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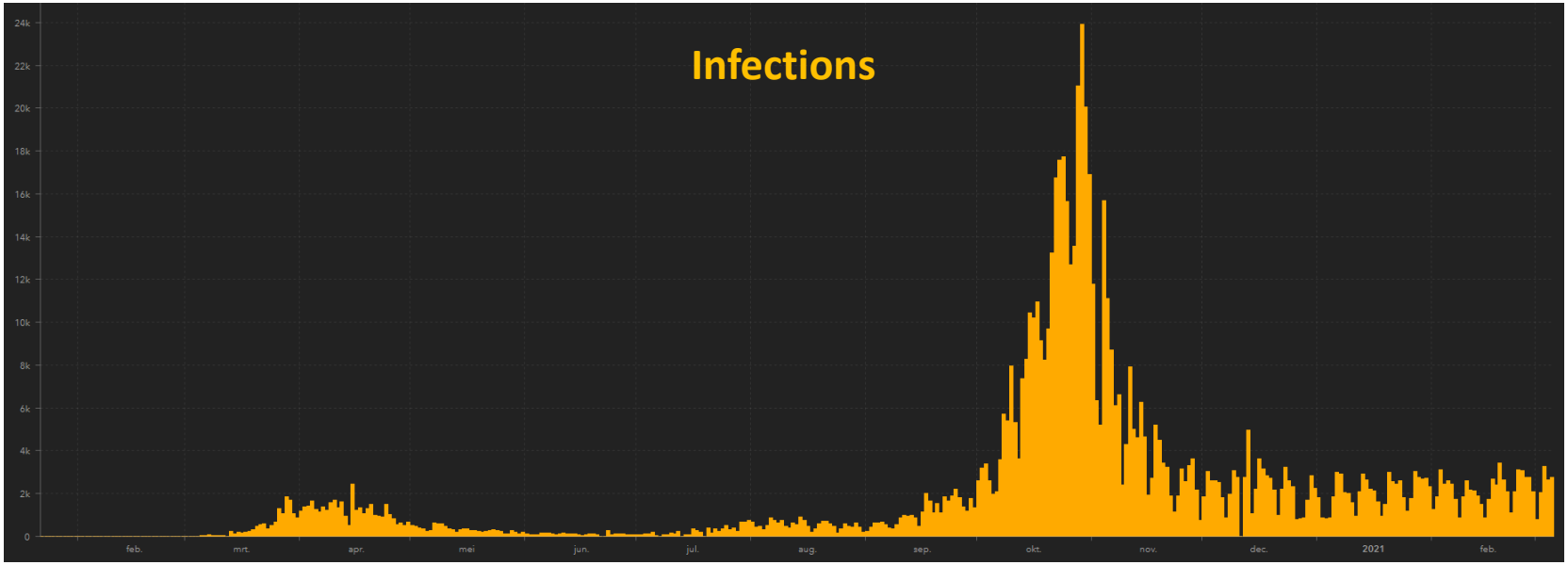
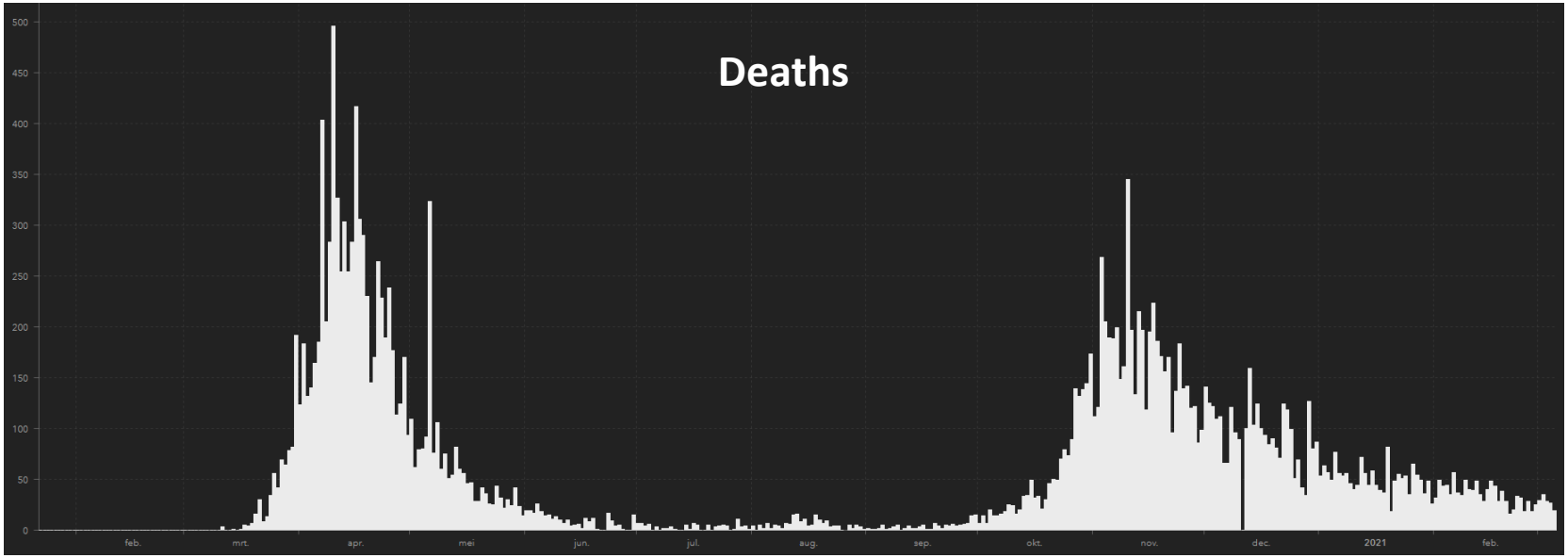
Scientific News
7th of March 2021
Sven Bulterijs

Business/Conferences/ General news

Belgium





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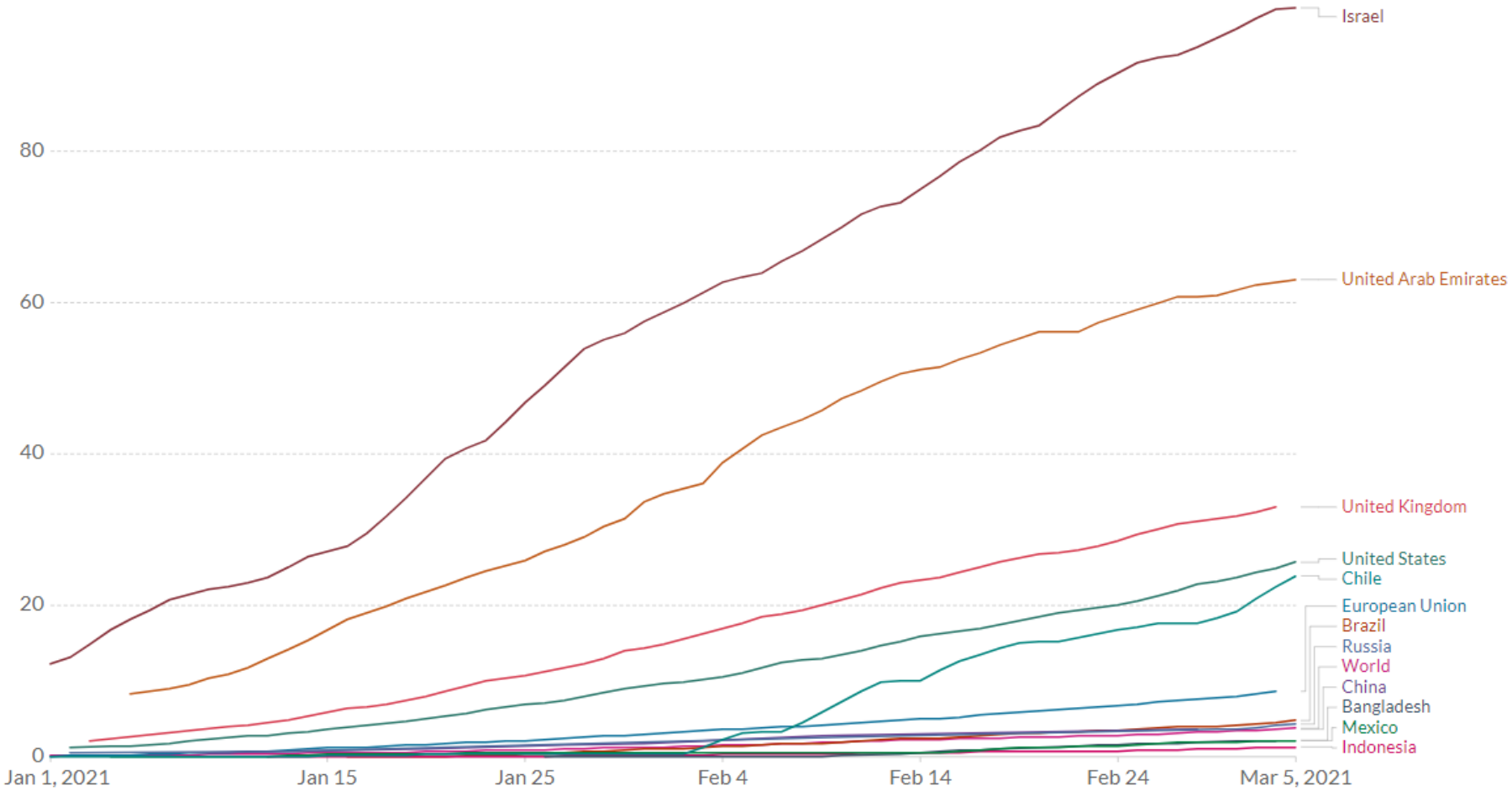
Cumulative COVID-19 vaccination doses administered per 100 people

This is counted as a single dose, and may not equal the total number of people vaccinated, depending on the specific dose regime (e.g. people receive multiple doses).

