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Scientific News
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Sven Bulterijs

Business/Conferences/ General news

The 1% gift to humanity: The Human Genome Project II

Data generation goals

- Sequence the genomes of > 1% of the world population with maximal genetic representation (80 M individuals from > 100 countries);
- Contribute 50,000 telomere-to-telomere (T2T) phased diploid reference genomes from > 20 countries to a Human Pangenome Project and expand the pangenome reference to cover most diversity;
- Define standards and methodologies for integrating multi-omics into precision medicine, and;
- Create large multi-omics cohorts totaling > 0.1% of the world population from diverse populations and collect their multi-omics data (8 M individuals from > 10 countries).

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Aging research articles

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Targeted partial reprogramming of age-associated cell states improves markers of health in mouse models of aging

SANJEEB KUMAR SAHU, PRADEEP REDDY, JINLONG LU, YANJIAO SHAO, CHAO WANG, MAKO TSUJI, ESTRELLA NUÑEZ DELICADO, CONCEPCION RODRIGUEZ ESTEBAN, AND JUAN CARLOS IZPISUA BELMONTE Authors Info & Affiliations

Aging is a complex multifactorial process associated with epigenome dysregulation, increased cellular senescence, and decreased rejuvenation capacity. Short-term cyclic expression of *octamer-binding transcription factor 4* (*Oct4*), *sex-determining region Y-box 2* (*Sox2*), *Kruppel-like factor 4* (*Klf4*), and *cellular myelocytomatosis oncogene* (*cMyc*) (*OSKM*) in wild-type mice improves health but fails to distinguish cell states, posing risks to healthy cells. Here, we delivered a single dose of adeno-associated viruses (AAVs) harboring *OSK* under the control of the *cyclin-dependent kinase inhibitor 2a* (*Cdkn2a*) promoter to specifically partially reprogram aged and stressed cells in a mouse model of Hutchinson-Gilford progeria syndrome (HGPS). Mice showed reduced expression of proinflammatory cytokines and extended life spans upon aged cell–specific *OSK* expression. The bone marrow and spleen, in particular, showed pronounced gene expression changes, and partial reprogramming in aged HGPS mice led to a shift in the cellular composition of the hematopoietic stem cell compartment toward that of young mice. Administration of AAVs carrying *Cdkn2a-OSK* to naturally aged wild-type mice also delayed aging phenotypes and extended life spans without altering the incidence of tumor development. Furthermore, intradermal injection of AAVs carrying *Cdkn2a-OSK* led to improved wound healing in aged wild-type mice. Expression of *CDKN2A-OSK* in aging or stressed human primary fibroblasts led to reduced expression of inflammation-related genes but did not alter the expression of cell cycle–related genes. This targeted partial reprogramming approach may therefore facilitate the development of strategies to improve health and life span and enhance resilience in the elderly.

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PREPRINT

Modulating DNA Polα Enhances Cell Reprogramming Across Species

Rajesh Ranjan, Binbin Ma, Ryan J. Gleason, Yijun Liao, Yingshan Bi, Brendon E. M. Davis, Guanghui Yang, Maggie Clark, Vikrant Mahajan, Madison Condon, Nichole A. Broderick, Xin Chen

As a fundamental biological process, DNA replication ensures the accurate copying of genetic information. However, the impact of this process on cellular plasticity in multicellular organisms remains elusive. Here, we find that reducing the level or activity of a replication component, DNA Polymerase α (Polα), facilitates cell reprogramming in diverse stem cell systems across species. In *Drosophila* male and female germline stem cell lineages, reducing Polα levels using heterozygotes significantly enhances fertility of both sexes, promoting reproductivity during aging without compromising their longevity. Consistently, in *C. elegans* the *pola* heterozygous hermaphrodites exhibit increased fertility without a reduction in lifespan, suggesting that this phenomenon is conserved. Moreover, in male germline and female intestinal stem cell lineages of *Drosophila*, *polα* heterozygotes exhibit increased resistance to tissue damage caused by genetic ablation or pathogen infection, leading to enhanced regeneration and improved survival during post-injury recovery, respectively. Additionally, fine tuning of an inhibitor to modulate Polα activity significantly enhances the efficiency of reprogramming human embryonic fibroblasts into induced pluripotent cells. Together, these findings unveil novel roles of a DNA replication component in regulating cellular reprogramming potential, and thus hold promise for promoting tissue health, facilitating post-injury rehabilitation, and enhancing healthspan.

