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Scientific News
7th of November 2021
Sven Bulterijs

Business/Conferences/ General news

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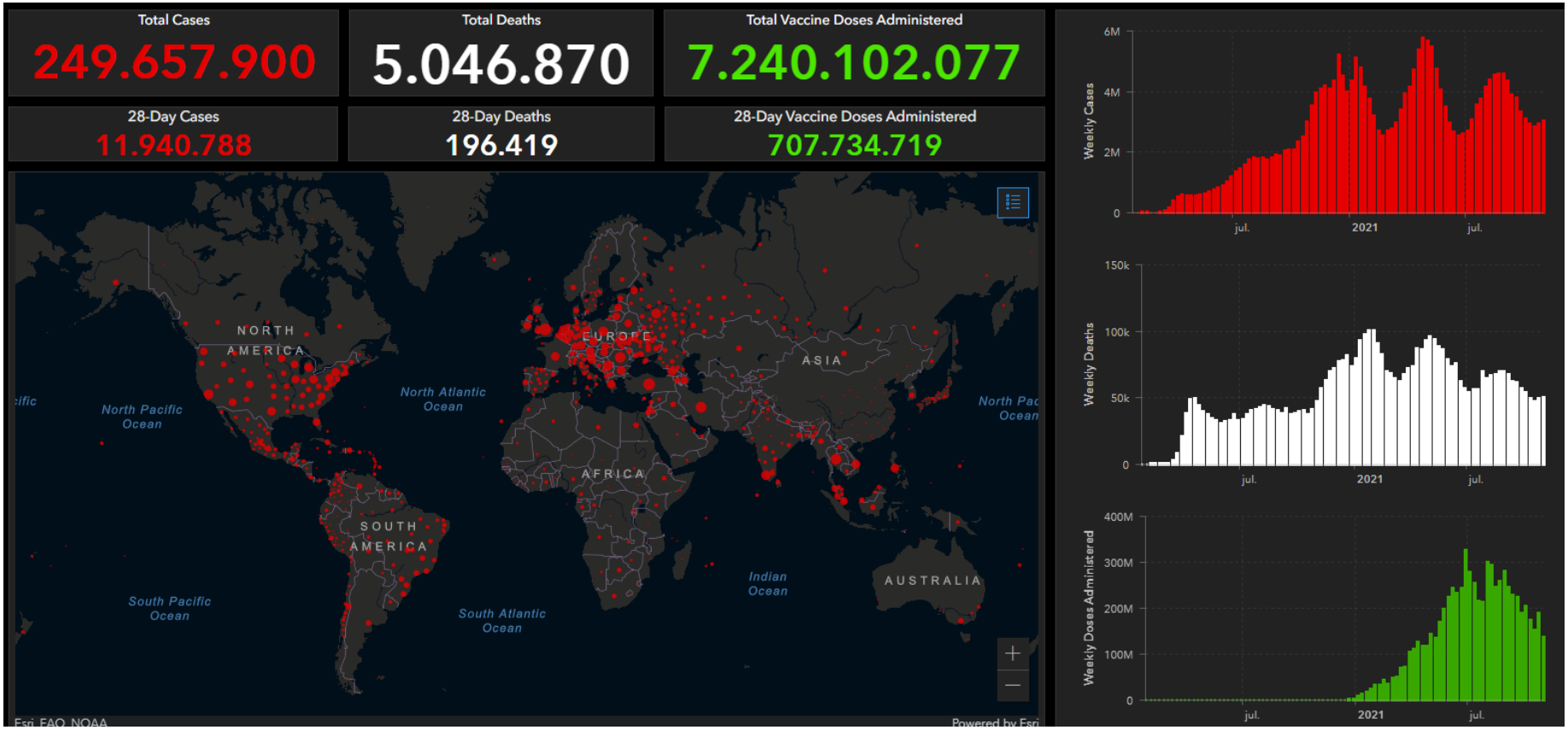
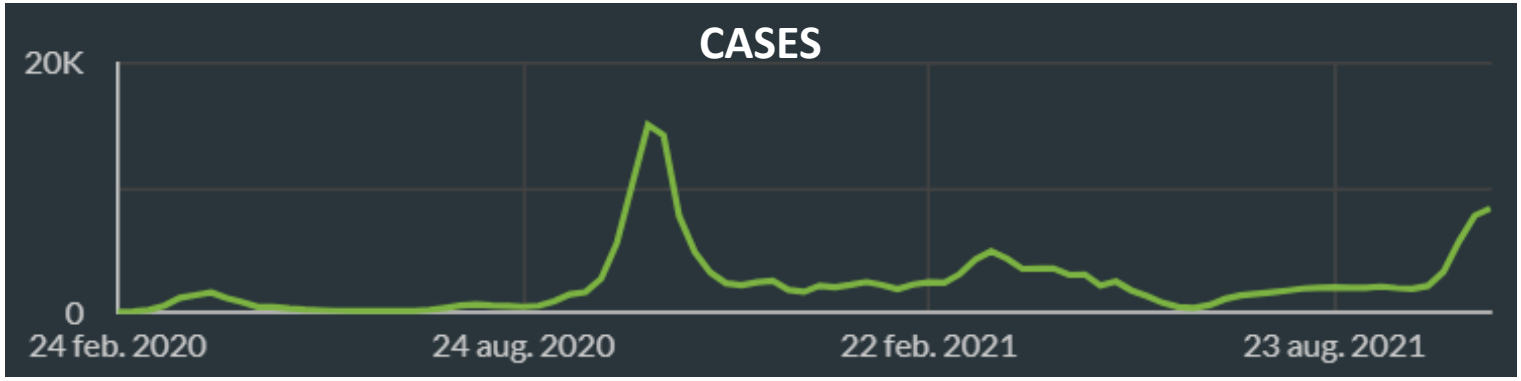
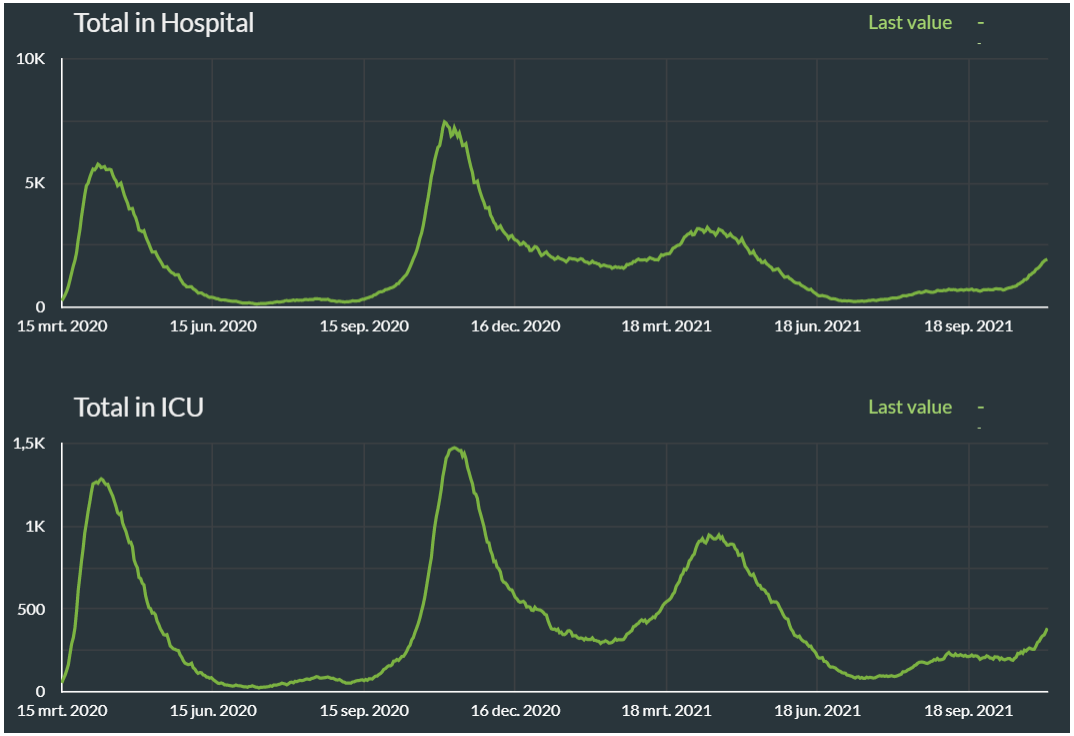
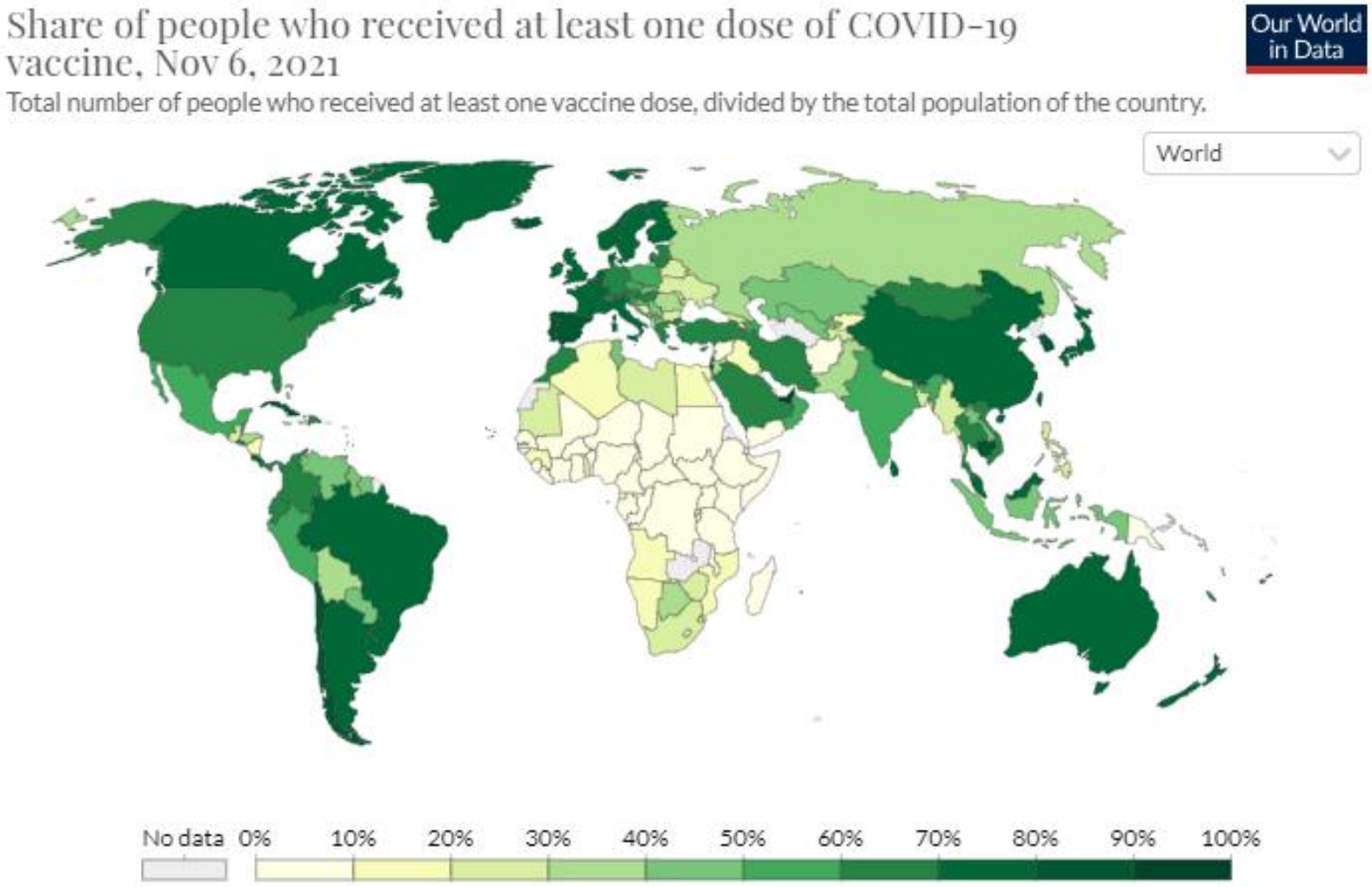


