjarigen, heeft veel minder bereik gehad dan de andere fases. 'We hadden verwacht dat we hoger zouden eindigen.'

Nikolas Vanhecke, Dries De Smet
Woensdag 9 maart 2022 om 15.38 uur

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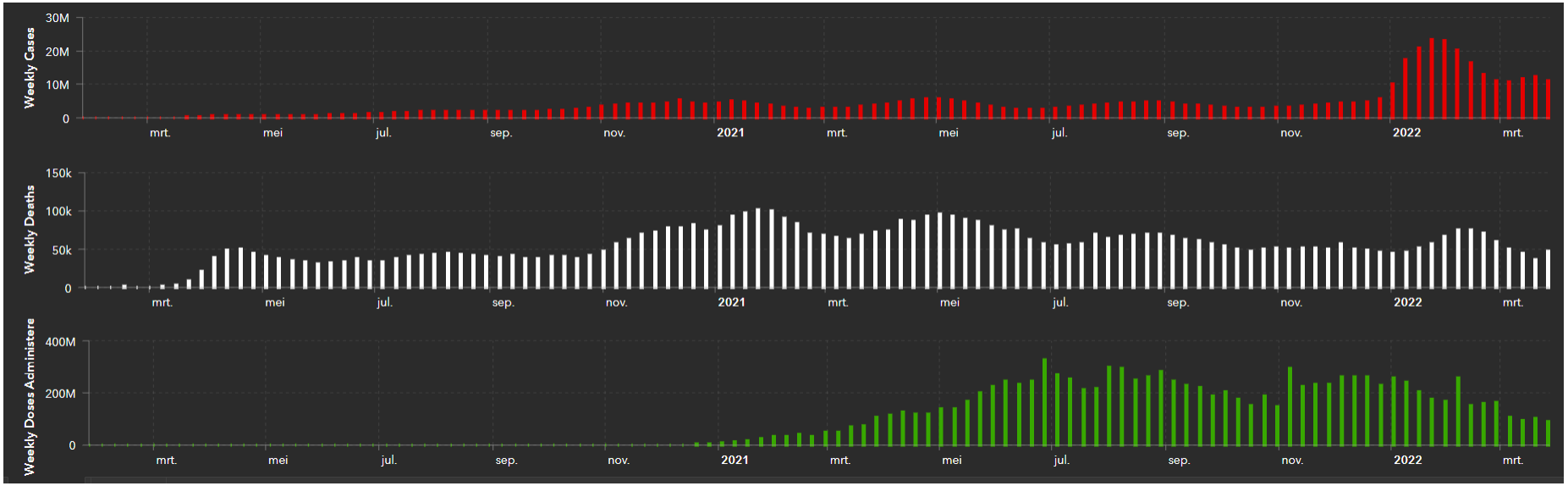
World

Total Cases	Total Deaths	Total Vaccine Doses Administered
490.788.678	6.151.682	10.979.590.336
28-Day Cases	**28-Day Deaths**	**28-Day Vaccine Doses Administered**
45.379.895	159.839	426.809.630



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Historically High Excess Mortality During the COVID-19 Pandemic in Switzerland, Sweden, and Spain

Kaspar Staub, PhD*; Radoslaw Panczak, PhD*; Katarina L. Matthes, PhD; Joël Floris, PhD; Claudia Berlin, PhD; Christoph Junker, MD; Rolf Weitkunat, PhD; Svenn-Erik Mamelund, PhD; Marcel Zwahlen, PhD†; and Julien Riou, PhD†

Background: Excess mortality quantifies the overall mortality impact of a pandemic. Mortality data have been accessible for many countries in recent decades, but few continuous data have been available for longer periods.

Objective: To assess the historical dimension of the COVID-19 pandemic in 2020 for 3 countries with reliable death count data over an uninterrupted span of more than 100 years.

Design: Observational study.

Setting: Switzerland, Sweden, and Spain, which were militarily neutral and not involved in combat during either world war and have not been affected by significant changes in their territory since the end of the 19th century.

Participants: Complete populations of these 3 countries.

Measurements: Continuous series of recorded deaths (from all causes) by month from the earliest available year (1877 for Switzerland, 1851 for Sweden, and 1908 for Spain) were jointly modeled with annual age group–specific death and total population counts using negative binomial and multinomial models, which accounted for temporal trends and seasonal variability of prepandemic years. The aim was to estimate the expected number of deaths in a pandemic year for a nonpandemic scenario and the difference in observed and expected deaths aggregated over the year.

Results: In 2020, the number of excess deaths recorded per 100 000 persons was 100 (95% credible interval [CrI], 60 to 135) for Switzerland, 75 (CrI, 40 to 105) for Sweden, and 155 (CrI, 110 to 195) for Spain. In 1918, excess mortality was 6 to 7 times higher. In all 3 countries, the peaks of monthly excess mortality in 2020 were greater than most monthly excess mortality since 1918, including many peaks due to seasonal influenza and heat waves during that period.

Limitation: Historical vital statistics might be affected by minor completeness issues before the beginning of the 20th century.

Conclusion: In 2020, the COVID-19 pandemic led to the second-largest infection-related mortality disaster in Switzerland, Sweden, and Spain since the beginning of the 20th century.

Primary Funding Source: Foundation for Research in Science and the Humanities at the University of Zurich, Swiss National Science Foundation, and National Institute of Allergy and Infectious Diseases.

Ann Intern Med. doi:10.7326/M21-3824 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 1 February 2022.

* Drs. Staub and Panczak contributed equally to this work and share first authorship.

† Drs. Zwahlen and Riou contributed equally to this work and share senior authorship.

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SARS-CoV-2 is associated with changes in brain structure in UK Biobank

There is strong evidence for brain-related abnormalities in COVID-19[1–13]. It remains unknown however whether the impact of SARS-CoV-2 infection can be detected in milder cases, and whether this can reveal possible mechanisms contributing to brain pathology. Here, we investigated brain changes in 785 UK Biobank participants (aged 51–81) imaged twice, including 401 cases who tested positive for infection with SARS-CoV-2 between their two scans, with 141 days on average separating their diagnosis and second scan, and 384 controls. The availability of pre-infection imaging data reduces the likelihood of pre-existing risk factors being misinterpreted as disease effects. We identified significant longitudinal effects when comparing the two groups, including: (i) greater reduction in grey matter thickness and tissue-contrast in the orbitofrontal cortex and parahippocampal gyrus, (ii) greater changes in markers of tissue damage in regions functionally-connected to the primary olfactory cortex, and (iii) greater reduction in global brain size. The infected participants also showed on average larger cognitive decline between the two timepoints. Importantly, these imaging and cognitive longitudinal effects were still seen after excluding the 15 cases who had been hospitalised. These mainly limbic brain imaging results may be the in vivo hallmarks of a degenerative spread of the disease via olfactory pathways, of neuroinflammatory events, or of the loss of sensory input due to anosmia. Whether this deleterious impact can be partially reversed, or whether these effects will persist in the long term, remains to be investigated with additional follow up.