Identifying specific functional roles for senescence across cell types

Huan Zhao [1,10] · Zixin Liu [1,10] · Hui Chen [1,10] … · Xin Ma [8] · Jan S. Tchorz [9] · Bin Zhou [1,2,3,11] … Show more

Cellular senescence plays critical roles in aging, regeneration, and disease; yet, the ability to discern its contributions across various cell types to these biological processes remains limited. In this study, we generated an *in vivo* genetic toolbox consisting of three $p16^{Ink4a}$-related intersectional genetic systems, enabling pulse-chase tracing (Sn-pTracer), Cre-based tracing and ablation (Sn-cTracer), and gene manipulation combined with tracing (Sn-gTracer) of defined $p16^{Ink4a+}$ cell types. Using liver injury and repair as an example, we found that macrophages and endothelial cells (ECs) represent distinct senescent cell populations with different fates and functions during liver fibrosis and repair. Notably, clearance of $p16^{Ink4a+}$ macrophages significantly mitigates hepatocellular damage, whereas eliminating $p16^{Ink4a+}$ ECs aggravates liver injury. Additionally, targeted reprogramming of $p16^{Ink4a+}$ ECs through *Kdr* overexpression markedly reduces liver fibrosis. This study illuminates the functional diversity of $p16^{Ink4a+}$ cells and offers insights for developing cell-type-specific senolytic therapies in the future.

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Elimination of physiological senescent cutaneous cells in a novel p16-dependent senolytic mouse model impacts lipid metabolism in skin aging

Yuma Sugiyama, Yoichiro Kawabe, Tanenobu Harada, Yu Aoki, Keiko Tsuji, Daijiro Sugiyama, Mitsuo Maruyama

The evidence of the correlation between cellular senescence and aging has increased in research with animal models. These models have been intentionally generated to target and regulate cellular senescent cells with the promoter activity of $p16^{Ink4a}$ or $p19^{Arf}$, genes that are highly expressed in aging cells. However, the senolytic efficiency in various organs and cells from these models represents unexpected variation and diversity in some cases. We have generated a novel knock-in model, *p16*tdT-hDTR mice, which possess tdTomato and human diphtheria toxin receptor (hDTR) downstream of *Cdkn2a*, an endogenous $p16^{Ink4a}$ gene. We successfully demonstrated that p16-derived tdTomato and hDTR expressions are observed in these mouse embryo fibroblasts and following treatment with diphtheria toxin (DT) eliminates those cells. Furthermore, we demonstrated the efficacy of eliminating p16-positive cells in vivo, and also observed a tendency to decrease their cutaneous SA-β-gal activity after subcutaneous DT injection into *p16*tdT-hDTR mice. In particular, comprehensive gene expression analysis in skin revealed that upregulated genes related to lipid metabolisms with aging exhibited remarkable expressions under the senolysis. These results clearly unveiled p16-positive senescent cells contribute to age-related changes in skin.