Belgium





Half of world population is vaccinated



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Endorse our Healthy Longevity proposal!

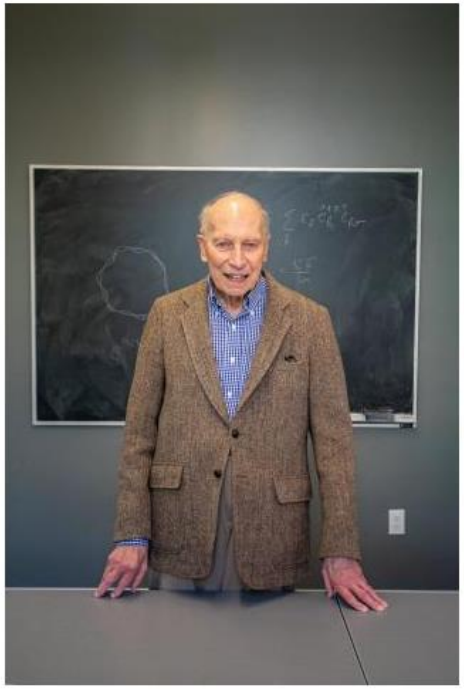
Please endorse and share our European Longevity Initiative's proposal at the Conference on Future Of Europe website called Science-intensive healthy longevity technologies: development and access. This is an unprecedented, real-life political test to show the commitment of the longevity community and give a strong push to the healthy longevity cause/mission at the EU level.

Our proposal is already the top voted across all categories!