Our World in Data

LINEAR LOG



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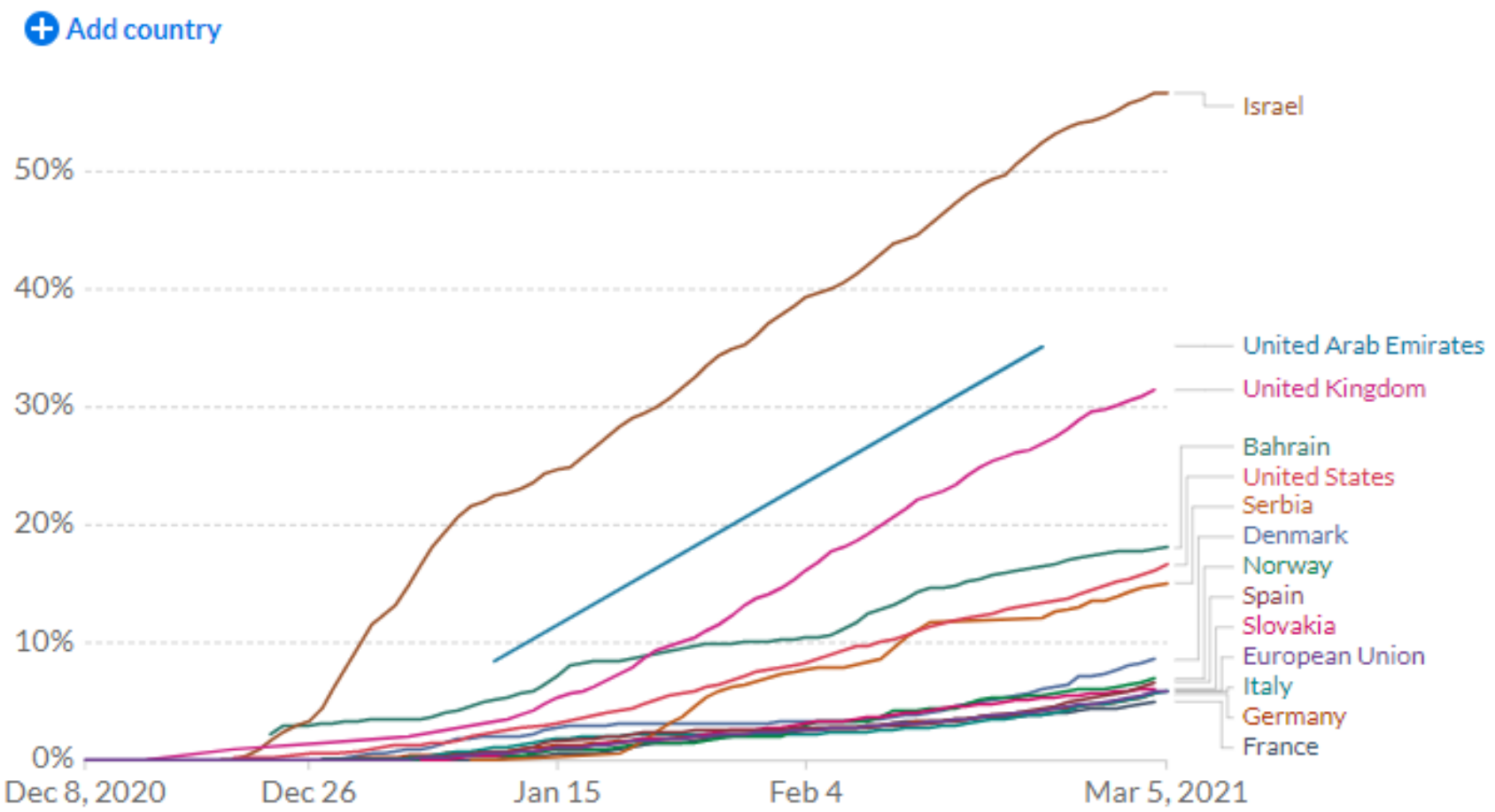
Share of people who received at least one dose of COVID-19 vaccine

Our World in Data

Share of the total population that received at least one vaccine dose. This may not equal the share that are fully vaccinated if the vaccine requires two doses.



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Neutralizing Activity of BNT162b2-Elicited Serum — Preliminary Report

TO THE EDITOR:

BNT162b2 is a nucleoside-modified RNA vaccine expressing the full-length prefusion spike glycoprotein (S) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In a randomized, placebo-controlled clinical trial involving approximately 44,000 participants, immunization conferred 95% efficacy against coronavirus disease 2019 (Covid-19).[1]

New, highly transmissible SARS-CoV-2 variants that were first detected in the United Kingdom (B.1.1.7 lineage), South Africa (B.1.351 lineage), and Brazil (P.1 lineage) with mutations in the S gene are spreading globally. To analyze effects on neutralization elicited by BNT162b2, we engineered S

331, and 184, respectively (Figure 1 and Table S1). Thus, as compared with neutralization of USA-WA1/2020, neutralization of Δ242-244+D614G virus was similar and neutralization of the B.1.351-spike virus was weaker by approximately two thirds. Our data are also consistent with poorer neutralization of the virus with the full set of B.1.351-spike mutations than virus with either subset of mutations and suggested that virus with mutant residues in the receptor-binding site (K417N, E484K, and N501Y) is more poorly neutralized than virus with Δ242-244, which is located in the N-terminal domain of the spike protein.

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Serum Neutralizing Activity Elicited by mRNA-1273 Vaccine — Preliminary Report

Both the full panel of mutations in S and a subset of mutations affecting the receptor-binding domain (RBD) region of the B.1.1.7 variant had no significant effect on neutralization by serum obtained from participants who had received the mRNA-1273 vaccine in the phase 1 trial (Figure 1A and 1B). In contrast, we observed a decrease in titers of neutralizing antibodies against the B.1.351 variant and a subset of its mutations affecting the RBD. In serum samples obtained 1 week after the participants received the second dose of vaccine, we detected reductions by a factor of 2.7 in titers of neutralizing antibodies against the partial panel of mutations and by a factor of 6.4 against the full panel of mutations (Figure 1C and 1D). However, in serum samples obtained from eight participants in the phase 1 trial, the geometric mean neutralizing titer against B.1.351 was 1:290, and all the serum samples neutralized the rVSV pseudovirus, albeit at relatively low dilutions (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). With the use of both rVSV and lentiviral neutralization assays, we observed a similar trend in serum samples obtained from macaque monkeys (Figs. S2 and S3).

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Bring on the boosters: Studies show Pfizer, Moderna COVID-19 vaccines are less potent against aggressive variant

by Arlene Weintraub | Feb 18, 2021 12:26pm

Revised booster shots may be necessary to protect against aggressive new variants of COVID-19, analysts suggested. (Getty/bymuratdeniz)

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AstraZeneca, Oxford race to update COVID-19 vaccine as study flags weak action against variant

by Angus Liu | Feb 8, 2021 8:25am

AstraZeneca and the University of Oxford have started developing a booster shot to their AZD1222 COVID-19 vaccine after a study found it didn't work well against a virus strain first found in South Africa. (Kunal Mahto/iStock/Getty Images Plus/Getty Images)

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As transmission rate rises above 1, virus czar says 4th lockdown a possibility

Asked about Netanyahu's assertion Thursday that the pandemic is largely over in Israel, Ash says: 'I don't know what the prime minister meant'

By TOI STAFF
5 March 2021, 1:17 pm | 1

448 shares

Israel's coronavirus czar Prof. Nachman Ash visits the coronavirus department at the Ziv hospital in Tzfat, northern Israel. December 24, 2020. (David Cohen/Flash90)

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PREPRINT

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial

Background Tocilizumab is a monoclonal antibody that binds to the receptor for interleukin (IL)-6, reducing inflammation, and is commonly used to treat rheumatoid arthritis. We evaluated the safety and efficacy of tocilizumab in adult patients admitted to hospital with COVID-19 with evidence of both hypoxia and systemic inflammation.