Analysis of the senescence-associated cell surfaceome reveals potential senotherapeutic targets

Yushuang Deng, Ting Liu, Enzo Scifo, Tao Li, Kan Xie, Bernd Taschler, Sarah Morsy, Kristina Schaaf, Armin Ehninger, Daniele Bano, Dan Ehninger

The accumulation of senescent cells is thought to play a crucial role in aging-associated physiological decline and the pathogenesis of various age-related pathologies. Targeting senescence-associated cell surface molecules through immunotherapy emerges as a promising avenue for the selective removal of these cells. Despite its potential, a thorough characterization of senescence-specific surface proteins remains to be achieved. Our study addresses this gap by conducting an extensive analysis of the cell surface proteome, or "surfaceome", in senescent cells, spanning various senescence induction regimes and encompassing both murine and human cell types. Utilizing quantitative mass spectrometry, we investigated enriched cell surface proteins across eight distinct models of senescence. Our results uncover significant changes in surfaceome expression profiles during senescence, highlighting extensive modifications in cell mechanics and extracellular matrix remodeling. Our research also reveals substantive heterogeneity of senescence, predominantly influenced by cell type and senescence inducer. A key discovery of our study is the identification of four unique cell surface proteins with extracellular epitopes. These proteins are expressed in senescent cells, absent or present at low levels in their proliferating counterparts, and notably upregulated in tissues from aged mice and an Alzheimer's disease mouse model. These proteins stand out as promising candidates for senotherapeutic targeting, offering potential pathways for the detection and strategic targeting of senescent cell populations in aging and age-related diseases.

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PREPRINT

Structural and mechanistic diversity in p53-mediated regulation of organismal longevity across taxonomical orders

Romani Osbourne, Kelly M. Thayer

The accumulation of senescent cells induces several aging phenotypes, and the p53 tumor suppressor protein regulates one of the two known cellular senescence pathways. p53's regulation of senescence is however not clear. For example, p53 deficiency in some mice has been shown to rescue premature aging while others display significant aging phenotype when p53-deficient. This study seeks to elucidate, structurally and mechanistically, p53's roles in longevity. Through a relative evolutionary scoring (RES) algorithm, we quantify the level of evolutionary change in the residues of p53 across organisms of varying average lifespans in six taxonomic orders. Secondly, we used PEPPI to assess the likelihood of interaction between p53–or p53-linked proteins–and known senescence-regulating proteins across organisms in the orders Primates and Perciformes. Our RES algorithm found variations in the alignments within and across orders, suggesting that mechanisms of p53-mediated regulation of longevity may vary. PEPPI results suggest that longer-lived species may have evolved to regulate induction and inhibition of cellular senescence better than their shorter-lived counterparts. With experimental verification, these predictions could help elucidate the mechanisms of p53-mediated cellular senescence, ultimately clarifying our understanding of p53's connection to aging in a multiple-species context.

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PREPRINT

Deep learning reveals diverging effects of altitude on aging

Amanuel Abraha Teklu, Indra Heckenbach, Michael Angelo Petr, Daniela Bakula, Guido Keijzers, Morten Scheibye-Knudsen

Aging is influenced by a complex interplay of multifarious factors, including an individual's genetics, environment, and lifestyle. Notably, high altitude may impact aging and age-related diseases through exposures such as hypoxia and ultraviolet radiation. To investigate this, we mined summary exposure value as a measure of risk exposure levels, and disability-adjusted life years (DALYs) as a measure of disease burden from the Global Health Data Exchange (GHDx) for each subnational region of Ethiopia, a country with considerable differences in the living altitude. We conducted a cross-sectional clinical trial involving 227 highland and 202 lowland dwellers from the Tigray region in Northern Ethiopia to gain a general insight into the biological aging at high altitudes. Notably, we observed significantly lower risk exposure rates and a reduced disease burden in higher-altitude regions of Ethiopia. When assessing biological aging using facial photographs, we found a faster rate of aging with increasing elevation, likely due to greater UV exposure. Conversely, analysis of nuclear morphologies of peripheral blood mononuclear cells in blood smears (PBMCs) with five different senescence predictors revealed a significant decrease in DNA damage-induced senescence in both monocytes and lymphocytes with increasing elevation. Overall, our findings suggest that disease and DNA damage-induced senescence decreases with altitude in agreement with the idea that oxidative stress may drive aging.