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Neuropathology and virus in brain of SARS-CoV-2 infected non-human primates

Neurological manifestations are a significant complication of coronavirus disease (COVID-19), but underlying mechanisms aren't well understood. The development of animal models that recapitulate the neuropathological findings of autopsied brain tissue from patients who died from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are critical for elucidating the neuropathogenesis of infection and disease. Here, we show neuroinflammation, microhemorrhages, brain hypoxia, and neuropathology that is consistent with hypoxic-ischemic injury in SARS-CoV-2 infected non-human primates (NHPs), including evidence of neuron degeneration and apoptosis. Importantly, this is seen among infected animals that do not develop severe respiratory disease, which may provide insight into neurological symptoms associated with "long COVID". Sparse virus is detected in brain endothelial cells but does not associate with the severity of central nervous system (CNS) injury. We anticipate our findings will advance our current understanding of the neuropathogenesis of SARS-CoV-2 infection and demonstrate SARS-CoV-2 infected NHPs are a highly relevant animal model for investigating COVID-19 neuropathogenesis among human subjects.

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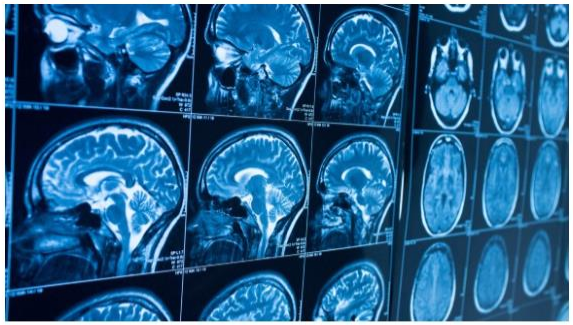
Collection | 29 March 2022

2021 Top 25 Health Sciences Articles

We are pleased to share with you the 25 most downloaded *Nature Communications* articles* in health sciences published in 2021. (Please note we have a separate collection on the Top 25 COVID-19 papers.) Featuring authors from around the world, these papers highlight valuable...
show more



Research highlights

Article
Open Access
20 Apr 2021
Nature Communications

Association of sleep duration in middle and old age with incidence of dementia

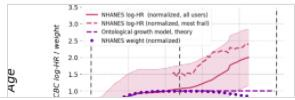
Sleep dysregulation has been linked to dementia, but it is unknown whether sleep duration earlier in life is associated with dementia risk. Here, the authors show higher dementia risk associated with short sleep duration (six hours or less) in a longitudinal study of middle and older age adults.

Séverine Sabia, Aurore Fayosse ... Archana Singh-Manoux

Article
Open Access
25 May 2021

Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts human lifespan limit

Aging is associated with an increased risk of chronic diseases and functional decline. Here, the authors investigate the



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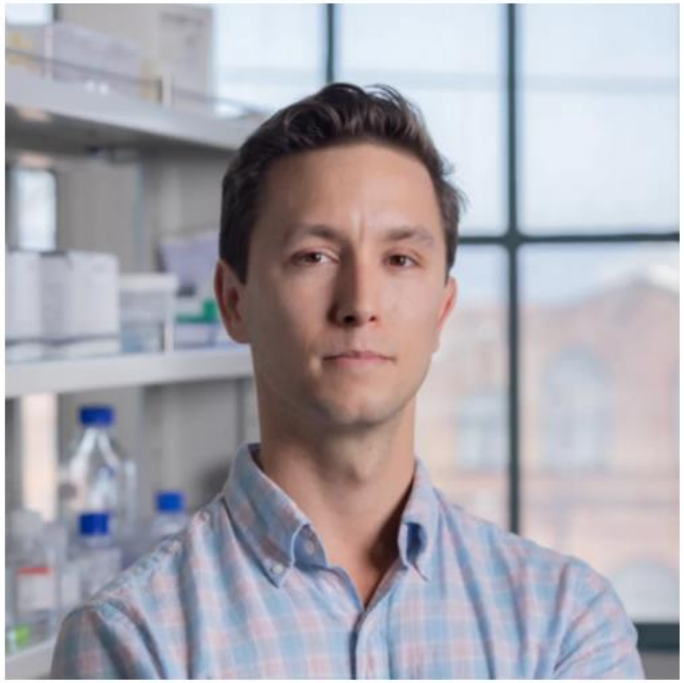
Kizoo Portfolio Company Revel Pharmaceuticals Announces $8.4M Seed to Develop Repairing-Based Approaches to Reversing Aging

03/17/2022



Dr. Aaron Cravens, CEO Revel Pharmaceuticals

San Francisco, CA, U.S., – Revel Pharmaceuticals, a longevity therapeutics company developing enzymes to repair damage from aging, announced today that it has raised $8.4M in Seed financing. The oversubscribed round was led by Kizoo Technology Capital, a leading early-stage investor in breakthrough rejuvenation technologies, and Starbloom Capital with participation from Tubus LLC. The funds will support Revel as it advances its repair-based enzyme therapy pipeline towards the clinic.

Today, enzymes are applied therapeutically in only a handful of applications, including for wrinkle treatment (Botox), cancer (Asparaginase), and cystic fibrosis (DNase). Revel

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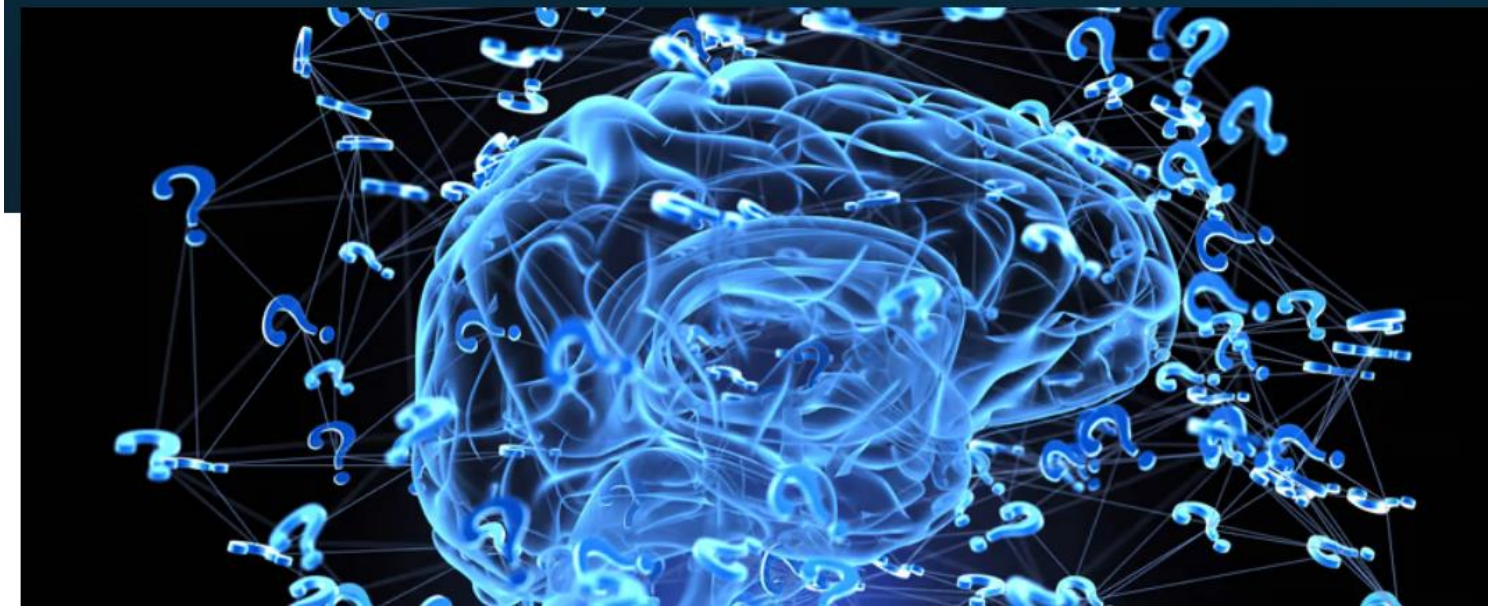
Sage's phase 2 Alzheimer's drug shows signs of cognitive improvement—but there's a catch