1. **Voters need to register at** https://futureu.europa.eu/ (the website is confusing and slow, please be patient)
2. **Once logged in, please go to** https://futureu.europa.eu/processes/Health/f/3/proposals/826
3. **Click 'Endorse'**

Inspirational story

Brown Physics Student Manfred Steiner Earns Ph.D. at Age 89



At 89-years-old Manfred Steiner is finally what he always wanted to be: a physicist. On September 15, 2021, Steiner successfully defended his Ph.D. dissertation, "Corrections to the Geometrical Interpretation of Bosonization" in Brown University's Department of Physics with Professor Brad Marston serving as his adviser and Professors James Valles and Antal Jevicki serving as readers. "It's an old dream that starts in my childhood," says Steiner, "I always wanted to become a physicist."

To say that Steiner's path to a Ph.D. in physics was not a traditional one would be an understatement. As a young man, Steiner fled the chaos of his birthplace of Vienna as World War II ended and eventually made his way to the United States. Steiner says, "I knew physics was my true passion by the time I graduated high school. But after the war, my uncle and my mother advised me to take up medicine because it would be a better choice in these turbulent after-war years."

Although he excelled at and loved physics, Steiner followed his family's advice. He says, "my uncle was a physician, an ear, nose and throat specialist, and he had taught in the United States for a while. He taught plastic surgery — showing people how to make noses smaller or how to straighten them out. My family's advice was that medicine was the best path for me. So I reconciled myself, 'they are older and wiser,' and I followed their advice."

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MAIA Biotechnology, Inc. Announces $6.2 Million Financing to Advance Targeted Immuno-Oncology Studies

October 14, 2021 08:00 AM Eastern Daylight Time

CHICAGO--(BUSINESS WIRE)--MAIA Biotechnology, Inc., a targeted therapy, immuno-oncology company focused on developing potential first-in-class oncology drugs ("MAIA"), announced today that it has raised an additional $6.2 million in an equity offering at $8/share. The proceeds of the financing will advance the company's programs and will support the initiation of a Phase 2 clinical trial (THIO-101) evaluating the administration of THIO followed by cemiplimab in patients with advanced Non-Small Cell Lung Cancer (NSCLC). The THIO-101 trial is expected to begin this year.

"We are excited to have closed this latest financing round, which brings MAIA additional capital as we continue to advance our THIO program"

Tweet this

"We are excited to have closed this latest financing round, which brings MAIA additional capital as we continue to advance our THIO program," said Vlad Vitoc, M.D., MAIA's Chairman and Chief Executive Officer. "We appreciate the continued support of our high-quality investors who share our vision developing novel cancer therapies aimed at overcoming treatment resistant diseases."

About the Phase 2 Clinical Trial in Advanced Non-Small Cell Lung Cancer (NSCLC)

This trial (THIO-101) will be the first to test THIO's immune system activation by administering THIO in advance of administration of the checkpoint inhibitor (co-developed by Regeneron and Sanofi), potentially allowing for immune activation and PD-1 sensitivity to take effect. The trial will test the hypothesis that low doses of THIO administered prior to checkpoint inhibitor treatment will enhance and prolong immune response in patients with advanced NSCLC who previously did not respond or progressed after first-line treatment regimen containing a checkpoint inhibitor.

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Rejuvenate Biomed raises a EUR 15.7 million Series B to accelerate clinical development of its sarcopenia treatment for healthy aging

Rejuvenate Biomed NV ('Rejuvenate'), a biomedical company developing novel combination drugs for age-related diseases, today announces a EUR 15.7 million Series B round. The funding is being used to accelerate the clinical development of Rejuvenate's lead candidate RJx-01 in both acute and chronic sarcopenia (disuse-induced and age-related muscle failure).

The Series B round is being led by Rejuveron Life Sciences AG ('Rejuveron'), a Zürich-based biotechnology company developing therapies to promote healthy aging, and Luxembourg-based Vesalius Biocapital. Rejuveron will ultimately acquire a majority shareholding in Rejuvenate, further expanding the Swiss company's presence in the field of longevity research.

Aging research articles

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p21 produces a bioactive secretome that places stressed cells under immunosurveillance

RESULTS

We found that p21—in addition to its function in maintaining the cell-cycle arrest of SNCs—has a prominent role in establishing the SASP through retinoblastoma protein (Rb)–dependent transcription involving select SMAD and STAT transcription factors. Although this transcriptional program remains active in SNCs, p21 initiates this program as a first response to stress occurring in parallel with cell-cycle arrest. The resulting immediate-early secretome, which we term the p21-activated secretory phenotype (PASP), comprises several hundred factors, including the chemokine CXCL14, which recruits macrophages to surveil stressed cells with elevated p21. In mouse liver, these macrophages disengage if cells normalize p21 levels within 4 days after its induction. However, if p21 remains elevated, the adjoined macrophages polarize toward an M1 phenotype, and cytotoxic T lymphocytes arrive to execute target cell elimination when classical markers of senescence are not yet detectable. This scenario also occurs with oncogenic KRAS-mediated p21 induction, highlighting the physiological relevance of the uncovered immunosurveillance mechanism to tumor suppression. By contrast, CDK inhibitor p16, which is often elevated in SNCs and also halts cell-cycle progression through Rb hypophosphorylation, does not induce immunosurveillance when overexpressed in mouse liver. Although p16 induction yields an immediate-early secretome that consists largely of factors that overlap with the PASP, there are far fewer factors, and CXCL14 is absent. Studies on CDK inhibitor p27 further suggested that coordinated induction of cell-cycle arrest and immunosurveillance is a distinctive feature of p21.

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Senescent immune cells release grancalcin to promote skeletal aging

Chang-Jun Li [1], Ye Xiao [2], Yu-Chen Sun [2], Wen-Zhen He [2], Ling Liu [2], Mei Huang [2], Chen He [2], Min Huang [2], Kai-Xuan Chen [2], Jing Hou [2], Xu Feng [2], Tian Su [2], Qi Guo [2], Yan Huang [2], Hui Peng [2], Mi Yang [2], Guang-Hui Liu [3], Xiang-Hang Luo [4]

Affiliations + expand

PMID: 34614408 DOI: 10.1016/j.cmet.2021.08.009

Abstract

Skeletal aging is characterized by low bone turnover and marrow fat accumulation. However, the underlying mechanism for this imbalance is unclear. Here, we show that during aging in rats and mice proinflammatory and senescent subtypes of immune cells, including macrophages and neutrophils, accumulate in the bone marrow and secrete abundant grancalcin. The injection of recombinant grancalcin into young mice was sufficient to induce premature skeletal aging. In contrast, genetic deletion of Gca in neutrophils and macrophages delayed skeletal aging. Mechanistically, we found that grancalcin binds to the plexin-b2 receptor and partially inactivates its downstream signaling pathways, thus repressing osteogenesis and promoting adipogenesis of bone marrow mesenchymal stromal cells. Heterozygous genetic deletion of Plexnb2 in skeletal stem cells abrogated the improved bone phenotype of Gca-knockout mice. Finally, we developed a grancalcin-neutralizing antibody and showed that its treatment of older mice improved bone health. Together, our data suggest that grancalcin could be a potential target for the treatment of age-related osteoporosis.