CheekAge, a next-generation epigenetic buccal clock, is predictive of mortality in human blood

While earlier first-generation epigenetic aging clocks were trained to estimate chronological age as accurately as possible, more recent next-generation clocks incorporate DNA methylation information more pertinent to health, lifestyle, and/or outcomes. Recently, we produced a non-invasive next-generation epigenetic clock trained using Infinium MethylationEPIC data from more than 8,000 diverse adult buccal samples. While this clock correlated with various health, lifestyle, and disease factors, we did not assess its ability to capture mortality. To address this gap, we applied CheekAge to the longitudinal Lothian Birth Cohorts of 1921 and 1936. Despite missing nearly half of its CpG inputs, CheekAge was significantly associated with mortality in this longitudinal blood dataset. Specifically, a change in one standard deviation corresponded to a hazard ratio (HR) of 1.21 (FDR q = 1.66e-6). CheekAge performed better than all first-generation clocks tested and displayed a comparable HR to the next-generation, blood-trained DNAm PhenoAge clock (HR = 1.23, q = 2.45e-9). To better understand the relative importance of each CheekAge input in blood, we iteratively removed each clock CpG and re-calculated the overall mortality association. The most significant effect came from omitting the CpG cg14386193, which is annotated to the gene *ALPK2*. Excluding this DNA methylation site increased the FDR value by nearly threefold (to 4.92e-06). We additionally performed enrichment analyses of the top annotated CpGs that impact mortality to better understand their associated biology. Taken together, we provide important validation for CheekAge and highlight novel CpGs that underlie a newly identified mortality association.

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Fundamental equations linking methylation dynamics to maximum lifespan in mammals

Steve Horvath ✉, Joshua Zhang, Amin Haghani, Ake T. Lu & Zhe Fei ✉

We describe a framework that addresses concern that the rate of change in any aging biomarker displays a trivial inverse relation with maximum lifespan. We apply this framework to methylation data from the Mammalian Methylation Consortium. We study the relationship of lifespan with the average rate of change in methylation (AROCM) from two datasets: one with 90 dog breeds and the other with 125 mammalian species. After examining 54 chromatin states, we conclude three key findings: First, a reciprocal relationship exists between the AROCM in bivalent promoter regions and maximum mammalian lifespan: AROCM $\propto$ 1/MaxLifespan. Second, the correlation between average methylation and age bears no relation to maximum lifespan, Cor(Methyl,Age) $\perp$ MaxLifespan. Third, the rate of methylation change in young animals is related to that in old animals: Young animals' AROCM $\propto$ Old AROCM. These findings critically hinge on the chromatin context, as different results emerge in other chromatin contexts.

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Probabilistic inference of epigenetic age acceleration from cellular dynamics

Jan K. Dabrowski, Emma J. Yang, Samuel J. C. Crofts, Robert F. Hillary, Daniel J. Simpson, Daniel L. McCartney, Riccardo E. Marioni, Kristina Kirschner, Eric Latorre-Crespo ✉ & Tamir Chandra ✉

The emergence of epigenetic predictors was a pivotal moment in geroscience, propelling the measurement and concept of biological aging into a quantitative era; however, while current epigenetic clocks show strong predictive power, they are data-driven in nature and are not based on the underlying biological mechanisms driving methylation dynamics. We show that predictions of these clocks are susceptible to several confounding non-age-related phenomena that make interpretation of these estimates and associations difficult. To address these limitations, we developed a probabilistic model describing methylation transitions at the cellular level. Our approach reveals two measurable components, acceleration and bias, which directly reflect perturbations of the underlying cellular dynamics. Acceleration is the proportional increase in the speed of methylation transitions across CpG sites, whereas bias corresponds to global changes in methylation levels. Using data from 15,900 participants from the Generation Scotland study, we develop a robust inference framework and show that these are two distinct processes confounding current epigenetic predictors. Our results show improved associations of acceleration and bias with physiological traits known to impact healthy aging, such as smoking and alcohol consumption, respectively. Furthermore, a genome-wide association study of epigenetic age acceleration identified seven genomic loci.