By **Annalee Armstrong** • Apr 1, 2022 04:29pm

Sage Therapeutics | Alzheimer's disease | dementia | cognitive function



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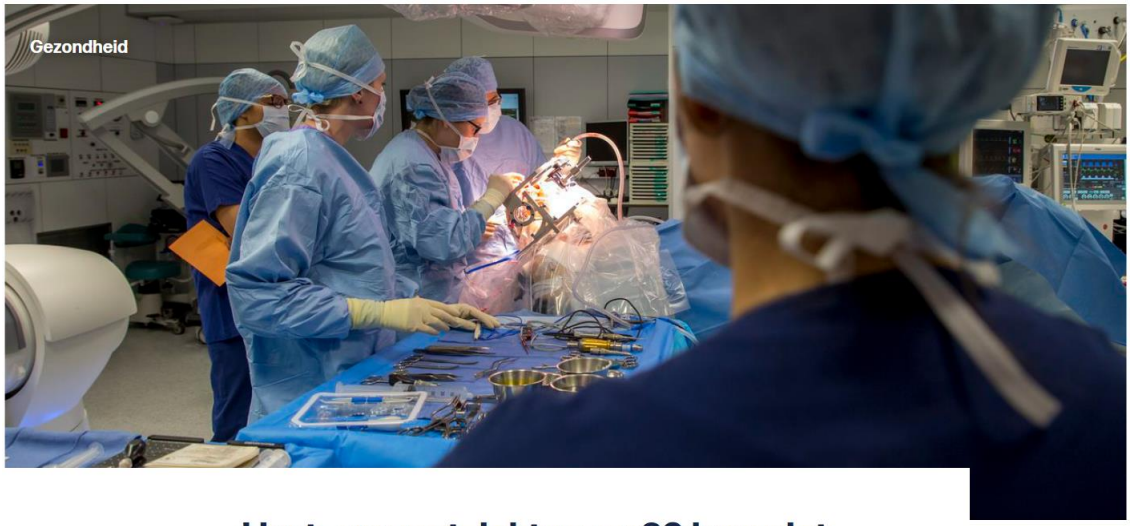
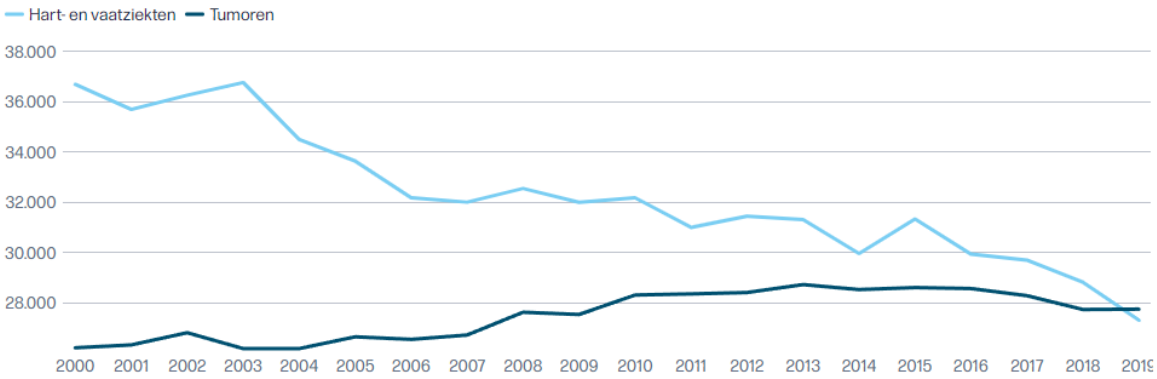


Hart- en vaatziekten na 20 jaar niet meer belangrijkste doodsoorzaak in België, tumoren op eerste plek

Lina El Bakkali, Belga
di 29 mrt 18:13

Totaal aantal overlijdens door tumoren en hart- en vaatziekten in België



Bron: Statbel

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ARDD 2022

THE 9th AGING RESEARCH & DRUG DISCOVERY MEETING

29 AUGUST — 2 SEPTEMBER

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Aging research articles

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In vivo partial reprogramming alters age-associated molecular changes during physiological aging in mice

Kristen C. Browder, Pradeep Reddy, ... Juan Carlos Izpisua Belmonte + Show authors

Nature Aging **2**, 243–253 (2022) | Cite this article

6906 Accesses | **2** Citations | **1093** Altmetric | Metrics

Abstract

Partial reprogramming by expression of reprogramming factors (Oct4, Sox2, Klf4 and c-Myc) for short periods of time restores a youthful epigenetic signature to aging cells and extends the life span of a premature aging mouse model. However, the effects of longer-term partial reprogramming in physiologically aging wild-type mice are unknown. Here, we performed various long-term partial reprogramming regimens, including different onset timings, during physiological aging. Long-term partial reprogramming lead to rejuvenating effects in different tissues, such as the kidney and skin, and at the organismal level; duration of the treatment determined the extent of the beneficial effects. The rejuvenating effects were associated with a reversion of the epigenetic clock and metabolic and transcriptomic changes, including reduced expression of genes involved in the inflammation, senescence and stress response pathways. Overall, our observations indicate that partial reprogramming protocols can be designed to be safe and effective in preventing age-related physiological changes. We further conclude that longer-term partial reprogramming regimens are more effective in delaying aging phenotypes than short-term reprogramming.

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Targeted clearance of p21- but not p16-positive senescent cells prevents radiation-induced osteoporosis and increased marrow adiposity

Abhishek Chandra [1 2], Anthony B Lagnado [1 2], Joshua N Farr [1 2 3], Madison Doolittle [2 3], Tamara Tchkonia [1 2], James L Kirkland [1 2], Nathan K LeBrasseur [2 4], Paul D Robbins [5], Laura J Niedernhofer [5], Yuji Ikeno [6], João F Passos [1 2], David G Monroe [2 3], Robert J Pignolo [1 2 3], Sundeep Khosla [1 2 3]