Findings Between 23 April 2020 and 24 January 2021, 4116 adults were included in the assessment of tocilizumab, including 562 (14%) patients receiving invasive mechanical ventilation, 1686 (41%) receiving non-invasive respiratory support, and 1868 (45%) receiving no respiratory support other than oxygen. Median CRP was 143 [IQR 107-204] mg/L and 3385 (82%) patients were receiving systemic corticosteroids at randomisation. Overall, 596 (29%) of the 2022 patients allocated tocilizumab and 694 (33%) of the 2094 patients allocated to usual care died within 28 days (rate ratio 0·86; 95% confidence interval [CI] 0·77-0·96; p=0·007). Consistent results were seen in all pre-specified subgroups of patients. In particular, a clear mortality benefit was seen in those receiving systemic corticosteroids. Patients allocated to tocilizumab were more likely to be discharged from hospital alive within 28 days (54% vs. 47%; rate ratio 1·22; 95% CI 1·12-1·34; p<0·0001). Among those not receiving invasive mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (33% vs. 38%; risk ratio 0·85; 95% CI 0·78-0·93; p=0·0005).

Interpretation In hospitalised COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved survival and other clinical outcomes. These benefits were seen regardless of the level of respiratory support and were additional to the benefits of systemic corticosteroids.

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COVID-19 tracker: Some Catholics resist J&J vaccine; United States' hoarding of raw materials could choke world supply

by Kevin Dunleavy, Fraiser Kansteiner, Eric Sagonowsky, Angus Liu, Conor Hale | Mar 5, 2021 3:52pm

Manufacturers of COVID-19 vaccines around the world could soon be feeling the pinch of the United States' move to lock up raw materials and supplies for **Pfizer**. The **Serum Institute of India**, the world's largest producer of vaccines, and the **World Health Organization** are warning of supply bottlenecks that could slow production. Story

The **AstraZeneca** vaccine is effective against the **Brazilian** coronavirus variant, P1, and will not need to be modified to protect against it, according to a study at **Oxford** cited by Reuters. Earlier results showed that the AZ vaccine was less effective against the **South African** variant, which is similar to P1. Brazil is suffering through a brutal second coronavirus wave. On Wednesday, the country recorded its daily record of 1,910 deaths.

Oxford has closed a trial for **colchicine**, an anti-inflammatory medicine used to combat gout which had been named as a possible treatment for COVID-19. The study provided no convincing evidence that the drug was effective in hospitalized coronavirus patients.

As the world battles the coronavirus pandemic, not only are vaccines a precious commodity, so are syringes. In a typical year, 16 billion syringes are used in the world, with only 5% to 10% used for vaccinations. But the global pandemic has brought the need for 8 to 10 billion syringes alone.

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LongCovidSOS

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CNN Exclusive: Aged 118, the world's oldest living person will carry the Olympic flame in Japan

By Blake Essig, Junko Ogura and Emiko Jozuka, CNN At 118 years old, the world's oldest living person is preparing to carry the Olympic torch this May in Japan.

Thursday, March 4th 2021, 9:32 PM EST
Updated: Thursday, March 4th 2021, 10:47 PM EST

By Blake Essig, Junko Ogura and Emiko Jozuka, CNN

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The Economist

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Books & arts

Feb 6th 2021 edition ›

Who wants to live for ever?

Ageing can be cured—and, in part, it soon will be

That is Andrew Steele's thesis in "Ageless"

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Forever young? Biotech's next frontier

Investments into the longevity sector is stepping up, bolstered by the pandemic

Seth O'Farrell February 12, 2021

Short explainer video: Insilico Medicine Achieves Industry-First Nominating Preclinical Candidate

Rejuvenate Biomed Secures EUR 3.2 Million Series A Round to Advance Development of Healthy Aging Products

Heusden-Zolder, Belgium, 2 March 2021 – Rejuvenate Biomed NV ("Rejuvenate"), a biomedical company developing prescription drugs for age-related diseases, announces it has completed a EUR 3.2 million Series A round. The funding is being used to advance the development of Rejuvenate's lead candidate RJx-01 in both acute and chronic sarcopenia (disuse-induced and age-related muscle failure).

The financing included lead investor Vesalius Biocapital III and private non-disclosed investors, as well as existing investors. Additionally, Rejuvenate gratefully acknowledges the ongoing support of Flanders Innovation and Entrepreneurship (VLAIO) in non-dilutive funding. Concurrent with the closing, the company has bolstered its scientific advisory board, which is now composed of Dr. Johan Auwerx, MD, PhD, Dr. Eric Verdin, MD, PhD, Dr. Marco Sandri, MD, PhD, Dr. Bart Braeckman, PhD, Dr. Björn Schumacher, PhD, and Dr. Andrea Maier, MD, PhD. Furthermore, a clinical advisory board has been established which is led by Dr. Jean-Yves Reginster, MD, PhD.

Rejuvenate's lead candidate RJx-01 is a novel, safe, orally administered, small molecule combination product being developed for sarcopenia, defined by loss of muscle strength, quality and mass. The product was derived from an extensive in silico systems biology program, which mapped existing drugs with curated longevity pathways to create innovative, synergistic and highly effective combinations. RJx-01 has demonstrated strong preclinical evidence in multiple models and, with human safety data on hand for the individual compounds, the company plans to move the program into Phase Ib/IIb clinic trials later this year.

Dr. Ann Beliën, PhD, Founder and CEO of Rejuvenate: "We are very pleased to welcome our lead investor Vesalius Biocapital III as well as the other new investors and wish to thank our existing shareholders for their continued support. Our team is highly driven to deliver therapeutics with a meaningful impact on the treatment and prevention of multiple age-related diseases by tackling their root causes. Using safe products as building blocks to develop innovative combinations such as RJx-01 has created unique opportunities in this field. Our dream of extending people's health span is becoming a reality."

Mr. Stéphane Verdood, MBA, MSc, Managing Partner at Vesalius Biocapital III: "Rejuvenate's data show the potential for RJx-01 to drive our natural capacity to self-restore our cells. The company has a solid scientific and clinical basis coupled with a management team that is rapidly advancing RJx-01 for sarcopenia, and we are excited to be part of the next stage of the company's growth."

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Rejuvenation Research, Just Accepted |

Aging of the Suprachiasmatic Nucleus, CIRCLONSA syndrome, implications for regenerative medicine and restoration of the master body clock

Mr. Victor Björk

Published Online: 11 Feb 2021 | https://doi.org/10.1089/rej.2020.2388

View article Tools Share

Abstract

The suprachiasmatic nucleus (SCN) in the brain is the master regulator of the circadian clocks throughout the human body. With increasing age the circadian clock in humans and other mammals becomes increasingly disorganized leading to a large number of more or less well categorized problems. While a lot of aging research has focused on the peripheral clocks in tissues across organisms, it remains a paramount task to quantify aging of the most important master clock, the human SCN. Furthermore, a pipeline needs to be developed with therapies to mitigate the systemic cellular circadian dysfunction in the elderly and ultimately repair and reverse aging of the SCN itself. A disease classification for the aging SCN, Circadian Clock Neuronal Senile Atrophy, (CIRCLONSA syndrome), would improve research funding and goal-oriented biotechnological entrepreneurship.

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Towards a Large-Scale Assessment of the Relationship Between Biological and Chronological Aging: The Inspire Mouse Cohort

Aging is the major risk factor for the development of chronic diseases. After decades of research focused on extending lifespan, current efforts seek primarily to promote healthy aging. Recent advances suggest that biological processes linked to aging are more reliable than chronological age to account for an individual's functional status, i.e. frail or robust. It is becoming increasingly apparent that biological aging may be detectable as a progressive loss of resilience much earlier than the appearance of clinical signs of frailty. In this context, the INSPIRE program was built to identify the mechanisms of accelerated aging and the early biological signs predicting frailty and pathological aging. To address this issue, we designed a cohort of outbred SWISS mice (1576 male and female mice) in which we will continuously monitor spontaneous and voluntary physical activity from 6 to 24 months of age under either normal or high fat/high sucrose diet. At different age points (6, 12, 18, 24 months), multiorgan functional phenotyping will be carried out to identify early signs of organ dysfunction and generate a large biological fluids/feces/organs biobank (100,000 samples). A comprehensive correlation between functional and biological phenotypes will be assessed to determine: 1) the early signs of biological aging and their relationship with chronological age; 2) the role of dietary and exercise interventions on accelerating or decelerating the rate of biological aging; and 3) novel targets for the promotion of healthy aging. All the functional and omics data, as well as the biobank generated in the framework of the INSPIRE cohort will be available to the aging scientific community. The present article describes the scientific background and the strategies employed for the design of the INSPIRE Mouse cohort.