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PREPRINT

A universal limit for mammalian lifespan revealed by epigenetic entropy

Juan José Alba-Linares, Juan Ramón Tejedor, Agustín F. Fernández, Raúl F. Pérez, Mario F. Fraga

Age-associated DNA methylation patterns have shown strong associations with species lifespan. However, it remains unclear whether epigenetic noise levels can account for the observed differences between mammalian species. In this study, we examined the rate of loss of epigenetic information with age by measuring entropy at mammalian conserved CpG sites across a diverse range of species. Longer-lived mammals tend to gain fewer noisy CpGs with age, irrespective of whether these originate from hyper- or hypomethylation processes. Importantly, we found that the rate of epigenetic entropy gain declines in a linear fashion with species maximum lifespan, pointing to the existence of a universal limit for mammalian lifespan in the vicinity of 220 years.

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PREPRINT

Longitudinal changes in epigenetic clocks predict survival in the InCHIANTI cohort

Pei-Lun Kuo, Ann Zenobia Moore, Toshiko Tanaka, Daniel W Belsky, Ake Tzu-Hui Lu, Steve Horvath, Stefania Bandinelli, Luigi Ferrucci

Setting InCHIANTI, a population-based study of community dwelling individuals in Tuscany, Italy.

Participants 699 InCHIANTI study participants aged 21-95 years at baseline with longitudinal measurements of DNA methylation.

Exposure Baseline levels and longitudinal changes in seven epigenetic clocks, including two first-generation clocks developed using chronological age for reference (Hannum Clock, Horvath Clock), three second-generation clocks developed using time-to-death for references (DNAmPhenoAge, DNAmGrimAge, DNAmGrimAge Version 2), and two third-generation clocks developed using longitudinal rate of change of multiple phenotypes for reference (DunedinPOAm_38, DunedinPACE).

Main Outcomes and Measures Mortality was the primary outcome. Cox regression was used to estimate independent associations of baseline and longitudinal changes in epigenetic clocks with mortality.

Results Adjusting for age, sex, study sites, and epigenetic clock at the baseline, longitudinal changes of the following epigenetic clocks were associated with mortality: Hannum clock (aHR = 1.14, 95% CI:[1.03, 1.26]), DNAmPhenoAge (aHR = 1.23, 95% CI: [1.10,1.37]), DNAmGrimAge (aHR = 1.13, 95% CI: [1.02,1.26]), DNAmGrimAge Version 2 (aHR = 1.18, 95% CI:[1.06,1.31]), and DunedinPOAm_38 (aHR = 1.15, 95%CI: [1.01,1.30]).

Metformin decelerates aging clock in male monkeys

Yuanhan Yang [1,10,23] · Xiaoyong Lu [2,3,10,23] · Ning Liu [7,8,23] · … · Jing Qu [1,4,5,10,13,22] ✉ · Weiqi Zhang [2,3,4,5,10,22] ✉ · Guang-Hui Liu [1,4,5,6,10,22,25] ✉ … Show more

In a rigorous 40-month study, we evaluated the geroprotective effects of metformin on adult male cynomolgus monkeys, addressing a gap in primate aging research. The study encompassed a comprehensive suite of physiological, imaging, histological, and molecular evaluations, substantiating metformin's influence on delaying age-related phenotypes at the organismal level. Specifically, we leveraged pan-tissue transcriptomics, DNA methylomics, plasma proteomics, and metabolomics to develop innovative monkey aging clocks and applied these to gauge metformin's effects on aging. The results highlighted a significant slowing of aging indicators, notably a roughly 6-year regression in brain aging. Metformin exerts a substantial neuroprotective effect, preserving brain structure and enhancing cognitive ability. The geroprotective effects on primate neurons were partially mediated by the activation of Nrf2, a transcription factor with anti-oxidative capabilities. Our research pioneers the systemic reduction of multi-dimensional biological age in primates through metformin, paving the way for advancing pharmaceutical strategies against human aging.