Affiliations + expand

PMID: 35363946 DOI: 10.1111/acel.13602

Abstract

Cellular senescence, which is a major cause of tissue dysfunction with aging and multiple other conditions, is known to be triggered by $p16^{Ink4a}$ or $p21^{Cip1}$, but the relative contributions of each pathway toward inducing senescence are unclear. Here, we directly addressed this issue by first developing and validating a p21-ATTAC mouse with the $p21^{Cip1}$ promoter driving a "suicide" transgene encoding an inducible caspase-8 which, upon induction, selectively kills $p21^{Cip1}$ -expressing senescent cells. Next, we used the p21-ATTAC mouse and the established p16-INK-ATTAC mouse to directly compare the contributions of $p21^{Cip1}$ versus $p16^{Ink4a}$ in driving cellular senescence in a condition where a tissue phenotype (bone loss and increased marrow adiposity) is clearly driven by cellular senescence-specifically, radiation-induced osteoporosis. Using RNA in situ hybridization, we confirmed the reduction in radiation-induced $p21^{Cip1}$ - or $p16^{Ink4a}$ -driven transcripts following senescent cell clearance in both models. However, only clearance of $p21^{Cip1}$ +, but not $p16^{Ink4a}$ +, senescent cells prevented both radiation-induced osteoporosis and increased marrow adiposity. Reduction in senescent cells with dysfunctional telomeres following clearance of $p21^{Cip1}$ +, but not $p16^{Ink4a}$ +, senescent cells also reduced several of the radiation-induced pro-inflammatory senescence-associated secretory phenotype factors. Thus, by directly comparing senescent cell clearance using two parallel genetic models, we demonstrate that radiation-induced osteoporosis is driven predominantly by $p21^{Cip1}$ - rather than $p16^{Ink4a}$ -mediated cellular senescence. Further, this approach can be used to dissect the contributions of these pathways in other senescence-associated conditions, including aging across tissues.

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Distinct biological ages of organs and systems identified from a multi-omics study

Chao Nie [10] • Yan Li [10] • Rui Li [10] • ... Claudio Franceschi • Brian K. Kennedy •
Xun Xu [11] • Show all authors • Show footnotes

Biological age (BA) has been proposed to evaluate the aging status instead of chronological age (CA). Our study shows evidence that there might be multiple “clocks” within the whole-body system: systemic aging drivers/clocks overlaid with organ/tissue-specific counterparts. We utilize multi-omics data, including clinical tests, immune repertoire, targeted metabolomic molecules, gut microbiomes, physical fitness examinations, and facial skin examinations, to estimate the BA of different organs (e.g., liver, kidney) and systems (immune and metabolic system). The aging rates of organs/systems are diverse. People’s aging patterns are different. We also demonstrate several applications of organs/systems BA in two independent datasets. Mortality predictions are compared among organs' BA in the dataset of the United States National Health and Nutrition Examination Survey. Polygenic risk score of BAs constructed in the Chinese Longitudinal Healthy Longevity Survey cohort can predict the possibility of becoming centenarian.

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Different responses to DNA damage determine ageing differences between organs

Maria Vougioukalaki, Joris Demmers, Wilbert P. Vermeij, Marjolein Baar, Serena Bruens, Aristea Magaraki, Ewart Kuijk, Myrthe Jager, Sarra Merzouk, Renata M.C. Brandt, Janneke Kouwenberg, Ruben van Boxtel, Edwin Cuppen, Joris Pothof, Jan H. J. Hoeijmakers

Organs age differently, causing wide heterogeneity in multimorbidity, but underlying mechanisms are largely elusive. To investigate the basis of organ-specific ageing, we utilized progeroid repair-deficient *Ercc1*$^{\Delta/-}$ mouse mutants and systematically compared at the tissue, stem cell and organoid level two organs representing ageing extremes. *Ercc1*$^{\Delta/-}$ intestine shows hardly any accelerated ageing. Nevertheless, we found apoptosis and reduced numbers of intestinal stem cells (ISCs), but cell loss appears compensated by over-proliferation. ISCs retain their organoid-forming capacity, but organoids perform poorly in culture, compared with WT. Conversely, liver ages dramatically, even causing early death in *Ercc1*-KO mice. Apoptosis, p21, polyploidization and proliferation of various (stem) cells were prominently elevated in *Ercc1*$^{\Delta/-}$ liver and stem cell populations were either largely unaffected (Sox9+), or expanding (Lgr5+), but were functionally exhausted in organoid formation and development *in vitro*. Paradoxically, while intestine displays less ageing, repair in WT ISCs appears inferior to liver as shown by enhanced sensitivity to various DNA-damaging agents, and lower lesion removal. Our findings reveal organ-specific anti-ageing strategies. Intestine, with short lifespan limiting time for damage accumulation and repair, favours apoptosis of damaged cells relying on ISC plasticity. Liver with low renewal rates depends more on repair pathways specifically protecting the transcribed compartment of the genome to promote sustained functionality and cell preservation. As shown before, the hematopoietic system with intermediate self-renewal mainly invokes replication-linked mechanisms, apoptosis and senescence. Hence, organs employ different genome maintenance strategies, explaining heterogeneity in organ ageing and the segmental nature of DNA-repair-deficient progerias.

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Transposable element landscapes in aging *Drosophila*

Nachen Yang, Satyam P. Srivastav co, Reazur Rahman co, Qicheng Ma co, Gargi Dayama, Sizheng Li, Madoka Chinen, Elissa P. Lei, Michael Rosbash, Nelson C. Lau ✉

Genetic mechanisms that repress transposable elements (TEs) in young animals decline during aging, as reflected by increased TE expression in aged animals. Does increased TE expression during aging lead to more genomic TE copies in older animals? To address this question, we quantified TE Landscapes (TLs) via whole genome sequencing of young and aged *Drosophila* strains of wild-type and mutant backgrounds. We quantified TLs in whole flies and dissected brains and validated the feasibility of our approach in detecting new TE insertions in aging *Drosophila* genomes when small RNA and RNA interference (RNAi) pathways are compromised. We also describe improved sequencing methods to quantify extra-chromosomal DNA circles (eccDNAs) in *Drosophila* as an additional source of TE copies that accumulate during aging. Lastly, to combat the natural progression of aging-associated TE expression, we show that knocking down *PAF1*, a conserved transcription elongation factor that antagonizes RNAi pathways, may bolster suppression of TEs during aging and extend lifespan. Our study suggests that in addition to a possible influence by different genetic backgrounds, small RNA and RNAi mechanisms may mitigate genomic TL expansion despite the increase in TE transcripts during aging.

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Biological mechanisms of aging predict age-related disease co-occurrence in patients

Helen C. Fraser, Valerie Kuan, Ronja Johnen, Magdalena Zwierzyna, Aroon D. Hingorani, Andreas Beyer ✉, Linda Partridge ✉

Genetic, environmental, and pharmacological interventions into the aging process can confer resistance to multiple age-related diseases in laboratory animals, including rhesus monkeys. These findings imply that individual mechanisms of aging might contribute to the co-occurrence of age-related diseases in humans and could be targeted to prevent these conditions simultaneously. To address this question, we text mined 917,645 literature abstracts followed by manual curation and found strong, non-random associations between age-related diseases and aging mechanisms in humans, confirmed by gene set enrichment analysis of GWAS data. Integration of these associations with clinical data from 3.01 million patients showed that age-related diseases associated with each of five aging mechanisms were more likely than chance to be present together in patients. Genetic evidence revealed that innate and adaptive immunity, the intrinsic apoptotic signaling pathway and activity of the ERK1/2 pathway were associated with multiple aging mechanisms and diverse age-related diseases. Mechanisms of aging hence contribute both together and individually to age-related disease co-occurrence in humans and could potentially be targeted accordingly to prevent multimorbidity.