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Forestalling age-impaired angiogenesis and blood flow by targeting NOX: Interplay of NOX1, IL-6, and SASP in propagating cell senescence

In an aging population, intense interest has shifted toward prolonging health span. Mounting evidence suggests that cellular reactive species are propagators of cell damage, inflammation, and cellular senescence. Thus, such species have emerged as putative provocateurs and targets for senolysis, and a clearer understanding of their molecular origin and regulation is of paramount importance. In an inquiry into signaling triggered by aging and proxy instigator, hyperglycemia, we show that NADPH Oxidase (NOX) drives cell DNA damage and alters nuclear envelope integrity, inflammation, tissue dysfunction, and cellular senescence in mice and humans with similar causality. Most notably, selective NOX1 inhibition rescues age-impaired blood flow and angiogenesis, vasodilation, and the endothelial cell wound response. Indeed, NOX1i delivery in vivo completely reversed age-impaired hind-limb blood flow and angiogenesis while disrupting a NOX1-IL-6 senescence-associated secretory phenotype (SASP) proinflammatory signaling loop. Relevant to its comorbidity with age, clinical samples from diabetic versus nondiabetic subjects reveal as operant this NOX1-mediated vascular senescence and inflammation in humans. On a mechanistic level, our findings support a previously unidentified role for IL-6 in this feedforward inflammatory loop and peroxisome proliferator–activated receptor gamma (PPARγ) down-regulation as inversely modulating p65-mediated NOX1 transcription. Targeting this previously unidentified NOX1-SASP signaling axis in aging is predicted to be an effective strategy for mitigating senescence in the vasculature and other organ systems.

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An inducible *p21*-Cre mouse model to monitor and manipulate *p21*-highly-expressing senescent cells in vivo

Binsheng Wang, Lichao Wang, Nathan S. Gasek, Yueying Zhou, Taewan Kim, Chun Guo, Evan R. Jellison, Laura Haynes, Sumit Yadav, Tamar Tchkonia, George A. Kuchel, James L. Kirkland & Ming Xu

Nature Aging **1**, 962–973 (2021) | Cite this article

Abstract

The role of senescent cells has been implicated in various tissue dysfunctions associated with aging, obesity and other pathological conditions. Currently, most transgenic mouse models target only $p16^{Ink4a}$-highly expressing ($p16^{high}$) cells. In the present technical report, we generated a *p21*-Cre mouse model, containing a *p21* promoter-driving inducible Cre, enabling us to examine $p21^{Cip1}$-highly expressing ($p21^{high}$) cells, a previously unexplored cell population exhibiting several characteristics typical of senescent cells. By crossing *p21*-Cre mice with different floxed mice, we managed to monitor, sort, image, eliminate or modulate $p21^{high}$ cells in vivo. We showed that $p21^{high}$ cells can be induced by various conditions, and percentages of $p21^{high}$ cells varied from 1.5% to 10% across different tissues in 23-month-old mice. Intermittent clearance of $p21^{high}$ cells improved physical function in 23-month-old mice. Our report demonstrates that the *p21*-Cre mouse model is a valuable and powerful tool for studying $p21^{high}$ cells to further understand the biology of senescent cells.

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Senolytics and the compression of late-life mortality

Axel Kowald [1], Thomas B L Kirkwood [2]

Affiliations + expand

PMID: 34637949 DOI: 10.1016/j.exger.2021.111588

Abstract

Senescent cells play an important role in mammalian ageing and in the etiology of age-related diseases. Treatment of mice with senolytics - drugs that selectively remove senescent cells - causes an extension of median lifespan but has little effect on maximum lifespan. Postponement of some mortality to later ages, without a corresponding increase in maximum mortality, can be termed 'compression of mortality'. When we fit the standard Gompertz mortality model to the survival data following senolytic treatment, we find an increase in the slope parameter, commonly described as the 'actuarial ageing rate'. These observations raise important questions about the actions of senolytic treatments and their effects on health and survival, which are not yet sufficiently understood. To explore how the survival data from senolytics experiments might be explained, we combine a recent exploration of the evolutionary basis of cellular senescence with theoretical consideration of the molecular processes that might be involved. We perform numerical simulations of senescent cell accumulation and senolytic treatment in an ageing population. The simulations suggest that while senolytics diminish the burden of senescent cells, they may also impair the general repair capacity of the organism, leading to a faster accumulation post-treatment of new senescent cells. Our results suggest a framework to address the benefits and possible side effects of senolytic therapies, with the potential to aid in the design of optimal treatment regimens.

Many chronological aging clocks can be found throughout the epigenome: Implications for quantifying biological aging

Hunter L. Porter, Chase A. Brown, Xiavan Roopnarinesingh, Cory B. Giles, Constantin Georgescu, Willard M. Freeman, Jonathan D. Wren

First published: 16 October 2021 | https://doi.org/10.1111/acel.13492

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Abstract

Epigenetic alterations are a hallmark of aging and age-related diseases. Computational models using DNA methylation data can create "epigenetic clocks" which are proposed to reflect "biological" aging. Thus, it is important to understand the relationship between predictive clock sites and aging biology. To do this, we examined over 450,000 methylation sites from 9,699 samples. We found ~20% of the measured genomic cytosines can be used to make many different epigenetic clocks whose age prediction performance surpasses that of telomere length. Of these predictive sites, the average methylation change over a lifetime was small (~1.5%) and these sites were under-represented in canonical regions of epigenetic regulation. There was only a weak association between "accelerated" epigenetic aging and disease. We also compare tissue-specific and pan-tissue clock performance. This is critical to applying clocks both to new sample sets in basic research, as well as understanding if clinically available tissues will be feasible samples to evaluate "epigenetic aging" in unavailable tissues (e.g., brain). Despite the reproducible and accurate age predictions from DNA methylation data, these findings suggest they may have limited utility as currently designed in understanding the molecular biology of aging and may not be suitable as surrogate endpoints in studies of anti-aging interventions. Purpose-built clocks for specific tissues age ranges or phenotypes may perform better for their specific purpose. However, if purpose-built clocks are necessary for meaningful predictions, then the utility of clocks and their application in the field needs to be considered in that context.