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PREPRINT

High-dimensional Ageome Representations of Biological Aging across Functional Modules

Kejun Ying, Alexander Tyshkovskiy, Qingwen Chen, Eric Latorre-Crespo, Bohan Zhang, Hanna Liu, Benyamin Matei-Dediu, Jesse R. Poganik, Mahdi Moqri, Kristina Kirschne, Jessica Lasky-Su, Vadim N. Gladyshev

The aging process involves numerous molecular changes that lead to functional decline and increased disease and mortality risk. While epigenetic aging clocks have shown accuracy in predicting biological age, they typically provide single estimates for the samples and lack mechanistic insights. In this study, we challenge the paradigm that aging can be sufficiently described with a single biological age estimate. We describe Ageome, a computational framework for measuring the epigenetic age of thousands of molecular pathways simultaneously in mice and humans. Ageome is based on the premise that an organism's overall biological age can be approximated by the collective ages of its functional modules, which may age at different rates and have different biological ages. We show that, unlike conventional clocks, Ageome provides a high-dimensional representation of biological aging across cellular functions, enabling comprehensive assessment of aging dynamics within an individual, in a population, and across species. Application of Ageome to longevity intervention models revealed distinct patterns of pathway-specific age deceleration. Notably, cell reprogramming, while rejuvenating cells, also accelerated aging of some functional modules. When applied to human cohorts, Ageome demonstrated heterogeneity in predictive power for mortality risk, and some modules showed better performance in predicting the onset of age-related diseases, especially cancer, compared to existing clocks. Together, the Ageome framework offers a comprehensive and interpretable approach for assessing aging, providing insights into mechanisms and targets for intervention.

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PREPRINT

Pan-tissue Transcriptome Analysis Reveals Sex-dimorphic Human Aging

Siqi Wang, Danyue Dong, Xin Li, Zefeng Wang

Complex diseases often exhibit sex-dimorphism in morbidity and prognosis, many of which are age-related. However, the underlying mechanisms of the sex-dimorphic aging remain foggy, with limited studies across multiple tissues. We systematically analyzed ~17,000 transcriptomes from 35 human tissues to quantitatively evaluate the individual and combined contributions of sex and age to transcriptomic variations. We discovered extensive sex-dimorphisms during aging with distinct patterns of change in gene expression and alternative splicing (AS). Intriguingly, the male-biased age-associated AS events have a stronger association with Alzheimer's disease, and the females-biased events are often regulated by several sex-biased splicing factors that may be controlled by estrogen receptors. Breakpoint analysis showed sex-dimorphic aging rates that are significantly associated with decline of sex hormones, with males having a larger and earlier transcriptome change. Collectively, this study uncovered an essential role of sex during aging at the molecular and multi-tissue levels, providing insight into sex-dimorphic regulatory patterns.

Prebiotics improve frailty status in community-dwelling older individuals in a double-blind, randomized, controlled trial

Jie Yang,[1] Liming Hou,[1] Anhui Wang,[2] Lei Shang,[3] Xin Jia,[1] Rong Xu,[1] and Xiaoming Wang[1]

BACKGROUND. Frailty significantly affects morbidity and mortality rates in the older population (age >65 years). Age-related degenerative diseases are influenced by the intestinal microbiota. However, limited research exists on alterations in the intestinal microbiota in frail older individuals, and the effectiveness of prebiotic intervention for treating frailty remains uncertain.

OBJECTIVE. We sought to examine the biological characteristics of the intestinal microbiome in frail older individuals and assess changes in both frailty status and gut microbiota following intervention with a prebiotic blend consisting of inulin and oligofructose.