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Hallmarks of aging-based dual-purpose disease and age-associated targets predicted using PandaOmics AI-powered discovery engine

Frank W. Pun[1,*], Geoffrey Ho Duen Leung[1,*], Hoi Wing Leung[1,*], Bonnie Hei Man Liu[1], Xi Long[1], Ivan V. Ozerov[1], Ju Wang[1], Feng Ren[1], Alexander Aliper[1], Evgeny Izumchenko[2], Alexey Moskalev[3], João Pedro de Magalhães[4], Alex Zhavoronkov[1,5]

Aging biology is a promising and burgeoning research area that can yield dual-purpose pathways and protein targets that may impact multiple diseases, while retarding or possibly even reversing age-associated processes. One widely used approach to classify a multiplicity of mechanisms driving the aging process is the hallmarks of aging. In addition to the classic nine hallmarks of aging, processes such as extracellular matrix stiffness, chronic inflammation and activation of retrotransposons are also often considered, given their strong association with aging. In this study, we used a variety of target identification and prioritization techniques offered by the AI-powered PandaOmics platform, to propose a list of promising novel aging-associated targets that may be used for drug discovery. We also propose a list of more classical targets that may be used for drug repurposing within each hallmark of aging. Most of the top targets generated by this comprehensive analysis play a role in inflammation and extracellular matrix stiffness, highlighting the relevance of these processes as therapeutic targets in aging and age-related diseases. Overall, our study reveals both high confidence and novel targets associated with multiple hallmarks of aging and demonstrates application of the PandaOmics platform to target discovery across multiple disease areas.

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PREPRINT

Deep Phenotyping and Lifetime Trajectories Reveal Limited Effects of Longevity Regulators on the Aging Process in C57BL/6J Mice

Current concepts regarding the biology of aging are based on studies aimed at identifying factors regulating natural lifespan. However, lifespan as a sole proxy measure for aging can be of limited value because it may be restricted by specific sets of pathologies, rather than by general physiological decline. Here, we employed large-scale phenotyping to analyze hundreds of phenotypes and thousands of molecular markers across tissues and organ systems in a single study of aging male C57BL/6J mice. For each phenotype, we established lifetime profiles to determine when age-dependent phenotypic change is first detectable relative to the young adult baseline. We examined central genetic and environmental lifespan regulators (putative anti-aging interventions, PAAIs; the following PAAIs were examined: mTOR loss-of-function, loss-of-function in growth hormone signaling, dietary restriction) for a possible countering of the signs and symptoms of aging. Importantly, in our study design, we included young treated groups of animals, subjected to PAAIs prior to the onset of detectable age-dependent phenotypic change. In parallel to our studies in mice, we assessed genetic variants for their effects on age-sensitive phenotypes in humans. We observed that, surprisingly, many PAAI effects influenced phenotypes long before the onset of detectable age-dependent changes, rather than altering the rate at which these phenotypes developed with age. Accordingly, this subset of PAAI effects does not reflect a targeting of age-dependent phenotypic change. Overall, our findings suggest that comprehensive phenotyping, including the controls built in our study, is critical for the investigation of PAAIs as it facilitates the proper interpretation of the mechanistic mode by which PAAIs influence biological aging.

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PREPRINT

Deterioration of the human transcriptome with age due to increasing intron retention and spurious splicing

Marco Mariotti, Csaba Kerepesi, Winona Oliveros, Marta Mele, Vadim N. Gladyshev

doi: https://doi.org/10.1101/2022.03.14.484341

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

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Abstract Full Text Info/History Metrics Preview PDF

Abstract

Adult aging is characterized by a progressive deterioration of biological functions at physiological, cellular and molecular levels, but its damaging effects on the transcriptome are not well characterized. Here, by analyzing splicing patterns in ~1,000 human subjects sampled across multiple tissues, we found that splicing fidelity declines with age. Most prominently, genuine introns fail to be spliced out, manifesting as a broad surge in intron retention, and this is exacerbated by the increase in diverse spurious exon-exon junctions with age. Both of these effects are prominently detected in the majority of human tissues. Collectively, they result in the progressive deterioration of the active transcriptome, wherein functional mRNAs are increasingly diluted with non-functional splicing isoforms. We discuss the concept of "splicing damage" and formulate methods to quantify it. Using these tools, we show that splicing damage increases both with age and with the incidence of diseases. Altogether, this work uncovers transcriptome damage as a critical molecular indicator of human aging and healthspan.

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Association between lithium use and the incidence of dementia and its subtypes: A retrospective cohort study

Shanquan Chen, Benjamin R. Underwood, Peter B. Jones, Jonathan R. Lewis, Rudolf N. Cardinal

Methods and findings

We conducted a retrospective cohort study comparing patients treated between January 1, 2005 and December 31, 2019, using data from electronic clinical records of secondary care mental health (MH) services in Cambridgeshire and Peterborough NHS Foundation Trust (CPFT), United Kingdom (catchment area population approximately 0.86 million). Eligible patients were those aged 50 years or over at baseline and who had at least 1 year follow-up, excluding patients with a diagnosis of mild cognitive impairment (MCI) or dementia before, or less than 1 year after, their start date. The intervention was the use of lithium. The main outcomes were dementia and its subtypes, diagnosed and classified according to the International Classification of Diseases-10th Revision (ICD-10).

In this cohort, 29,618 patients (of whom 548 were exposed to lithium) were included. Their mean age was 73.9 years. A total of 40.2% were male, 33.3% were married or in a civil partnership, and 71.0% were of white ethnicity. Lithium-exposed patients were more likely to be married, cohabiting or in a civil partnership, to be a current/former smoker, to have used antipsychotics, and to have comorbid depression, mania/bipolar affective disorder (BPAD), hypertension, central vascular disease, diabetes mellitus, or hyperlipidemias. No significant difference between the 2 groups was observed for other characteristics, including age, sex, and alcohol-related disorders. In the exposed cohort, 53 (9.7%) patients were diagnosed with dementia, including 36 (6.8%) with Alzheimer disease (AD) and 13 (2.6%) with vascular dementia (VD). In the unexposed cohort, corresponding numbers were the following: dementia 3,244 (11.2%), AD 2,276 (8.1%), and VD 698 (2.6%). After controlling for sociodemographic factors, smoking status, other medications, other mental comorbidities, and physical comorbidities, lithium use was associated with a lower risk of dementia (hazard ratio [HR] 0.56, 95% confidence interval [CI] 0.40 to 0.78), including AD (HR 0.55, 95% CI 0.37 to 0.82) and VD (HR 0.36, 95% CI 0.19 to 0.69). Lithium appeared protective in short-term (≤1-year exposure) and long-term lithium users (>5-year exposure); a lack of difference for intermediate durations was likely due to lack of power, but there was some evidence for additional benefit with longer exposure durations. The main limitation was the handling of BPAD, the most common reason for lithium prescription but also a risk factor for dementia. This potential confounder would most likely cause an increase in dementia in the exposed group, whereas we found the opposite, and the sensitivity analysis confirmed the primary results. However, the specific nature of the group of patients exposed to lithium means that caution is needed in extending these findings to the general population. Another limitation is that our sample size of patients using lithium was small, reflected in the wide CIs for results relating to some durations of lithium exposure, although again sensitivity analyses remained consistent with our primary findings.