Aging research articles

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770 mice!

Longitudinal Functional Study of Murine Aging: A Resource for Future Study Designs

Daniel S Evans, Monique N O'Leary, Ryan Murphy, Minna Schmidt, Kristin Koenig, Michael Presley, Brittany Garrett, Ha-Neui Kim, Li Han, Emmeline C Academia, Matt J Laye, Daniel Edgar, Christopher A Zambataro, Tracey Barhydt, Colleen M Dewey, Jarrott Mayfield, Joy Wilson, Silvestre Alavez, Mark Lucanic, Brian K Kennedy, Maria Almeida, Julie K Andersen, Pankaj Kapahi, Gordon J Lithgow, Simon Melov ... See fewer authors

Aging is characterized by systemic declines in tissue and organ functions. Interventions that slow these declines represent promising therapeutics to protect against age-related disease and improve the quality of life. In this study, several interventions associated with lifespan extension in invertebrates or improvement of age-related disease were tested in mouse models to determine if they were effective in slowing tissue aging in a broad spectrum of functional assays. Benzoxazole, which extends the lifespan of *Caenorhabditis elegans*, slowed age-related femoral bone loss in mice. Rates of change were established for clinically significant parameters in untreated mice, including kyphosis, blood glucose, body composition, activity, metabolic measures, and detailed parameters of skeletal aging in bone. These findings have implications for the study of preclinical physiological aging and therapies targeting aging. Finally, an online application was created that includes the calculated rates of change and that enables power and variance to be calculated for many clinically important metrics of aging with an emphasis on bone. This resource will help in future study designs employing novel interventions in aging mice. © 2021 The Authors. *JBMR Plus* published by Wiley Periodicals LLC. on behalf of American Society for Bone and Mineral Research.

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Background radiation impacts human longevity and cancer mortality: reconsidering the linear no-threshold paradigm

Elroei David, Marina Wolfson & Vadim E. Fraifeld

The current linear no-threshold paradigm assumes that any exposure to ionizing radiation carries some risk, thus every effort should be made to maintain the exposures as low as possible. We examined whether background radiation impacts human longevity and cancer mortality. Our data covered the entire US population of the 3139 US counties, encompassing over 320 million people. This is the first large-scale study which takes into account the two major sources of background radiation (terrestrial radiation and cosmic radiation), covering the entire US population. Here, we show that life expectancy, the most integrative index of population health, was approximately 2.5 years longer in people living in areas with a relatively high vs. low background radiation. (≥ 180 mrem/year and ≤ 100 mrem/year, respectively; $p < 0.005$; 95% confidence interval [CI]). This radiation-induced lifespan extension could to a great extent be associated with the decrease in cancer mortality rate observed for several common cancers (lung, pancreas and colon cancers for both genders, and brain and bladder cancers for males only; $p < 0.05$; 95% CI). Exposure to a high background radiation displays clear beneficial health effects in humans. These hormetic effects provide clear indications for re-considering the linear no-threshold paradigm, at least within the natural range of low-dose radiation.

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Protection of nuclear DNA by lifespan-extending compounds in the yeast *Saccharomyces cerevisiae*

Wei-Hsuan Su, Christelle E.T. Chan, Ting Lian, Mareena Biju, Ayaka Miura, Sarah A. Alkhafaji, Kelton K. Do, Brandon Latifi, Thi T. Nguyen, Samuel E. Schriner

DNA damage has been hypothesized to be a driving force of the aging process. At the same time, there exists multiple compounds that can extend lifespan in model organisms, such as yeast, worms, flies, and mice. One possible mechanism of action for these compounds is a protective effect against DNA damage. We investigated whether five of these lifespan-extending compounds, dinitrophenol, metformin, rapamycin, resveratrol, and spermidine, could protect nuclear DNA in the yeast *Saccharomyces cerevisiae* at the same doses under which they confer lifespan extension. We found that rapamycin and spermidine were able to decrease the spontaneous mutation rate at the *CAN1* locus, whereas dinitrophenol, metformin, and resveratrol were able to protect yeast against *CAN1* mutations induced by ethyl methanesulfonate (EMS). We also tested whether these compounds could enhance survival against EMS, ultraviolet (UV) light, or hydrogen peroxide (H_2O_2) insult. All five compounds conferred a protective effect against EMS, while metformin and spermidine protected yeast against UV light. Somewhat surprisingly, none of the compounds were able to afford a significant protection against H_2O_2, with spermidine dramatically sensitizing cells. We also examined the ability of these compounds to increase lifespan when growth-arrested by hydroxyurea; only spermidine was found to have a positive effect. Overall, our results suggest that lifespan-extending compounds may act in part by protecting nuclear DNA.

Uncovering molecular mechanisms of regulated cell death in the naked mole rat

Alexei Evdokimov[1, *], Alexei Popov[1, *], Elena Ryabchikova[1], Olga Koval[1], Svetlana Romanenko[2], Vladimir Trifonov[2], Irina Petruseva[1], Inna Lavrik[3, #], Olga Lavrik[1, #]

The naked mole rat (NMR), *Heterocephalus glaber,* is the longest-living rodent species, and is extraordinarily resistant to cancer and aging-related diseases. The molecular basis for these unique phenotypic traits of the NMR is under extensive research. However, the role of regulated cell death (RCD) in the longevity and the protection from cancer in the NMR is still largely unknown. RCD is a mechanism restricting the proliferation of damaged or premalignant cells, which counteracts aging and oncotransformation. In this study, DNA damage-induced cell death in NMR fibroblasts was investigated in comparison to RCD in fibroblasts from *Mus musculus*. The effects of methyl methanesulfonate, 5-fluorouracil, and etoposide in both cell types were examined using contemporary cell death analyses. Skin fibroblasts from *Heterocephalus glaber* were found to be more resistant to the action of DNA damaging agents compared to fibroblasts from *Mus musculus*. Strikingly, our results revealed that NMR cells also exhibit a limited apoptotic response and seem to undergo regulated necrosis. Taken together, this study provides new insights into the mechanisms of cell death in NMR expanding our understanding of longevity, and it paves the way towards the development of innovative therapeutic approaches.

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NAD+ boosting reduces age-associated amyloidosis and restores mitochondrial homeostasis in muscle

Mario Romani [1, 5], Vincenzo Sorrentino [1, 5], Chang-Myung Oh [1, 2, 3, 5], Hao Li [1], Tanes Imamura de Lima [1], Hongbo Zhang [1], Minho Shong [4], Johan Auwerx [1, 6]

Aging is characterized by loss of proteostasis and mitochondrial homeostasis. Here, we provide bioinformatic evidence of dysregulation of mitochondrial and proteostasis pathways in muscle aging and diseases. Moreover, we show accumulation of amyloid-like deposits and mitochondrial dysfunction during natural aging in the body wall muscle of *C. elegans*, in human primary myotubes, and in mouse skeletal muscle, partially phenocopying inclusion body myositis (IBM). Importantly, NAD+ homeostasis is critical to control age-associated muscle amyloidosis. Treatment of either aged N2 worms, a nematode model of amyloid-beta muscle proteotoxicity, human aged myotubes, or old mice with the NAD+ boosters nicotinamide riboside (NR) and olaparib (AZD) increases mitochondrial function and muscle homeostasis while attenuating amyloid accumulation. Hence, our data reveal that age-related amyloidosis is a contributing factor to mitochondrial dysfunction and that both are features of the aging muscle that can be ameliorated by NAD+ metabolism-enhancing approaches, warranting further clinical studies.

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IL-6 can singlehandedly drive many features of frailty in mice

Mladen Jergović, Heather L. Thompson, Christine M. Bradshaw, Sandip Ashok Sonar, Arveen Ashgar, Niels Mohty, Bellal Joseph, Mindy J. Fain, Kristan Cleveland, Rick G. Schnellman & Janko Nikolich-Žugich

GeroScience (2021) | Cite this article

111 Accesses | **10** Altmetric | Metrics

Abstract

Frailty is a geriatric syndrome characterized by age-related declines in function and reserve resulting in increased vulnerability to stressors. The most consistent laboratory finding in frail subjects is elevation of serum IL-6, but it is unclear whether IL-6 is a causal driver of frailty. Here, we characterize a new mouse model of inducible IL-6 expression (IL-$6^{TET\text{-}ON/+}$ mice) following administration of doxycycline (Dox) in food. In this model, IL-6 induction was Dox dose-dependent. The Dox dose that increased IL-6 levels to those observed in frail old mice directly led to an increase in frailty index, decrease in grip strength, and disrupted muscle mitochondrial homeostasis. Littermate mice lacking the knock-in construct failed to exhibit frailty after Dox feeding. Both naturally old mice and young Dox-induced IL-$6^{TET\text{-}ON/+}$ mice exhibited increased IL-6 levels in sera and spleen homogenates but not in other tissues. Moreover, Dox-induced IL-$6^{TET\text{-}ON/+}$ mice exhibited selective elevation in IL-6 but not in other cytokines. Finally, bone marrow chimera and splenectomy experiments demonstrated that non-hematopoietic cells are the key source of IL-6 in our model. We conclude that elevated IL-6 serum levels directly drive age-related frailty, possibly via mitochondrial mechanisms.