METHODS. The study consisted of 3 components: an observational analysis with a sample size of 1,693, a cross-sectional analysis (n = 300), and a multicenter double-blind, randomized, placebo-controlled trial (n = 200). Body composition, commonly used scales, biochemical markers, intestinal microbiota, and metabolites were examined in 3 groups of older individuals (nonfrail, prefrail, and frail). Subsequently, changes in these indicators were reevaluated after a 3-month intervention using the prebiotic mixture for the prefrail and frail groups.

RESULTS. The intervention utilizing a combination of prebiotics significantly improved frailty and renal function among the older population, leading to notable increases in protein levels, body fat percentage, walking speed, and grip strength. Additionally, it stimulated an elevation in gut probiotic count and induced alterations in microbial metabolite expression levels as well as corresponding metabolic pathways.

CONCLUSIONS. The findings suggest a potential link between changes in the gut microbiota and frailty in older adults. Prebiotics have the potential to modify the gut microbiota and metabolome, resulting in improved frailty status and prevention of its occurrence.

DNA damage (8-OHdG) and telomere length in captive Psittacidae birds with different longevity

Aging is a complex process influenced by internal and external factors. Oxidative stress damages DNA, leading to 8-hydroxy-2′ deoxyguanosine formation (8-OHdG). Telomere shortening is considered a biomarker of aging and oxidative stress may enhance its attrition. The ability to manage and repair oxidative stress varies among species and life histories. Avian species, such as Psittacidae birds, exhibit exceptional lifespans despite their physiological characteristics that might suggest otherwise. This study investigates 8-OHdG levels in serum samples from long- and short-lived birds of the order Psittaciformes, examining their relationship with telomere length and antioxidant capacity based on lifespan strategies. Among 43 individuals analyzed 26 belonged to the "long-lived species" group and 17 belonged to the "short-lived species" one. Relative telomere length (rTL) was measured in DNA isolated from whole blood by qPCR, and oxidative stress markers, such as Total Antioxidant Capacity (TAC) and 8-OHdG, were determined by spectrophotometry in serum samples. Long-lived birds had longer rTL than short-lived ones [1.308 $\pm$ 0.11 vs. 0.565 $\pm$ 0.13, ($p < 0.001$)]. On the contrary, short-lived birds showed more DNA damage than their counterparts [3.847 $\pm$ 0.351 vs. 2.012 $\pm$ 0.308, respectively, ($p < 0.001$)]. Old birds had shorter rTL than young ones, for both longevity groups ($p < 0.001$). Although no correlation was found between 8-OHdG levels and age, nor 8-OHdG and telomere length, long-lived birds exhibited 75.42-unit increased TAC levels when increased 8-OHdG concentrations ($p = 0.046$). These findings highlight distinct patterns of telomere length and oxidative stress influenced by lifespan strategies among avian longevity groups.

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PREPRINT

Genetic associations with human longevity are enriched for oncogenic genes

Junyoung Park, Andrés Peña-Tauber, Lia Talozzi, Michael D. Greicius, Yann Le Guen

Human lifespan is shaped by both genetic and environmental exposures and their interaction. To enable precision health, it is essential to understand how genetic variants contribute to earlier death or prolonged survival. In this study, we tested the association of common genetic variants and the burden of rare non-synonymous variants in a survival analysis, using age-at-death (N = 35,551, median [min, max] = 72.4 [40.9, 85.2]), and last-known-age (N = 358,282, median [min, max] = 71.9 [52.6, 88.7]), in European ancestry participants of the UK Biobank. The associations we identified seemed predominantly driven by cancer, likely due to the age range of the cohort. Common variant analysis highlighted three longevity-associated loci: *APOE*, *ZSCAN23*, and *MUC5B*. We identified six genes whose burden of loss-of-function variants is significantly associated with reduced lifespan: *TET2*, *ATM*, *BRCA2*, *CKMT1B*, *BRCA1* and *ASXL1*. Additionally, in eight genes, the burden of pathogenic missense variants was associated with reduced lifespan: *DNMT3A*, *SF3B1*, *CHL1*, *TET2*, *PTEN*, *SOX21*, *TP53* and *SRSF2*. Most of these genes have previously been linked to oncogenic-related pathways and some are linked to and are known to harbor somatic variants that predispose to clonal hematopoiesis. A direction-agnostic (SKAT-O) approach additionally identified significant associations with *C1orf52*, *TERT*, *IDH2*, and *RLIM*, highlighting a link between telomerase function and longevity as well as identifying additional oncogenic genes.