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A metabolome atlas of the aging mouse brain

Jun Ding, Jian Ji, Zachary Rabow, Tong Shen, Jacob Folz, Christopher R. Brydges, Sili Fan, Xinchen Lu, Sajjan Mehta, Megan R. Showalter, Ying Zhang, Renee Araiza, Lynette R. Bower, K. C. Kent Lloyd & Oliver Fiehn

Nature Communications **12**, Article number: 6021 (2021) | Cite this article

10k Accesses | **202** Altmetric | Metrics

Abstract

The mammalian brain relies on neurochemistry to fulfill its functions. Yet, the complexity of the brain metabolome and its changes during diseases or aging remain poorly understood. Here, we generate a metabolome atlas of the aging wildtype mouse brain from 10 anatomical regions spanning from adolescence to old age. We combine data from three assays and structurally annotate 1,547 metabolites. Almost all metabolites significantly differ between brain regions or age groups, but not by sex. A shift in sphingolipid patterns during aging related to myelin remodeling is accompanied by large changes in other metabolic pathways. Functionally related brain regions (brain stem, cerebrum and cerebellum) are also metabolically similar. In cerebrum, metabolic correlations markedly weaken between adolescence and adulthood, whereas at old age, cross-region correlation patterns reflect decreased brain segregation. We show that metabolic changes can be mapped to existing gene and protein brain atlases. The brain metabolome atlas is publicly available (https://mouse.atlas.metabolomics.us/) and serves as a foundation dataset for future metabolomic studies.

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Life Expectancy in Marine Mammals Is Unrelated to Telomere Length but Is Associated With Body Size

 Kittisak Buddhachat[1,2],  Janine L. Brown[3], Manthanee Kaewkool[4], Anocha Poommouang[4],  Patcharaporn Kaewmong[5], Kongkiat Kittiwattanawong[5*] and  Korakot Nganvongpanit[2,4*]

[1]Department of Biology, Faculty of Science, Naresuan University, Phitsanulok, Thailand
[2]Excellence Center in Veterinary Bioscience, Chiang Mai University, Chiang Mai, Thailand
[3]Smithsonian Conservation Biology Institute, Center for Species Survival, Front Royal, VA, United States
[4]Department of Veterinary Biosciences and Public Health, Faculty of Veterinary Medicine, Chiang Mai University, Chiang Mai, Thailand
[5]Phuket Marine Biological Center, Phuket, Thailand

Marine mammals vary greatly in size and lifespan across species. This study determined whether measures of adult body weight, length and relative telomere length were related to lifespan. Skin tissue samples (n = 338) were obtained from 23 marine mammal species, including four Mysticeti, 19 Odontoceti and one dugong species, and the DNA extracted to measure relative telomere length using real-time PCR. Life span, adult body weight, and adult body length of each species were retrieved from existing databases. The phylogenetic signal analysis revealed that body length might be a significant factor for shaping evolutionary processes of cetacean species through time, especially for genus *Balaenoptera* that have an enormous size. Further, our study found correlations between lifespan and adult body weight (R^2 = 0.6465, $p < 0.001$) and adult body length (R^2 = 0.6142, $p \leq 0.001$), but no correlations with relative telomere length (R^2 = −0.0476, p = 0.9826). While data support our hypothesis that larger marine mammals live longer, relative telomere length is not a good predictor of species longevity.

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Maintenance of genome sequence integrity in long- and short-lived rodent species

LEI ZHANG, XIAO DONG, XIAO TIAN, MOONSOOK LEE, JULIA ABLAEVA, DENIS FIRSANOV, SANG-GOO LEE, ALEXANDER Y. MASLOV, VADIM N. GLADYSHEV, [...] JAN VIJG +3 authors Authors Info & Affiliations

SCIENCE ADVANCES • 27 Oct 2021 • Vol 7, Issue 44 • DOI: 10.1126/sciadv.abj3284

561

Abstract

DNA mutations in somatic cells have been implicated in the causation of aging, with longer-lived species having a higher capacity to maintain genome sequence integrity than shorter-lived species. In an attempt to directly test this hypothesis, we used single-cell whole-genome sequencing to analyze spontaneous and bleomycin-induced somatic mutations in lung fibroblasts of four rodent species with distinct maximum life spans, including mouse, guinea pig, blind mole-rat, and naked mole-rat, as well as humans. As predicted, the mutagen-induced mutation frequencies inversely correlated with species-specific maximum life span, with the greatest difference observed between the mouse and all other species. These results suggest that long-lived species are capable of processing DNA damage in a more accurate way than short-lived species.

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SomaMutDB: a database of somatic mutations in normal human tissues

Shixiang Sun [1], Yujue Wang [1], Alexander Y Maslov [1 2], Xiao Dong [3], Jan Vijg [1 4]

Affiliations + expand

PMID: 34634815 DOI: 10.1093/nar/gkab914

Abstract

De novo mutations, a consequence of errors in DNA repair or replication, have been reported to accumulate with age in normal tissues of humans and model organisms. This accumulation during development and aging has been implicated as a causal factor in aging and age-related pathology, including but not limited to cancer. Due to their generally very low abundance mutations have been difficult to detect in normal tissues. Only with recent advances in DNA sequencing of single-cells, clonal lineages or ultra-high-depth sequencing of small tissue biopsies, somatic mutation frequencies and spectra have been unveiled in several tissue types. The rapid accumulation of such data prompted us to develop a platform called SomaMutDB (https://vijglab.einsteinmed.org/SomaMutDB) to catalog the 2.42 million single nucleotide variations (SNVs) and 0.12 million small insertions and deletions (INDELs) thus far identified using these advanced methods in nineteen human tissues or cell types as a function of age or environmental stress conditions. SomaMutDB employs a user-friendly interface to display and query somatic mutations with their functional annotations. Moreover, the database provides six powerful tools for analyzing mutational signatures associated with the data. We believe such an integrated resource will prove valuable for understanding somatic mutations and their possible role in human aging and age-related diseases.

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Reevaluation of the effect of dietary restriction on different recombinant inbred lines of male and female mice

Archana Unnikrishnan, Stephanie Matyi, Karla Garrett, Michelle Ranjo-Bishop, David B. Allison, Keisuke Ejima, Xiwei Chen, Stephanie Dickinson, Arlan Richardson

Dietary restriction (DR) was reported to either have no effect or reduce the lifespan of the majority of the 41-recombinant inbred (RI) lines studied by Liao et al. (*Aging Cell*, 2010, **9**, 92). In an appropriately power longevity study ($n > 30$ mice/group), we measured the lifespan of the four RI lines (115-RI, 97-RI, 98-RI, and 107-RI) that were reported to have the greatest decrease in lifespan when fed 40% DR. DR increased the median lifespan of female RI-115, 97-RI, and 107-RI mice and male 115-RI mice. DR had little effect (<4%) on the median lifespan of female and male 98-RI mice and male 97-RI mice and reduced the lifespan of male 107-RI mice over 20%. While our study was unable to replicate the effect of DR on the lifespan of the RI mice (except male 107-RI mice) reported by Liao et al. (*Aging Cell*, 2010, **9**, 92), we found that the genotype of a mouse had a major impact on the effect of DR on lifespan, with the effect of DR ranging from a 50% increase to a 22% decrease in median lifespan. No correlation was observed between the changes in either body composition or glucose tolerance induced by DR and the changes observed in lifespan of the four RI lines of male and female mice. These four RI lines of mice give the research community a unique resource where investigators for the first time can study the anti-aging mechanism of DR by comparing mice in which DR increases lifespan to mice where DR has either no effect or reduces lifespan.