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Respiratory Muscle Weakness as a Risk Factor for Pneumonia in Older People

Tatsuma Okazaki [1 2], Yoshimi Suzukamo [3], Midori Miyatake [3], Riyo Komatsu [4], Masahiro Yaekashiwa [5], Mayumi Nihei [5], Shinichi Izumi [3 6 7], Takae Ebihara [8]

Affiliations + expand

PMID: 33621975 DOI: 10.1159/000514007

Abstract

Introduction: The respiratory muscle strength regulates the effectiveness of coughing, which clears the airways and protects people from pneumonia. Sarcopenia is an aging-related loss of muscle mass and function, the worsening of which is associated with malnutrition. The loss of respiratory and swallowing muscle strength occurs with aging, but its effect on pneumonia is unclear. This study aimed to determine the risks of respiratory muscle weakness on the onset and relapse of pneumonia in older people in conjunction with other muscle-related factors such as malnutrition.

Methods: We conducted a longitudinal study with 47 pneumonia inpatients and 35 non-pneumonia controls aged 70 years and older. We evaluated the strength of respiratory and swallowing muscles, muscle mass, and malnutrition (assessed by serum albumin levels and somatic fat) during admission and confirmed pneumonia relapse within 6 months. The maximal inspiratory and expiratory pressures determined the respiratory muscle strength. Swallowing muscle strength was evaluated by tongue pressure. Bioelectrical impedance analysis was used to evaluate the muscle and fat mass.

Results: The respiratory muscle strength, body trunk muscle mass, serum albumin level, somatic fat mass, and tongue pressure were significantly lower in pneumonia patients than in controls. Risk factors for the onset of pneumonia were low inspiratory respiratory muscle strength (odds ratio [OR], 6.85; 95% confidence interval [CI], 1.56-30.11), low body trunk muscle mass divided by height2 (OR, 6.86; 95% CI, 1.49-31.65), and low serum albumin level (OR, 5.46; 95% CI, 1.51-19.79). For the relapse of pneumonia, low somatic fat mass divided by height2 was a risk factor (OR, 20.10; 95% CI, 2.10-192.42).

Discussion/conclusions: Respiratory muscle weakness, lower body trunk muscle mass, and malnutrition were risk factors for the onset of pneumonia in older people. For the relapse of pneumonia, malnutrition was a risk factor.

Keywords: Aged people; Muscle strength; Pneumonia; Respiratory muscles; Sarcopenia.

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Genome-wide meta-analysis of muscle weakness identifies 15 susceptibility loci in older men and women

Low muscle strength is an important heritable indicator of poor health linked to morbidity and mortality in older people. In a genome-wide association study meta-analysis of 256,523 Europeans aged 60 years and over from 22 cohorts we identify 15 loci associated with muscle weakness (European Working Group on Sarcopenia in Older People definition: n = 48,596 cases, 18.9% of total), including 12 loci not implicated in previous analyses of continuous measures of grip strength. Loci include genes reportedly involved in autoimmune disease (*HLA-DQA1* $p = 4 \times 10^{-17}$), arthritis (*GDF5* $p = 4 \times 10^{-13}$), cell cycle control and cancer protection, regulation of transcription, and others involved in the development and maintenance of the musculoskeletal system. Using Mendelian randomization we report possible overlapping causal pathways, including diabetes susceptibility, haematological parameters, and the immune system. We conclude that muscle weakness in older adults has distinct mechanisms from continuous strength, including several pathways considered to be hallmarks of ageing.

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Protein signatures of centenarians and their offspring suggest centenarians age slower than other humans

Paola Sebastiani, Anthony Federico, Melody Morris, Anastasia Gurinovich, Toshiko Tanaka, Kevin B. Chandler, Stacy L. Andersen, Gerald Denis, Catherine E. Costello, Luigi Ferrucci, Lori Jennings, David J. Glass, Stefano Monti, Thomas T. Perls ... See fewer authors

Using samples from the New England Centenarian Study (NECS), we sought to characterize the serum proteome of 77 centenarians, 82 centenarians' offspring, and 65 age-matched controls of the offspring (mean ages: 105, 80, and 79 years). We identified 1312 proteins that significantly differ between centenarians and their offspring and controls (FDR < 1%), and two different protein signatures that predict longer survival in centenarians and in younger people. By comparing the centenarian signature with 2 independent proteomic studies of aging, we replicated the association of 484 proteins of aging and we identified two serum protein signatures that are specific of extreme old age. The data suggest that centenarians acquire similar aging signatures as seen in younger cohorts that have short survival periods, suggesting that they do not escape normal aging markers, but rather acquire them much later than usual. For example, centenarian signatures are significantly enriched for senescence-associated secretory phenotypes, consistent with those seen with younger aged individuals, and from this finding, we provide a new list of serum proteins that can be used to measure cellular senescence. Protein co-expression network analysis suggests that a small number of biological drivers may regulate aging and extreme longevity, and that changes in gene regulation may be important to reach extreme old age. This centenarian study thus provides additional signatures that can be used to measure aging and provides specific circulating biomarkers of healthy aging and longevity, suggesting potential mechanisms that could help prolong health and support longevity.

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Ageing transcriptome meta-analysis reveals similarities and differences between key mammalian tissues

Daniel Palmer[1,3,*], Fabio Fabris[2,*], Aoife Doherty[1], Alex A. Freitas[2], João Pedro de Magalhães[1]

By combining transcriptomic data with other data sources, inferences can be made about functional changes during ageing. Thus, we conducted a meta-analysis on 127 publicly available microarray and RNA-Seq datasets from mice, rats and humans, identifying a transcriptomic signature of ageing across species and tissues. Analyses on subsets of these datasets produced transcriptomic signatures of ageing for brain, heart and muscle. We then applied enrichment analysis and machine learning to functionally describe these signatures, revealing overexpression of immune and stress response genes and underexpression of metabolic and developmental genes. Further analyses revealed little overlap between genes differentially expressed with age in different tissues, despite ageing differentially expressed genes typically being widely expressed across tissues. Additionally we show that the ageing gene expression signatures (particularly the overexpressed signatures) of the whole meta-analysis, brain and muscle tend to include genes that are central in protein-protein interaction networks. We also show that genes underexpressed with age in the brain are highly central in a co-expression network, suggesting that underexpression of these genes may have broad phenotypic consequences. In sum, we show numerous functional similarities between the ageing transcriptomes of these important tissues, along with unique network properties of genes differentially expressed with age in both a protein-protein interaction and co-expression networks.

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PREPRINT

Integration of differential gene expression with weighted gene correlation network analysis identifies genes whose expression is remodeled throughout physiological aging in mouse tissues

Gene expression alterations occur in all mouse tissues during aging, but recent works highlight minor rather than major dysregulation amplitude for most genes, questioning whether differentially expressed genes on their own provide deep insight into aging biology. To clarify this issue, we have combined differential gene expression with weighted gene correlation network analysis (WGCNA) to identify expression signatures accounting for the pairwise relations between gene expression profiles and the cumulative effect of genes with small fold- changes during aging in the brain, heart, liver, skeletal muscle, and pancreas of C57BL/6 mice. Functional enrichment analysis of the overlap of genes identified in both approaches showed that immunity-related responses, mitochondrial energy metabolism, tissue regeneration and detoxification are prominently altered in the brain, heart, muscle, and liver, respectively, reflecting an age-related global loss of tissue function. While data showed little overlap among the age-dysregulated genes between tissues, aging triggered common biological processes in distinct tissues, particularly proteostasis-related pathways, which we highlight as important features of murine tissue physiological aging.

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Transcriptomic profiling of long- and short-lived mutant mice implicates mitochondrial metabolism in ageing and shows signatures of normal ageing in progeroid mice

Matias Fuentealba [a, b], Daniel K. Fabian [a, b], Handan Melike Dönertaş [b], Janet M. Thornton [b], Linda Partridge [a, c]

Genetically modified mouse models of ageing are the living proof that lifespan and healthspan can be lengthened or shortened, and provide a powerful context in which to unravel the molecular mechanisms at work. In this study, we analysed and compared gene expression data from 10 long-lived and 8 short-lived mouse models of ageing. Transcriptome-wide correlation analysis revealed that mutations with equivalent effects on lifespan induce more similar transcriptomic changes, especially if they target the same pathway. Using functional enrichment analysis, we identified 58 gene sets with consistent changes in long- and short-lived mice, 55 of which were up-regulated in long-lived mice and down-regulated in short-lived mice. Half of these sets represented genes involved in energy and lipid metabolism, among which *Ppargc1a*, *Mif*, *Aldh5a1* and *Idh1* were frequently observed. Based on the gene sets with consistent changes, and also the whole transcriptome, the gene expression changes during normal ageing resembled the transcriptome of short-lived models, suggesting that accelerated ageing models reproduce partially the molecular changes of ageing. Finally, we identified new genetic interventions that may ameliorate ageing, by comparing the transcriptomes of 51 mouse mutants not previously associated with ageing to expression signatures of long- and short-lived mice and ageing-related changes.