Conclusions

We observed an association between lithium use and a decreased risk of developing dementia. This lends further support to the idea that lithium may be a disease-modifying treatment for dementia and that this is a promising treatment to take forwards to larger randomised controlled trials (RCTs) for this indication.

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Potential senotherapeutic candidates and their combinations derived from transcriptional connectivity and network measures

Cellular senescence, a state of permanent cell cycle arrest, is associated with organismal aging and malfunctioning. Various attempts have been made to find a unified gene signature for all senescence models in every cell type. However, with more studies being conducted, none look to be universally shared; instead, it seems that the senescence gene signature is cell-type specific. In the present study, 74 genes commonly expressed in different models of fibroblast senescence, derived from two independent studies were extracted. The shared signature of fibroblast senescence, which was functionally associated with aging, was further regarded as a target module to attenuate the fibroblast senescence phenotype. Utilizing Connectivity Map to discover the inversely connected compounds with this gene signature and analyzing network proximity of the targets of the inversely connected compounds with fibroblast senescence genes, we suggest glutamine, tangeretin, artemisinin, and castanospermine as potential senescence therapeutics. Moreover, to overcome this impaired gene expression system, we suggest the combination of glutamine with one of tangeretin, artemisinin, or castanospermine, that obey the complementary exposure pattern to reach better therapeutic efficacy while manifesting minimal adverse effects.

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PREPRINT

Impaired iron recycling from erythrocytes is an early iron-dependent hallmark of aging

Aging affects iron homeostasis and erythropoiesis, as evidenced by tissue iron loading in rodents and common anemia in the elderly. Since red pulp macrophages (RPMs) continuously process iron, their cellular functions might be susceptible to age-dependent decline, affecting organismal iron metabolism and red blood cell (RBCs) parameters. However, little is known about the effects of aging on the functioning of RPMs. To study aging RPMs, we employed 10-11-months-old female mice that show serum iron deficiency and iron overload primarily in spleens compared to young controls. We observed that this is associated with iron loading, oxidative stress, diminished lysosomal activity, and decreased erythrophagocytosis rate in RPMs. We uncovered that these impairments of RPMs lead to the retention of senescent RBCs in the spleen, their excessive local hemolysis, and the formation of iron- and heme-rich large extracellular protein aggregates, likely derived from damaged ferroptotic RPMs. We further found that feeding mice an iron-reduced diet alleviates iron accumulation and reactive oxygen species build-up in RPMs, improves their ability to clear and degrade erythrocytes, and limits ferroptosis. Consequently, this diet improves splenic RBCs fitness, limits hemolysis and the formation of iron-rich protein aggregates, and increases serum iron availability in aging mice. Using RPM-like cells, we show that diminished erythrophagocytic and lysosomal activities of RPMs can be attributed to a combination of increased iron levels and reduced expression of heme-catabolizing enzyme heme oxygenase 1 (HO-1). Taken together, we identified RPM dysfunction as an early hallmark of physiological aging and demonstrated that dietary iron reduction improves iron turnover efficacy.

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The Evolution of Brain Size in Ectothermic Tetrapods: Large Brain Mass Trades-Off with Lifespan in Reptiles

Gavin Stark & Daniel Pincheira-Donoso

The evolution of brain size is constrained by the trade-off between the energetic costs allocated towards its maintenance and the cognitive advantages that come with a larger brain, leading to a paradox. The cognitive benefits of larger brains (e.g., high behavioural flexibility) mitigate extrinsic mortality factors, which may indirectly select for slower ageing that prolongs lifespan ("cognitive buffer hypothesis"). However, substantial energetic costs imposed by the maintenance of neural tissue is expected to compromise the energetic budget of large-brained organisms, and their investment in somatic maintenance and repair, thus accelerating ageing that shortens lifespan (the "disposable soma theory"). The relationship between lifespan and brain size has mostly been investigated in birds and mammals. Thus, whether these trade-offs express across ectothermic vertebrates remains to be addressed on a large-scale. Our study presents the first large-scale analysis of the brain size-lifespan relationship in ectothermic tetrapods (amphibians and reptiles). Using a dataset spanning 265 species, we performed phylogenetic linear models to investigate the predicted trade-off between variation in brain size and longevity. Our findings revealed a negative relationship between brain size and lifespan across reptiles, whereas no association was observed across amphibians. Thus, the relationship between life history and brain evolution in ectotherms does not follow the general pattern found across other vertebrates. Among ectotherms, the high metabolic cost of producing neural tissue seems to transcend the cognitive benefits of evolving a larger brain. Consequently, our findings suggest that natural selection favours optimization of the energetic economy over the fitness-advantages that cognitive benefits may offer.

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Body temperature is a more important modulator of lifespan than metabolic rate in two small mammals

Zhijun Zhao ✉, Jing Cao, Chaoqun Niu, Menghuan Bao, Jiaqi Xu, Daliang Huo, Shasha Liao, Wei Liu & John R. Speakman ✉

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Abstract

The relationships between metabolic rate, body temperature (T_b), body composition and ageing are complex, and not fully resolved. In particular, T_b and metabolic rate often change in parallel, making disentangling their effects difficult. Here we show that in both sexes of mice and hamsters exposure to a temperature of 32.5 °C leads to a reduced lifespan, coincident with lowered metabolic rate and elevated T_b with no change in body composition. We exploit the unique situation that when small mammals are exposed to hot ambient temperatures their T_b goes up, at the same time that their metabolic rate goes down, allowing us to experimentally separate the impacts of T_b and metabolic rate on lifespan. The impact of ambient temperature on lifespan can be reversed by exposing the animals to elevated heat loss by forced convection, which reverses the effect on T_b but does not affect metabolic rate, demonstrating the causal effect of T_b on lifespan under laboratory conditions for these models. The impact of manipulations such as calorie restriction that increase lifespan may be mediated via effects on T_b, and measuring T_b may be a useful screening tool for putative therapeutics to extend the human lifespan.

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Hibernation slows epigenetic ageing in yellow-bellied marmots

Gabriela M. Pinho, Julien G. A. Martin, Colin Farrell, Amin Haghani, Joseph A. Zoller, Joshua Zhang, Sagi Snir, Matteo Pellegrini, Robert K. Wayne, Daniel T. Blumstein & Steve Horvath

Species that hibernate generally live longer than would be expected based solely on their body size. Hibernation is characterized by long periods of metabolic suppression (torpor) interspersed by short periods of increased metabolism (arousal). The torpor–arousal cycles occur multiple times during hibernation, and it has been suggested that processes controlling the transition between torpor and arousal states cause ageing suppression. Metabolic rate is also a known correlate of longevity; we thus proposed the 'hibernation–ageing hypothesis' whereby ageing is suspended during hibernation. We tested this hypothesis in a well-studied population of yellow-bellied marmots (*Marmota flaviventer*), which spend 7–8 months per year hibernating. We used two approaches to estimate epigenetic age: the epigenetic clock and the epigenetic pacemaker. Variation in epigenetic age of 149 samples collected throughout the life of 73 females was modelled using generalized additive mixed models (GAMM), where season (cyclic cubic spline) and chronological age (cubic spline) were fixed effects. As expected, the GAMM using epigenetic ages calculated from the epigenetic pacemaker was better able to detect nonlinear patterns in epigenetic ageing over time. We observed a logarithmic curve of epigenetic age with time, where the epigenetic age increased at a higher rate until females reached sexual maturity (two years old). With respect to circannual patterns, the epigenetic age increased during the active season and essentially stalled during the hibernation period. Taken together, our results are consistent with the hibernation–ageing hypothesis and may explain the enhanced longevity in hibernators.