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A collective analysis of lifespan-extending compounds in diverse model organisms, and of species whose lifespan can be extended the most by the application of compounds

Caglar Berkel & Ercan Cacan

Research on aging and lifespan-extending compounds has been carried out using diverse model organisms, including yeast, worms, flies and mice. Many studies reported the identification of novel lifespan-extending compounds in different species, some of which may have the potential to translate to the clinic. However, studies collectively and comparatively analyzing all the data available in these studies are highly limited. Here, by using data from the DrugAge database, we first identified top compounds in terms of their effects on percent change in average lifespan of diverse organisms, collectively (n = 1728). We found that, when data from all organisms studied were combined for each compound, aspirin resulted in the highest percent increase in average lifespan (52.01%), followed by minocycline (27.30%), *N*-acetyl cysteine (17.93%), nordihydroguaiaretic acid (17.65%) and rapamycin (15.66%), in average. We showed that minocycline led to the highest percent increase in average lifespan among other compounds, in both *Drosophila melanogaster* (28.09%) and *Caenorhabditis elegans* (26.67%), followed by curcumin (11.29%) and gluconic acid (5.51%) for *D. melanogaster* and by metformin (26.56%), resveratrol (15.82%) and quercetin (9.58%) for *C. elegans*. Moreover, we found that top 5 species whose lifespan can be extended the most by compounds with lifespan-extending properties are *Philodina acuticornis*, *Acheta domesticus*, *Aeolosoma viride*, *Mytilina brevispina* and *Saccharomyces cerevisiae* (211.80%, 76%, 70.26%, 55.18% and 45.71% in average, respectively). This study provides novel insights on lifespan extension in model organisms, and highlights the importance of databases with high quality content curated by researchers from multiple resources, in aging research.

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PREPRINT

Short term treatment with a cocktail of rapamycin, acarbose and phenylbutyrate slows aging in mice

Zhou Jiang, Juan Wang, Denise Imai, Tim Snider, Ruby Mangalindan, John Morton, Lida Zhu, Adam B. Salmon, Jackson Wezeman, Jenna Klug, Jiayi Hu, Vinal Menon, Nicholas Marka, Laura Neidernhofer, Warren Ladiges

doi: https://doi.org/10.1101/2021.10.21.465380

Abstract

Pharmaceutical intervention of aging requires targeting multiple pathways, thus there is rationale to test combinations of drugs each targeting different but overlapping processes. In order to determine if combining drugs previously shown to improve lifespan would have greater impact than any individuyal drug, a diet containing rapamycin at 14 ppm, acarbose at 1000 ppm, and phenylbutyrate at 1000 ppm was fed to 20-month-old C57BL/6 and HET3 4-way cross mice of both sexes for three months. Mice fed the cocktail diet showed a strain and gender-dependent phenotype consistent with healthy aging including decreased body fat and blood glucose, improved cognition, and increased grip strength and walking ability compared to mice fed individual drug or control diets. A cocktail diet containing ½ dosing of each compound was overall less effective than the full dose. The composite age-related lesion score of heart, lungs, liver and kidney was decreased in mice fed the cocktail diet compared to mice fed individual drug or control diets suggesting an interactive advantage of the three drugs. Senescence and inflammatory cytokine levels in kidneys from mice fed the cocktail diet were lower than in kidneys from mice fed control diet, and consistent with low expression levels in kidneys from young untreated mice, suggesting the cocktail diet delayed aging partly by senolytic and anti-inflammatory effects.

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Effect of Long-Term Treatment with C_{60} Fullerenes on the Lifespan and Health Status of CBA/Ca Mice

Dmytro Shytikov, Iryna Shytikova, Deepak Rohila, Anton Kulaga, Tatiana Dubiley, and Iryna Pishel

Published Online: 20 Oct 2021 | https://doi.org/10.1089/rej.2020.2403

Abstract

Several studies claimed C_{60} fullerenes as a prospective geroprotector drug due to their ability to capture free radicals effectively and caused a profound interest in C_{60} in life extension communities. Multiple additives are already sold for human consumption despite a small body of evidence supporting the beneficial effects of fullerenes on the lifespan. To test the effect of C_{60} fullerenes on lifespan and healthspan, we administered C_{60} fullerenes dissolved in virgin olive oil orally to 10–12 months old CBA/Ca mice of both genders for 7 months and assessed their survival. To uncover C_{60} and virgin olive effects, we established two control groups: mice treated with virgin olive oil (vehicle) and mice treated with drinking water. To measure healthspan, we conducted daily monitoring of health condition and lethality and monthly bodyweight measurements. We also assessed physical activity, glucose metabolism, and hematological parameters every 3 months. We did not observe health deterioration in the animals treated with C_{60} compared with the control groups. Treatment of mice with C_{60} fullerenes resulted in an increased lifespan of males and females compared with the olive oil-treated animals. The lifespan of C_{60}-treated mice was similar to the mice treated with water. These results suggest that the lifespan-extending effect in C_{60}-treated mice appears due to the protective effect of fullerenes in opposition to the negative effect of olive oil in CBA/Ca mice.

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Spontaneous Cleavage at Glu and Gln Residues in Long-Lived Proteins

Michael G. Friedrich*, Zhen Wang, Kevin L. Schey, and Roger J. W. Truscott

Cite this: *ACS Chem. Biol.* 2021, XXXX, XXX, XXX-XXX
Publication Date: October 22, 2021
https://doi.org/10.1021/acschembio.1c00379

Read Online | PDF (3 MB) | SI Supporting Info (1) »

SUBJECTS: Peptides and proteins, Central nervous system, Mon

Abstract

Long-lived proteins (LLPs) are prone to deterioration with time, and one prominent breakdown process is the scission of peptide bonds. These cleavages can either be enzymatic or spontaneous. In this study, human lens proteins were examined and many were found to have been cleaved on the C-terminal side of Glu and Gln residues. Such cleavages could be reproduced experimentally by *in vitro* incubation of Glu- or Gln-containing peptides at physiological pHs. Spontaneous cleavage was dependent on pH and amino acid sequence. These model peptide studies suggested that the mechanism involves a cyclic intermediate and is therefore analogous to that characterized for cleavage of peptide bonds adjacent to Asp and Asn residues. An increased amount of some Glu/Gln cleaved peptides in the insoluble fraction of human lenses suggests that cleavage may act to destabilize proteins. Spontaneous cleavage at Glu and Gln, as well as recently described cross-linking at these residues, can therefore be added to the similar processes affecting long-lived proteins that have already been documented for Asn and Asp residues.