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Tissue-Specific Landscape of Metabolic Dysregulation during Ageing

Fangrong Zhang [1], Jakob Kerbl-Knapp [1], Alena Akhmetshina [1], Melanie Korbelius [1], Katharina Barbara Kuentzel [1], Nemanja Vujić [1], Gerd Hörl [2], Margret Paar [2], Dagmar Kratky [1 3], Ernst Steyrer [1], Tobias Madl [1 3]

Affiliations + expand

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Free PMC article

Abstract

The dysregulation of cellular metabolism is a hallmark of ageing. To understand the metabolic changes that occur as a consequence of the ageing process and to find biomarkers for age-related diseases, we conducted metabolomic analyses of the brain, heart, kidney, liver, lung and spleen in young (9-10 weeks) and old (96-104 weeks) wild-type mice [mixed genetic background of 129/J and C57BL/6] using NMR spectroscopy. We found differences in the metabolic fingerprints of all tissues and distinguished several metabolites to be altered in most tissues, suggesting that they may be universal biomarkers of ageing. In addition, we found distinct tissue-clustered sets of metabolites throughout the organism. The associated metabolic changes may reveal novel therapeutic targets for the treatment of ageing and age-related diseases. Moreover, the identified metabolite biomarkers could provide a sensitive molecular read-out to determine the age of biologic tissues and organs and to validate the effectiveness and potential off-target effects of senolytic drug candidates on both a systemic and tissue-specific level.

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PREPRINT

Metabolomics of aging in primary fibroblasts from small and large breed dogs

Paul S. Brookes, Ana G. Jimenez

Among several animal groups (eutherian mammals, birds, reptiles) lifespan positively correlates with body mass over several orders of magnitude. Contradicting this pattern are domesticated dogs, with small dog breeds exhibiting significantly longer lifespans than large dog breeds. The underlying mechanisms of differing aging rates across body masses are unclear, but it is generally agreed that metabolism is a significant regulator of the aging process. Herein, we performed a targeted metabolomics analysis on primary fibroblasts isolated from small and large breed young and old dogs. Regardless of size, older dogs exhibited lower glutathione and ATP, consistent with a role for oxidative stress and bioenergetic decline in aging. Furthermore, several size-specific metabolic patterns were observed with aging, including: (i) An apparent defect in the lower half of glycolysis in large old dogs at the level of pyruvate kinase. (ii) Increased glutamine anaplerosis into the TCA cycle in large old dogs. (iii) A potential defect in co-enzyme A biosynthesis in large old dogs. (iv) Low nucleotide levels in small young dogs that corrected with age. (v) An age dependent increase in carnitine in small dogs that was absent in large dogs. Overall, these data support the hypothesis that alterations in metabolism may underlie the different lifespans of small versus large breed dogs, and further work in this area may afford potential therapeutic strategies to improve the lifespan of large dogs.

Distinct organization of adaptive immunity in the long-lived rodent *Spalax galili*

A balanced immune response is a cornerstone of healthy aging. Here, we uncover distinctive features of the long-lived blind mole-rat (*Spalax* spp.) adaptive immune system, relative to humans and mice. The T-cell repertoire remains diverse throughout the *Spalax* lifespan, suggesting a paucity of large long-lived clones of effector-memory T cells. Expression of master transcription factors of T-cell differentiation, as well as checkpoint and cytotoxicity genes, remains low as *Spalax* ages. The thymus shrinks as in mice and humans, while interleukin-7 and interleukin-7 receptor expression remains high, potentially reflecting the sustained homeostasis of naive T cells. With aging, immunoglobulin hypermutation level does not increase and the immunoglobulin-M repertoire remains diverse, suggesting shorter B-cell memory and sustained homeostasis of innate-like B cells. The *Spalax* adaptive immune system thus appears biased towards sustained functional and receptor diversity over specialized, long-lived effector-memory clones—a unique organizational strategy that potentially underlies this animal's extraordinary longevity and healthy aging.

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Translation elongation rate varies among organs and decreases with age

Maxim V Gerashchenko, Zalan Peterfi, Sun Hee Yim, Vadim N Gladyshev

There has been a surge of interest towards targeting protein synthesis to treat diseases and extend lifespan. Despite the progress, few options are available to assess translation in live animals, as their complexity limits the repertoire of experimental tools to monitor and manipulate processes within organs and individual cells. It this study, we developed a labeling-free method for measuring organ- and cell-type-specific translation elongation rates *in vivo*. It is based on time-resolved delivery of translation initiation and elongation inhibitors in live animals followed by ribosome profiling. It also reports translation initiation sites in an organ-specific manner. Using this method, we found that the elongation rates differ more than 50% among mouse organs and determined them to be 6.8, 5.0 and 4.3 amino acids per second for liver, kidney, and skeletal muscle, respectively. We further found that the elongation rate is reduced by 20% between young adulthood and mid-life. Thus, translation, a major metabolic process in cells, is tightly regulated at the level of elongation of nascent polypeptide chains.

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Breakdown of supersaturation barrier links protein folding to amyloid formation

The thermodynamic hypothesis of protein folding, known as the "Anfinsen's dogma" states that the native structure of a protein represents a free energy minimum determined by the amino acid sequence. However, inconsistent with the Anfinsen's dogma, globular proteins can misfold to form amyloid fibrils, which are ordered aggregates associated with diseases such as Alzheimer's and Parkinson's diseases. Here, we present a general concept for the link between folding and misfolding. We tested the accessibility of the amyloid state for various proteins upon heating and agitation. Many of them showed Anfinsen-like reversible unfolding upon heating, but formed amyloid fibrils upon agitation at high temperatures. We show that folding and amyloid formation are separated by the supersaturation barrier of a protein. Its breakdown is required to shift the protein to the amyloid pathway. Thus, the breakdown of supersaturation links the Anfinsen's intramolecular folding universe and the intermolecular misfolding universe.

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Blood-derived mitochondrial DNA copy number is associated with gene expression across multiple tissues and is predictive for incident neurodegenerative disease

Stephanie Y. Yang[1], Christina A. Castellani[1], Ryan J. Longchamps[1], Vamsee K. Pillalamarri[1], Brian O'Rourke[2], Eliseo Guallar[3] and Dan E. Arking[1,2]

Mitochondrial DNA copy number (mtDNA-CN) is a proxy for mitochondrial function and is associated with aging-related diseases. However, it is unclear how mtDNA-CN measured in blood can reflect diseases that primarily manifest in other tissues. Using the Genotype-Tissue Expression Project, we interrogated relationships between mtDNA-CN measured in whole blood and gene expression from whole blood and 47 additional tissues in 419 individuals. mtDNA-CN was significantly associated with expression of 700 genes in whole blood, including nuclear genes required for mtDNA replication. Significant enrichment was observed for splicing and ubiquitin-mediated proteolysis pathways, as well as target genes for the mitochondrial transcription factor NRF1. In nonblood tissues, there were more significantly associated genes than expected in 30 tissues, suggesting that global gene expression in those tissues is correlated with blood-derived mtDNA-CN. Neurodegenerative disease pathways were significantly associated in multiple tissues, and in an independent data set, the UK Biobank, we observed that higher mtDNA-CN was significantly associated with lower rates of both prevalent (OR = 0.89, CI = 0.83; 0.96) and incident neurodegenerative disease (HR = 0.95, 95% CI = 0.91;0.98). The observation that mtDNA-CN measured in blood is associated with gene expression in other tissues suggests that blood-derived mtDNA-CN can reflect metabolic health across multiple tissues. Identification of key pathways including splicing, RNA binding, and catalysis reinforces the importance of mitochondria in maintaining cellular homeostasis. Finally, validation of the role of mtDNA CN in neurodegenerative disease in a large independent cohort study solidifies the link between blood-derived mtDNA-CN, altered gene expression in multiple tissues, and aging-related disease.