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Comparing Effects of Polypharmacy on Inflammatory Profiles in Older Adults and Mice: Implications for Translational Ageing Research

Background: Ageing and multimorbidity are associated with inflammation. Polypharmacy is common in older people with multimorbidity. Given the potential for interactions between polypharmacy and inflammation, the relationship between inflammation and polypharmacy were studied in older adults with multimorbidity and in healthy ageing mice.

Methods: A cross-sectional analysis of data from the five-year wave of the Concord Health and Ageing in Men Project, a population-based study of community-dwelling men aged ≥ 70 years. Serum concentrations of 27 cytokines were measured using a multiplex immunoassay. Associations between polypharmacy (≥5 medications) and cytokines were evaluated using multivariable linear regression adjusting for age, frailty, comorbidities and individual drug classes. Interaction between polypharmacy and Drug Burden Index (DBI - drugs with anticholinergic and sedative effects) was analysed. Effects of polypharmacy and DBI on serum levels of 23 cytokines were determined in ageing male mice treated with chronic polypharmacy or control.

Results: Compared to the non-polypharmacy group (n=495), CHAMP participants with polypharmacy (n=409) had significantly higher concentrations of IL-8, IL-6, CCL3, Eotaxin, IL-1ra, IL-1β, IP-10 and lower concentrations of anti-inflammatory cytokine IL-4. In fully-adjusted multivariable models, polypharmacy was positively associated with concentrations of IL-8 and CCL3. There were no significant differences in inflammatory profiles between control and polypharmacy-treated mice. The relationship was not influenced by DBI in men or in mice.

Conclusions: Inflammatory markers associated with polypharmacy in older adults were not seen in healthy aged mice administered polypharmacy, and may be related to underlying diseases. The polypharmacy mouse model provides opportunities for mechanistic investigations in translational research.

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Applying the AFRAID and FRIGHT clocks to novel preclinical mouse models of polypharmacy

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Affiliations + expand

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Abstract

The Frailty Inferred Geriatric Health Timeline (FRIGHT) and Analysis of Frailty and Death (AFRAID) clocks were developed to predict biological age and lifespan respectively, in mice. Their utility within the context of polypharmacy (≥5 medications), which is very common in older adults, is unknown. In male C57BL/6J(B6) mice administered chronic polypharmacy, monotherapy and undergoing treatment cessation (deprescribing), we aimed to compare these clocks between treatment groups; investigate whether treatment affected correlation of these clocks with mortality; and explore factors that may explain variation in predictive performance. Treatment (control, polypharmacy, or monotherapy) commenced from age 12 months. At age 21 months, each treatment group was subdivided to continue treatment or have it deprescribed. Frailty Index was assessed and informed calculation of the clocks. AFRAID, FRIGHT, frailty index and mortality age did not differ between continued treatment groups and control. Compared to continued treatment, deprescribing some treatments had inconsistent negative impacts on some clocks and mortality. FRIGHT and frailty index, but not AFRAID, were associated with mortality. The bias and precision of AFRAID as a predictor of mortality varied between treatment groups. Effects of deprescribing some drugs on elements of the clocks, particularly on weight loss, contributed to bias. Overall, in this cohort, FRIGHT and AFRAID measures identified no treatment effects and limited deprescribing effects (unsurprising as very few effects on frailty or mortality), with variable prediction of mortality. These clocks have utility, but context is important. Future work should refine them for intervention studies to reduce bias from specific intervention effects.

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In vivo transcriptomic profiling using cell encapsulation identifies effector pathways of systemic aging

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.

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GlyNAC (Glycine and N-Acetylcysteine) Supplementation in Mice Increases Length of Life by Correcting Glutathione Deficiency, Oxidative Stress, Mitochondrial Dysfunction, Abnormalities in Mitophagy and Nutrient Sensing, and Genomic Damage

by Premranjan Kumar, Ob W. Osahon and Rajagopal V. Sekhar *

Determinants of length of life are not well understood, and therefore increasing lifespan is a challenge. Cardinal theories of aging suggest that oxidative stress (OxS) and mitochondrial dysfunction contribute to the aging process, but it is unclear if they could also impact lifespan. Glutathione (GSH), the most abundant intracellular antioxidant, protects cells from OxS and is necessary for maintaining mitochondrial health, but GSH levels decline with aging. Based on published human studies where we found that supplementing glycine and N-acetylcysteine (GlyNAC) improved/corrected GSH deficiency, OxS and mitochondrial dysfunction, we hypothesized that GlyNAC supplementation could increase longevity. We tested our hypothesis by evaluating the effect of supplementing GlyNAC vs. placebo in C57BL/6J mice on (a) length of life; and (b) age-associated GSH deficiency, OxS, mitochondrial dysfunction, abnormal mitophagy and nutrient-sensing, and genomic-damage in the heart, liver and kidneys. Results showed that mice receiving GlyNAC supplementation (1) lived 24% longer than control mice; (2) improved/corrected impaired GSH synthesis, GSH deficiency, OxS, mitochondrial dysfunction, abnormal mitophagy and nutrient-sensing, and genomic-damage. These studies provide proof-of-concept that GlyNAC supplementation can increase lifespan and improve multiple age-associated defects. GlyNAC could be a novel and simple nutritional supplement to improve lifespan and healthspan, and warrants additional investigation. View Full-Text

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C. elegans aging research

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Ageing induces tissue-specific transcriptomic changes in *Caenorhabditis elegans*

Ageing is a complex process with common and distinct features across tissues. Unveiling the underlying processes driving ageing in individual tissues is indispensable to decipher the mechanisms of organismal longevity. *Caenorhabditis elegans* is a well-established model organism that has spearheaded ageing research with the discovery of numerous genetic pathways controlling its lifespan. However, it remains challenging to dissect the ageing of worm tissues due to the limited description of tissue pathology and access to tissue-specific molecular changes during ageing. In this study, we isolated cells from five major tissues in young and old worms and profiled the age-induced transcriptomic changes within these tissues. We observed a striking diversity of ageing across tissues and identified different sets of longevity regulators therein. In addition, we found novel tissue-specific factors, including *irx-1* and *myrf-2*, which control the integrity of the intestinal barrier and sarcomere structure during ageing respectively. This study demonstrates the complexity of ageing across worm tissues and highlights the power of tissue-specific transcriptomic profiling during ageing, which can serve as a resource to the field.