C. elegans aging research

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PREPRINT

The longevity response to warm temperature is neurally controlled via the regulation of collagen genes

Sankara Naynar Palani, Durai Sellegounder, Yiyong Liu

doi: https://doi.org/10.1101/2021.09.26.461885

Abstract

Studies in diverse species have associated higher temperatures with shorter lifespan and lower temperatures with longer lifespan. However, the mechanisms behind these inverse effects of temperature on longevity are not well understood. Here, we demonstrate that in *Caenorhabditis elegans*, functional loss of NPR-8, a G protein-coupled receptor related to mammalian neuropeptide Y receptors, increases worm lifespan at 25°C but not at 20°C or 15°C, and that the lifespan increase at 25°C is regulated by the NPR-8-expressing AWB and AWC chemosensory neurons as well as AFD thermosensory neurons. RNA sequencing revealed that both warm temperature and old age profoundly alter gene expression. Further investigation uncovered that the NPR-8-dependent longevity response to warm temperature is achieved by regulating the expression of a subset of collagen genes. As elevated collagen expression is a common feature of many lifespan-extending interventions and enhanced stress resistance, collagen expression could be critical for healthy aging.

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C. elegans feed yolk to their young in a form of primitive lactation

Carina C. Kern, StJohn Townsend, Antoine Salzmann, Nigel B. Rendell, Graham W. Taylor, Ruxandra M. Comisel, Lazaros C. Foukas, Jürg Bähler & David Gems

Nature Communications **12**, Article number: 5801 (2021) | Cite this article

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Abstract

The nematode *Caenorhabditis elegans* exhibits rapid senescence that is promoted by the insulin/IGF-1 signalling (IIS) pathway via regulated processes that are poorly understood. IIS also promotes production of yolk for egg provisioning, which in post-reproductive animals continues in an apparently futile fashion, supported by destructive repurposing of intestinal biomass that contributes to senescence. Here we show that post-reproductive mothers vent yolk which can be consumed by larvae and promotes their growth. This implies that later yolk production is not futile; instead vented yolk functions similarly to milk. Moreover, yolk venting is promoted by IIS. These findings suggest that a self-destructive, lactation-like process effects resource transfer from postreproductive *C. elegans* mothers to offspring, in a fashion reminiscent of semelparous organisms that reproduce in a single, suicidal burst. That this process is promoted by IIS provides insights into how and why IIS shortens lifespan in *C. elegans*.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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The metabolic roots of senescence: mechanisms and opportunities for intervention

Christopher D. Wiley & Judith Campisi

Nature Metabolism **3**, 1290–1301 (2021) | Cite this article

10k Accesses | **99** Altmetric | Metrics

Abstract

Cellular senescence entails a permanent proliferative arrest, coupled to multiple phenotypic changes. Among these changes is the release of numerous biologically active molecules collectively known as the senescence-associated secretory phenotype, or SASP. A growing body of literature indicates that both senescence and the SASP are sensitive to cellular and organismal metabolic states, which in turn can drive phenotypes associated with metabolic dysfunction. Here, we review the current literature linking senescence and metabolism, with an eye toward findings at the cellular level, including both metabolic inducers of senescence and alterations in cellular metabolism associated with senescence. Additionally, we consider how interventions that target either metabolism or senescent cells might influence each other and mitigate some of the pro-aging effects of cellular senescence. We conclude that the most effective interventions will likely break a degenerative feedback cycle by which cellular senescence promotes metabolic diseases, which in turn promote senescence.

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Recent advances in the discovery of senolytics

Lei Zhang, Louise E. Pitcher, Vaishali Prahalad, Laura J. Niedernhofer, Paul D. Robbins

The demonstration in model organisms that cellular senescence drives aging and age-related diseases has led to widespread efforts to identify compounds able to selectively kill senescent cells, termed senolytics. Approaches used to identify senolytics include bioinformatic analysis of senescent cell anti-apoptotic pathways (SCAPs) for drug development and screening of drugs libraries on different senescent cell types in culture. Alternatively, cytotoxic compounds can be made specific to senescent cells through a prodrug strategy such as linking the compound to a galactose moiety where toxicity is activated by lysosomal β-galactosidase. Identified senolytics can then be optimized through medicinal chemistry or linking to E3 targeting moieties to facilitate proteolysis of their targets. This review will provide an overview of approaches to identify senolytics and an update of the classes of senolytics identified to date.

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Cytoplasmic DNA: sources, sensing, and role in aging and disease

Karl N. Miller [1, 6], Stella G. Victorelli [2, 3, 6], Hanna Salmonowicz [2, 3, 4, 5], Nirmalya Dasgupta [1], Tianhui Liu [1], João F. Passos [2, 3] ✉, Peter D. Adams [1] ✉

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https://doi.org/10.1016/j.cell.2021.09.034

Summary

Endogenous cytoplasmic DNA (cytoDNA) species are emerging as key mediators of inflammation in diverse physiological and pathological contexts. Although the role of endogenous cytoDNA in innate immune activation is well established, the cytoDNA species themselves are often poorly characterized and difficult to distinguish, and their mechanisms of formation, scope of function and contribution to disease are incompletely understood. Here, we summarize current knowledge in this rapidly progressing field with emphases on similarities and differences between distinct cytoDNAs, their underlying molecular mechanisms of formation and function, interactions between cytoDNA pathways, and therapeutic opportunities in the treatment of age-associated diseases.

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Dog Models of Aging

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Review in Advance first posted online on October 26, 2021. (Changes may still occur before final publication.)
https://doi.org/10.1146/annurev-animal-051021-080937

Audrey Ruple,[1] Evan MacLean,[2] Noah Snyder-Mackler,[3] Kate E. Creevy,[4] and Daniel Promislow[5]

As the most phenotypically diverse mammalian species that shares human environments and access to sophisticated healthcare, domestic dogs have unique potential to inform our understanding of the determinants of aging. Here we outline key concepts in the study of aging and illustrate the value of research with dogs, which can improve dog health and support translational discoveries. We consider similarities and differences in aging and age-related diseases in dogs and humans and summarize key advances in our understanding of genetic and environmental risk factors for morbidity and mortality in dogs. We address health outcomes ranging from cancer to cognitive function and highlight emerging research opportunities from large-scale cohort studies in companion dogs. We conclude that studying aging in dogs could overcome many limitations of laboratory models, most notably, the ability to assess how aging-associated pathways influence aging in real-world environments similar to those experienced by humans.