C. elegans aging research

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BiT age: A transcriptome-based aging clock near the theoretical limit of accuracy

David H. Meyer, Björn Schumacher

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Abstract

Aging clocks dissociate biological from chronological age. The estimation of biological age is important for identifying gerontogenes and assessing environmental, nutritional, or therapeutic impacts on the aging process. Recently, methylation markers were shown to allow estimation of biological age based on age-dependent somatic epigenetic alterations. However, DNA methylation is absent in some species such as *Caenorhabditis elegans* and it remains unclear whether and how the epigenetic clocks affect gene expression. Aging clocks based on transcriptomes have suffered from considerable variation in the data and relatively low accuracy. Here, we devised an approach that uses temporal scaling and binarization of *C. elegans* transcriptomes to define a gene set that predicts biological age with an accuracy that is close to the theoretical limit. Our model accurately predicts the longevity effects of diverse strains, treatments, and conditions. The involved genes support a role of specific transcription factors as well as innate immunity and neuronal signaling in the regulation of the aging process. We show that this binarized transcriptomic aging (BiT age) clock can also be applied to human age prediction with high accuracy. The BiT age clock could therefore find wide application in genetic, nutritional, environmental, and therapeutic interventions in the aging process.

Elevated Trehalose Levels in *C. elegans daf-2* Mutants Increase Stress Resistance, Not Lifespan

by Madina Rasulova †, Aleksandra Zečić †, Jose Manuel Monje Moreno, Lieselot Vandemeulebroucke, Ineke Dhondt and Bart P. Braeckman *

The *C. elegans* insulin/IGF-1 (insulin-like growth factor 1) signaling mutant *daf-2* recapitulates the dauer metabolic signature—a shift towards lipid and carbohydrate accumulation—which may be linked to its longevity and stress resistance phenotypes. Trehalose, a disaccharide of glucose, is highly upregulated in *daf-2* mutants and it has been linked to proteome stabilization and protection against heat, cold, desiccation, and hypoxia. Earlier studies suggested that elevated trehalose levels can explain up to 43% of the lifespan extension observed in *daf-2* mutants. Here we demonstrate that trehalose accumulation is responsible for increased osmotolerance, and to some degree thermotolerance, rather than longevity in *daf-2* mutants. This indicates that particular stress resistance phenotypes can be uncoupled from longevity. View Full-Text

Keywords: Caenorhabditis elegans; lifespan; trehalose; trehalose 6-phosphate synthase; maltose; glucose; glycogen

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Mutation of *daf-2* extends lifespan via tissue-specific effectors that suppress distinct life-limiting pathologies

Yuan Zhao, Bruce Zhang, Ioan Marcu, Faria Athar, Hongyuan Wang, Evgeniy R. Galimov, Hannah Chapman, David Gems

In aging *Caenorhabditis elegans*, as in higher organisms, there is more than one cause of death. *C. elegans* exhibit early death with a swollen, infected pharynx (P death), and later death with pharyngeal atrophy (p death). Interventions that alter lifespan can differentially affect frequency and timing of each type of death, generating complex survival curve shapes. Here, we use mortality deconvolution analysis to investigate how reduction of insulin/IGF-1 signaling (IIS), which increases lifespan (the Age phenotype), affects different forms of death. All *daf-2* insulin/IGF-1 receptor mutants exhibit increased lifespan in the p subpopulation (p Age), while pleiotropic class 2 *daf-2* mutants show an additional marked reduction in P death frequency. The latter is promoted by pharyngeal expression of the IIS-regulated DAF-16 FOXO transcription factor, and at higher temperature by reduced pharyngeal pumping rate. Pharyngeal DAF-16 also promotes p Age in class 2 *daf-2* mutants, revealing a previously unknown role for the pharynx in the regulation of aging. Necropsy analysis of *daf-2* interactions with the *daf-12* steroid receptor implies that previously described opposing effects of *daf-12* on *daf-2* longevity are attributable to internal hatching of larvae, rather than complex interactions between insulin/IGF-1 and steroid signaling. These findings support the view that wild-type IIS acts through multiple distinct mechanisms which promote different life-limiting pathologies, each of which contribute to late-life mortality. This study further demonstrates the utility of mortality deconvolution analysis to better understand the genetics of lifespan.

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Global, cell non-autonomous gene regulation drives individual lifespan among isogenic *C. elegans*

Holly E Kinser, Matthew C Mosley, Isaac B Plutzer, Zachary Pincus

Across species, lifespan is highly variable among individuals within a population. Even genetically identical *Caenorhabditis elegans* reared in homogeneous environments are as variable in lifespan as outbred human populations. We hypothesized that persistent inter-individual differences in expression of key regulatory genes drives this lifespan variability. As a test, we examined the relationship between future lifespan and the expression of 22 microRNA promoter::GFP constructs. Surprisingly, expression of nearly half of these reporters, well before death, could effectively predict lifespan. This indicates that prospectively long- vs. short-lived individuals have highly divergent patterns of transgene expression and transcriptional regulation. The gene-regulatory processes reported on by two of the most lifespan-predictive transgenes do not require DAF-16, the FOXO transcription factor that is a principal effector of insulin/insulin-like growth factor (IGF-1) signaling. Last, we demonstrate a hierarchy of redundancy in lifespan-predictive ability among three transgenes expressed in distinct tissues, suggesting that they collectively report on an organism-wide, cell non-autonomous process that acts to set each individual's lifespan.

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Cost-free lifespan extension via optimization of gene expression in adulthood aligns with the developmental theory of ageing

Martin I. Lind[†] ✉, Hanne Carlsson[†], Elizabeth M. L. Duxbury, Edward Ivimey-Cook and Alexei A. Maklakov ✉

Ageing evolves because the force of selection on traits declines with age but the proximate causes of ageing are incompletely understood. The 'disposable soma' theory of ageing (DST) upholds that competitive resource allocation between reproduction and somatic maintenance underpins the evolution of ageing and lifespan. In contrast, the developmental theory of ageing (DTA) suggests that organismal senescence is caused by suboptimal gene expression in adulthood. While the DST predicts the trade-off between reproduction and lifespan, the DTA predicts that age-specific optimization of gene expression can increase lifespan without reproduction costs. Here we investigated the consequences for lifespan, reproduction, egg size and individual fitness of early-life, adulthood and post-reproductive onset of RNAi knockdown of five 'longevity' genes involved in key biological processes in *Caenorhabditis elegans*. Downregulation of these genes in adulthood and/or during post-reproductive period increases lifespan, while we found limited evidence for a link between impaired reproduction and extended lifespan. Our findings demonstrate that suboptimal gene expression in adulthood often contributes to reduced lifespan directly rather than through competitive resource allocation between reproduction and somatic maintenance. Therefore, age-specific optimization of gene expression in evolutionarily conserved signalling pathways that regulate organismal life histories can increase lifespan without fitness costs.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Longevity pharmacology comes of age

João Pedro de Magalhães [1, 2]

With a globally aging population, longevity is becoming the most promising market for the biotech industry. In animals, aging can be retarded and longevity extended, which, if translated to humans, would result in huge health benefits with remarkable commercial value. The potential to slow down human aging has led to a race to discover the most promising longevity drugs in animals and ultimately translate them to humans. Indeed, in recent years, there has been exponential growth in longevity drugs discovered in animal models. Investment in longevity biotech is also booming, and several clinical trials will soon shed light on which drugs extend healthy lives. Thus, the longevity pharmacology field promises to revolutionize the healthcare of a growing aging population.

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The goal of geroscience is life extension

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ABSTRACT

Although numerous drugs seemingly extend healthspan in mice, only a few extend lifespan in mice and only one does it consistently. Some of them, alone or in combination, can be used in humans, without further clinical trials.

Aging and rejuvenation - a modular epigenome model

Priscila Chiavellini[1] , Martina Canatelli-Mallat[1] , Marianne Lehmann[1] , Maria D. Gallardo[1] , Claudia B. Herenu[2] , Jose L. Cordeiro[3] , James Clement[4] , Rodolfo G. Goya[1]

The view of aging has evolved in parallel with the advances in biomedical sciences. Long considered as an irreversible process where interventions were only aimed at slowing down its progression, breakthrough discoveries like animal cloning and cell reprogramming have deeply changed our understanding of postnatal development, giving rise to the emerging view that the epigenome is the driver of aging. The idea was significantly strengthened by the converging discovery that DNA methylation (DNAm) at specific CpG sites could be used as a highly accurate biomarker of age defined by an algorithm known as the Horvath clock. It was at this point where epigenetic rejuvenation came into play as a strategy to reveal to what extent biological age can be set back by making the clock tick backwards. Initial evidence suggests that when the clock is forced to tick backwards *in vivo*, it is only able to drag the phenotype to a partially rejuvenated condition. In order to explain the results, a bimodular epigenome is proposed, where module A represents the DNAm clock component and module B the remainder of the epigenome. Epigenetic rejuvenation seems to hold the key to arresting or even reversing organismal aging.