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The Rab GTPase activating protein TBC-2 regulates endosomal localization of DAF-16 FOXO and lifespan

İçten Meraş, Laëtitia Chotard, Thomas Liontis, Zakaria Ratemi, Benjamin Wiles, Jung Hwa Seo, Jeremy M. Van Raamsdonk, Christian E. Rocheleau

FOXO transcription factors have been shown to regulate longevity in model organisms and are associated with longevity in humans. To gain insight into how FOXO functions to increase lifespan, we examined the subcellular localization of DAF-16 in *C. elegans*. We show that DAF-16 is localized to endosomes and that this endosomal localization is increased by the insulin-IGF signaling (IIS) pathway. Endosomal localization of DAF-16 is modulated by endosomal trafficking proteins. Disruption of the Rab GTPase activating protein TBC-2 increases endosomal localization of DAF-16, while inhibition of TBC-2 targets, RAB-5 or RAB-7 GTPases, decreases endosomal localization of DAF-16. Importantly, the amount of DAF-16 that is localized to endosomes has functional consequences as increasing endosomal localization through mutations in *tbc-2* reduced the lifespan of long-lived *daf-2 IGFR* mutants, depleted their fat stores, and DAF-16 target gene expression. Overall, this work identifies endosomal localization as a mechanism regulating DAF-16 FOXO, which is important for its functions in metabolism and aging.

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REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Optimizing translational research for exceptional health and life span: A systematic narrative of studies to identify translatable therapeutic target(s) for exceptional health span in humans

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Abstract

Exceptional longevity as illustrated by the lower incidence and delayed onset of age-related disabilities/diseases that include cardiovascular disease, Alzheimer's disease (AD), cancer is believed to be influenced by inherent protective molecular factors in exceptionally long-lived individuals. Unraveling these protective factors could lead to the discovery of therapeutic target(s) and interventions to promote healthy aging. In this context, NIA has established a collection of translational longevity research projects (i.e., the Long Life Family Study, the Longevity Consortium, Longevity Genomics and the Integrative Longevity Omics) which are generating large omics data sets spanning the human genome to phenome and have embarked on cross-species multi-omic data analyses integrating human and non-human species that display wide variation in their lifespans. It is expected that these studies will discover key signaling pathways that influence exceptional health span and identify therapeutic targets for translation to enhance health and life span. Other efforts related to translational longevity research include the 'Comprehensive Evaluation of Aging-Related Clinical Outcomes and Geroproteins study', which focuses on potential effects in humans of polypeptides/proteins whose circulating levels change with age, and for which experimental evidence indicates reversal or acceleration of aging changes. The 'Predictive Human Mechanistic Markers Network' is devoted to the development of predictive markers of aging, for target engagement when testing novel interventions for healthy aging. We describe here, the significance, the unique study design, categories of data sets analytical strategies and a data portal to facilitate open science and sharing of resources from these longevity studies to identify and validate potential therapeutic targets for healthy aging.

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The p53 network: cellular and systemic DNA damage responses in cancer and aging

Pavana Lakshmi Vaddavalli [1, 2], Björn Schumacher [1, 2]

The tumor protein *TP53* gene, encoding the cellular tumor antigen p53, is the single most frequently mutated gene in human cancers. p53 plays a central role in responding to DNA damage and determines the outcome of the DNA damage checkpoint response by regulating cell cycle arrest and apoptosis. As a consequence of this function, dysfunctional p53 results in cells that, despite a damaged genome, continue to proliferate thus fueling malignant transformation. New insights have recently been gained into the complexity of the p53 regulation of the DNA damage response (DDR) and how it impacts a wide variety of cellular processes. In addition to cell-autonomous signaling mechanisms, non-cell-autonomous regulatory inputs influence p53 activity, which in turn can have systemic consequences on the organism. New inroads have also been made toward therapeutic targeting of p53 that for a long time has been anticipated.

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The central moTOR of metabolism

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Affiliations + expand

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Abstract

The protein kinase mechanistic target of rapamycin (mTOR) functions as a central regulator of metabolism, integrating diverse nutritional and hormonal cues to control anabolic processes, organismal physiology, and even aging. This review discusses the current state of knowledge regarding the regulation of mTOR signaling and the metabolic regulation of the four macromolecular building blocks of the cell: carbohydrate, nucleic acid, lipid, and protein by mTOR. We review the role of mTOR in the control of organismal physiology and aging through its action in key tissues and discuss the potential for clinical translation of mTOR inhibition for the treatment and prevention of diseases of aging.

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The importance of mitochondrial quality control for maintaining skeletal muscle function across health span

James Sligar, Danielle A. DeBruin, Nicholas J. Saner, Ashleigh M. Philp, and Andrew Philp

As the principal energy-producing organelles of the cell, mitochondria support numerous biological processes related to metabolism, growth, and regeneration in skeletal muscle. Deterioration in skeletal muscle functional capacity with age is thought to be driven in part by a reduction in skeletal muscle oxidative capacity and reduced fatigue resistance. Underlying this maladaptive response is the development of mitochondrial dysfunction caused by alterations in mitochondrial quality control (MQC), a term encompassing processes of mitochondrial synthesis (biogenesis), remodeling (dynamics), and degradation (mitophagy). Knowledge regarding the role and regulation of MQC in skeletal muscle and the influence of aging in this process has rapidly advanced in the past decade. Given the emerging link between aging and MQC, therapeutic approaches to manipulate MQC to prevent mitochondrial dysfunction during aging hold tremendous therapeutic potential.

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Evolutionarily conserved transcription factors as regulators of longevity and targets for geroprotection

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Aging is the single largest risk factor for many debilitating conditions, including heart diseases, stroke, cancer, diabetes, and neurodegenerative disorders. While far from understood in its full complexity, it is scientifically well-established that aging is influenced by genetic and environmental factors, and can be modulated by various interventions. One of aging's early hallmarks are aberrations in transcriptional networks, controlling for example metabolic homeostasis or the response to stress. Evidence in different model organisms abounds that a number of evolutionarily conserved transcription factors, which control such networks, can affect lifespan and healthspan across species. These transcription factors thus potentially represent conserved regulators of longevity and are emerging as important targets in the challenging quest to develop treatments to mitigate age-related diseases, and possibly even to slow aging itself. This review provides an overview of evolutionarily conserved transcription factors that impact longevity or age-related diseases in at least one multicellular model organism (nematodes, flies, or mice), and/or are tentatively linked to human aging. Discussed is the general evidence for transcriptional regulation of aging and disease, followed by a more detailed look at selected transcription factor families, the common metabolic pathways involved, and the targeting of transcription factors as a strategy for geroprotective interventions.

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OTHER RESEARCH & REVIEWS

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The complete sequence of a human genome

SERGEY NURK, SERGEY KOREN, ARANG RHIE, MIKKO RAUTIAINEN, ANDREY V. BZIKADZE, ALLA MIKHEENKO, MITCHELL R. VOLLGER, NICOLAS ALTEMOSE, LEV URALSKY, [...] ADAM M. PHILLIPPY +91 authors Authors Info & Affiliations

Since its initial release in 2000, the human reference genome has covered only the euchromatic fraction of the genome, leaving important heterochromatic regions unfinished. Addressing the remaining 8% of the genome, the Telomere-to-Telomere (T2T) Consortium presents a complete 3.055 billion–base pair sequence of a human genome, T2T-CHM13, that includes gapless assemblies for all chromosomes except Y, corrects errors in the prior references, and introduces nearly 200 million base pairs of sequence containing 1956 gene predictions, 99 of which are predicted to be protein coding. The completed regions include all centromeric satellite arrays, recent segmental duplications, and the short arms of all five acrocentric chromosomes, unlocking these complex regions of the genome to variational and functional studies.

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