The Biology of Aging in Insects: From *Drosophila* to Other Insects and Back

Annual Review of Entomology
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Review in Advance first posted online on September 30, 2021. (Changes may still occur before final publication.)
https://doi.org/10.1146/annurev-ento-061621-064341

Daniel E.L. Promislow,[1,2*] Thomas Flatt,[3*] and Russell Bonduriansky[4*]

An enormous amount of work has been done on aging in *Drosophila melanogaster*, a classical genetic and molecular model system, but also in numerous other insects. However, these two extensive bodies of work remain poorly integrated to date. Studies in *Drosophila* often explore genetic, developmental, physiological, and nutrition-related aspects of aging in the lab, while studies in other insects often explore ecological, social, and somatic aspects of aging in both lab and natural populations. Alongside exciting genomic and molecular research advances in aging in *Drosophila*, many new studies have also been published on aging in various other insects, including studies on aging in natural populations of diverse species. However, no broad synthesis of these largely separate bodies of work has been attempted. In this review, we endeavor to synthesize these two semi-independent literatures to facilitate collaboration and foster the exchange of ideas and research tools. While lab studies of *Drosophila* have illuminated many fundamental aspects of senescence, the stunning diversity of aging patterns among insects, especially in the context of their rich ecology, remains vastly understudied. Coupled with field studies and novel, more easily applicable molecular methods, this represents a major opportunity for deepening our understanding of the biology of aging in insects and beyond.

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Evaluation of Tissue Engineering Approaches for Intervertebral Disc Regeneration in Relevant Animal Models

Sweety Evangeli Malli, Pranav Kumbhkarn, Ankush Dewle, and Akshay Srivastava*

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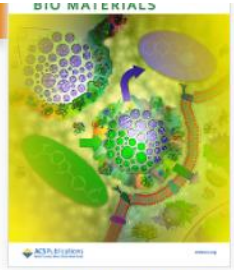
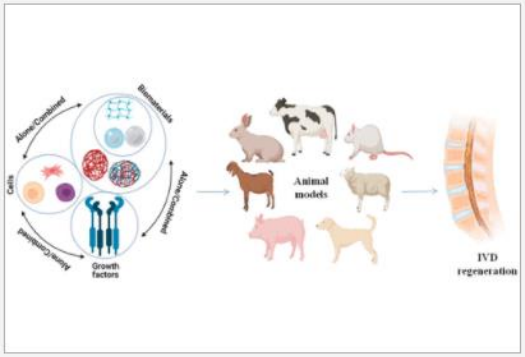


ACS Applied Bio Materials

Abstract

Translation of tissue engineering strategies for the regeneration of intervertebral disc (IVD) requires a strong understanding of pathophysiology through the relevant animal model. There is no relevant animal model due to differences in disc anatomy, cellular composition, extracellular matrix components, disc physiology, and mechanical strength from humans. However, available animal models if used correctly could provide clinically relevant information for the translation into humans. In this review, we have investigated different types of strategies for the development of clinically relevant animal models to study biomaterials, cells, biomolecular or their combination in developing tissue engineering-based treatment strategies. Tissue engineering strategies that utilize various animal models for IVD regeneration are summarized and outcomes have been discussed. The understanding of animal models for the validation of regenerative approaches is employed to understand and treat the pathophysiology of degenerative disc disease (DDD) before proceeding for human trials. These animal models play an important role in building a therapeutic regime for IVD tissue regeneration, which can serve as a platform for clinical applications.



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Can we make drug discovery targeting fundamental mechanisms of aging a reality?

David G. Le Couteur, Rozalyn M. Anderson & Rafael de Cabo

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1. Introduction

The discovery of drugs targeting the fundamental mechanisms of aging (herein called 'aging drugs') poses a far greater challenge than the discovery of drugs for individual diseases. There are multiple biological pathways and processes that change with aging in all organs and tissues, and this aging cascade is initiated by the simple passage of time intertwined with genetic and environmental factors. The nine Hallmarks of Aging provide a valuable framework for cataloging potential aging targets [1]. Although there are multiple Hallmarks, not all must be targeted in order to influence aging. The 'unitary theory of fundamental aging processes' proposes that the aging processes are interconnected and integrated, therefore perturbing one will eventually impact on all others and hence aging and lifespan [2]. This theory is supported by numerous reports that single drugs or manipulation of single genes can influence aging in multiple tissues as well as lifespan [3,4].

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Applying *C. elegans* to the Industrial Drug Discovery Process to Slow Aging

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[2]Magnitude Biosciences Ltd., NETpark Plexus, Sedgefield, United Kingdom

The increase in our molecular understanding of the biology of aging, coupled with a recent surge in investment, has led to the formation of several companies developing pharmaceuticals to slow aging. Research using the tiny nematode worm *Caenorhabditis elegans* was the first to show that mutations in single genes can extend lifespan, and subsequent research has shown that this model organism is uniquely suited to testing interventions to slow aging. Yet, with a few notable exceptions, *C. elegans* is not in the standard toolkit of longevity companies. Here we discuss the paths to overcome the barriers to using *C. elegans* in industrial drug discovery. We address the predictive power of *C. elegans* for human aging, how *C. elegans* research can be applied to specific challenges in the typical drug discovery pipeline, and how standardised and quantitative assays will help *C. elegans* fulfil its potential in the biotech and pharmaceutical industry. We argue that correct application of this model and its knowledge base will significantly accelerate progress to slow human aging.

OTHER RESEARCH & REVIEWS

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Every gene can (and possibly will) be associated with cancer

João Pedro de Magalhães [1]

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https://doi.org/10.1016/j.tig.2021.09.005

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A PubMed analysis shows that the vast majority of human genes have been studied in the context of cancer. As such, the study of nearly any human gene can be justified based on existing literature by its potential relevance to cancer. Moreover, these results have implications for analyzing and interpreting large-scale analyses.

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Low glycaemic diets alter lipid metabolism to influence tumour growth

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Check for updates

Evan C. Lien[1], Anna M. Westermark[1], Yin Zhang[2,3], Chen Yuan[2], Zhaoqi Li[1,4], Allison N. Lau[1], Kiera M. Sapp[1,4], Brian M. Wolpin[2] & Matthew G. Vander Heiden[1,2,4]✉

Dietary interventions can change metabolite levels in the tumour microenvironment, which might then affect cancer cell metabolism to alter tumour growth[1–5]. Although caloric restriction (CR) and a ketogenic diet (KD) are often thought to limit tumour progression by lowering blood glucose and insulin levels[6–8], we found that only CR inhibits the growth of select tumour allografts in mice, suggesting that other mechanisms contribute to tumour growth inhibition. A change in nutrient availability observed with CR, but not with KD, is lower lipid levels in the plasma and tumours. Upregulation of stearoyl-CoA desaturase (SCD), which synthesises monounsaturated fatty acids, is required for cancer cells to proliferate in a lipid-depleted environment, and CR also impairs tumour SCD activity to cause an imbalance between unsaturated and saturated fatty acids to slow tumour growth. Enforcing cancer cell SCD expression or raising circulating lipid levels through a higher-fat CR diet confers resistance to the effects of CR. By contrast, although KD also impairs tumour SCD activity, KD-driven increases in lipid availability maintain the unsaturated to saturated fatty acid ratios in tumours, and changing the KD fat composition to increase tumour saturated fatty acid levels cooperates with decreased tumour SCD activity to slow tumour growth. These data suggest that diet-induced mismatches between tumour fatty acid desaturation activity and the availability of specific fatty acid species determine whether low glycaemic diets impair tumour growth.