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Review Article | Published: 28 January 2021

Biomolecular condensates at the nexus of cellular stress, protein aggregation disease and ageing

Simon Alberti & Anthony A. Hyman

Nature Reviews Molecular Cell Biology **22**, 196–213(2021) | Cite this article

Abstract

Biomolecular condensates are membraneless intracellular assemblies that often form via liquid–liquid phase separation and have the ability to concentrate biopolymers. Research over the past 10 years has revealed that condensates play fundamental roles in cellular organization and physiology, and our understanding of the molecular principles, components and forces underlying their formation has substantially increased. Condensate assembly is tightly regulated in the intracellular environment, and failure to control condensate properties, formation and dissolution can lead to protein misfolding and aggregation, which are often the cause of ageing-associated diseases. In this Review, we describe the mechanisms and regulation of condensate assembly and dissolution, highlight recent advances in understanding the role of biomolecular condensates in ageing and disease, and discuss how cellular stress, ageing-related loss of homeostasis and a decline in protein quality control may contribute to the formation of aberrant, disease-causing condensates. Our improved understanding of condensate pathology provides a promising path for the treatment of protein aggregation diseases.

Protein glycation – biomarkers of metabolic dysfunction and early-stage decline in health in the era of precision medicine

Naila Rabbani [a], Paul J. Thornalley [b]

Protein glycation provides a biomarker in widespread clinical use, glycated hemoglobin HbA_{1c} (A1C). It is a biomarker for diagnosis of diabetes and prediabetes and of medium-term glycemic control in patients with established diabetes. A1C is an early-stage glycation adduct of hemoglobin with glucose; a fructosamine derivative. Glucose is an amino group-directed glycating agent, modifying N-terminal and lysine sidechain amino groups. A similar fructosamine derivative of serum albumin, glycated albumin (GA), finds use as a biomarker of glycemic control, particularly where there is interference in use of A1C. Later stage adducts, advanced glycation endproducts (AGEs), are formed by the degradation of fructosamines and by the reaction of reactive dicarbonyl metabolites, such as methylglyoxal. Dicarbonyls are arginine-directed glycating agents forming mainly hydroimidazolone AGEs. Glucosepane and pentosidine, an intense fluorophore, are AGE covalent crosslinks. Cellular proteolysis of glycated proteins forms glycated amino acids, which are released into plasma and excreted in urine. Development of diagnostic algorithms by artificial intelligence machine learning is enhancing the applications of glycation biomarkers. Investigational glycation biomarkers are in development for: (i) healthy aging; (ii) risk prediction of vascular complications of diabetes; (iii) diagnosis of autism; and (iv) diagnosis and classification of early-stage arthritis. Protein glycation biomarkers are influenced by heritability, aging, decline in metabolic, vascular, renal and skeletal health, and other factors. They are applicable to populations of differing ethnicities, bridging the gap between genotype and phenotype. They are thereby likely to find continued and expanding clinical use, including in the current era of developing precision medicine, reporting on multiple pathogenic processes and supporting a precision medicine approach.

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Hallmarks and detection techniques of cellular senescence and cellular ageing in immune cells

Dingxi Zhou, Mariana Borsa, Anna Katharina Simon

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Abstract

The ageing of the global population brings about unprecedented challenges. Chronic age-related diseases in an increasing number of people represent an enormous burden for health and social care. The immune system deteriorates during ageing and contributes to many of these age-associated diseases due to its pivotal role in pathogen clearance, tissue homeostasis and maintenance. Moreover, in order to develop treatments for COVID-19, we urgently need to acquire more knowledge about the aged immune system, as older adults are disproportionally and more severely affected. Changes with age lead to impaired responses to infections, malignancies and vaccination, and are accompanied by chronic, low-degree inflammation, which together is termed immunosenescence. However, the molecular and cellular mechanisms that underlie immunosenescence, termed immune cell senescence, are mostly unknown. Cellular senescence, characterised by an irreversible cell cycle arrest, is thought to be the cause of tissue and organismal ageing. Thus, better understanding of cellular senescence in immune populations at single-cell level may provide us with insight into how immune cell senescence develops over the life time of an individual. In this review, we will briefly introduce the phenotypic characterisation of aged innate and adaptive immune cells, which also contributes to overall immunosenescence, including subsets and function. Next, we will focus on the different hallmarks of cellular senescence and cellular ageing, and the detection techniques most suitable for immune cells. Applying these techniques will deepen our understanding of immune cell senescence and to discover potential druggable pathways, which can be modulated to reverse immune ageing.

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Cell-to-cell variation in gene expression and the aging process

Alexander R. Mendenhall, George M. Martin, Matt Kaeberlein & Rozalyn M. Anderson

There is tremendous variation in biological traits, and much of it is not accounted for by variation in DNA sequence, including human diseases and lifespan. Emerging evidence points to differences in the execution of the genetic program as a key source of variation, be it stochastic variation or programmed variation. Here we discuss variation in gene expression as an intrinsic property and how it could contribute to variation in traits, including the rate of aging. The review is divided into sections describing the historical context and evidence to date for nongenetic variation, the different approaches that may be used to detect nongenetic variation, and recent findings showing that the amount of variation in gene expression can be both genetically programmed and epigenetically controlled. Finally, we present evidence that changes in cell-to-cell variation in gene expression emerge as part of the aging process and may be linked to disease vulnerability as a function of age. These emerging concepts are likely to be important across the spectrum of biomedical research and may well underpin what we understand as biological aging.

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Gene–Environment interactions and stochastic variations in the Gero–Exposome

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Affiliations + expand

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Abstract

The limited heritability of human lifespans suggests an important role for gene-environment (GxE) interactions across the lifespan (T), from gametes to geronts. Multi-level GxExT interactions of aging phenotypes are conceptualized in the Gero-Exposome as Exogenous and Endogenous domains. Stochastic variations in the Endogenous domain contribute to the diversity of aging phenotypes, shown for the diversity of inbred Caenorhabditis elegans lifespans in the same culture environment, and for variegated gene expression of somatic cells in nematodes and mammals. These phenotypic complexities can be analyzed as three-way interactions of gene, environment, and stochastic variations, the Tripartite Phenotype of Aging. Single cell analyses provide tools to explore this broadening frontier of biogerontology.

Keywords: APOE; Air pollution; Exposome; Gerogens; Sex; Tripartite Phenotype of Aging.

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Principles of the Molecular and Cellular Mechanisms of Aging

Paulo F.L. da Silva • Björn Schumacher

Aging can be defined as a state of progressive functional decline accompanied by an increase in mortality. Time-dependent accumulation of cellular damage, namely lesions and mutations in the DNA and misfolded proteins, impair organellar and cellular function. Ensuing cell fate alterations lead to the accumulation of dysfunctional cells and hamper homeostatic processes, thus limiting regenerative potential; trigger low-grade inflammation; and alter intercellular and intertissue communication. The accumulation of molecular damage together with modifications in the epigenetic landscape, dysregulation of gene expression, and altered endocrine communication, drive the aging process and establish age as the main risk factor for age-associated diseases and multimorbidity.

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Aging biomarkers and the brain

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Abstract

Quantifying biological aging is critical for understanding why aging is the primary driver of morbidity and mortality and for assessing novel therapies to counter pathological aging. In the past decade, many biomarkers relevant to brain aging have been developed using various data types and modeling techniques. Aging involves numerous interconnected processes, and thus many complementary biomarkers are needed, each capturing a different slice of aging biology. Here we present a hierarchical framework highlighting how these biomarkers are related to each other and the underlying biological processes. We review those measures most studied in the context of brain aging: epigenetic clocks, proteomic clocks, and neuroimaging age predictors. Many studies have linked these biomarkers to cognition, mental health, brain structure, and pathology during aging. We also delve into the challenges and complexities in interpreting these biomarkers and suggest areas for further innovation. Ultimately, a robust mechanistic understanding of these biomarkers will be needed to effectively intervene in the aging process to prevent and treat age-related disease.

OTHER RESEARCH & REVIEWS

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A Decade of FDA-Approved Drugs (2010–2019): Trends and Future Directions

Dean G. Brown* and Heike J. Wobst*

A total of 378 novel drugs and 27 biosimilars approved by the U.S. Food and Drug Administration (FDA) between 2010 and 2019 were evaluated according to approval numbers by year, therapeutic areas, modalities, route of administration, first-in-class designation, approval times, and expedited review categories. From this review, oncology remains the top therapy area (25%), followed by infection (15%) and central nervous system disorders (11%). Regulatory incentives have been effective as evidenced by an increase in orphan drugs as well as antibacterial drugs approved under the GAIN act. Clinical development times may be increasing, perhaps as a result of the increase in orphan drug indications. Small molecules continue to mostly adhere to "Rule of 5" (Ro5) parameters, but innovation in new modalities is rapidly progressing with approvals for antisense oligonucleotides (ASO), small-interfering RNA (siRNAs), and antibody-directed conjugates (ADCs). Finally, novel targets and scientific breakthroughs that address areas of unmet clinical need are discussed in detail.