Our results emphasize the importance of understanding genetic factors driving the most prevalent causes of mortality at a population level, highlighting the potential of early genetic testing to identify germline and somatic variants increasing one's susceptibility to cancer and/or early death.

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PREPRINT

The Greenland shark (*Somniosus microcephalus*) genome provides insights into extreme longevity

Arne Sahm, Alexander Cherkasov, Hequn Liu, Danila Voronov, Kanstantsin Siniuk, Robert Schwarz, Oliver Ohlenschläger, Silke Förste, Martin Bens, Marco Groth, Ivonne Görlich, Sonia Paturej, Sven Klages, Bjoern Braendl, Jesper Olsen, Peter Bushnell, Amalie Bech Poulsen, Sara Ferrando, Fulvio Garibaldi, Davide Lorenzo Drago, Eva Terzibasi Tozzini, Franz-Josef Müller, Martin Fischer, Helene Kretzmer, Paolo Domenici, John Fleng Steffensen, Alessandro Cellerino, Steve Hoffmann

The Greenland shark (*Somniosus microcephalus*) is the longest-lived vertebrate known, with an estimated lifespan of ~ 400 years. Here, we present a chromosome-level assembly of the 6.45 Gb Greenland shark, rendering it one of the largest non-tetrapod genomes sequenced so far. Expansion of the genome is mostly accounted for by a substantial expansion of transposable elements. Using public shark genomes as a comparison, we found that genes specifically duplicated in the Greenland shark form a functionally connected network enriched for DNA repair function. Furthermore, we identified a unique insertion in the conserved C-terminal region of the key tumor suppressor p53. We also provide a public browser to explore its genome.

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Safety and efficacy of rapamycin on healthspan metrics after one year: PEARL Trial Results

Girish Harinath, Virginia Lee, Andy Nyquist, Mauricio Moel, Stefanie L. Morgan, Anar Isman, Sajad Zalzala

Background Low-dose rapamycin promotes longevity in mice, but clinical safety and longevity data effects in humans remain limited.

Objectives Evaluate the long-term safety of intermittent low-dose rapamycin in a healthy, normative-aging human cohort.

Design This decentralized double-blinded, randomized, placebo-controlled trial (NCT04488601, registered 2020-07-28) was performed over 48 weeks. Participants received placebo, 5mg or 10mg compounded rapamycin (equivalent to 1.43mg or 2.86mg of generic formulations) weekly. The primary outcome measure was visceral adiposity (by DXA scan), secondary outcomes were blood biomarkers, and lean tissue and bone mineral content (by DXA scan). Established surveys were utilized to evaluate health and well-being. Safety was assessed through adverse events and blood biomarker monitoring.

Results Adverse and serious adverse events were similar across all groups. Visceral adiposity did not change significantly (η_p^2=0.001, p=0.942), and changes in blood biomarkers remained within normal ranges. Lean tissue mass (ε^2=0.202, p=0.013) and self-reported pain (ε^2=0.168, p=0.015) improved significantly for women using 10mg rapamycin. Trends of improvement in bone mineral density were observed in males using 10mg rapamycin (ε^2=0.221, p=0.061), but no other significant effects were observed.

Conclusions Low-dose, intermittent rapamycin administration over 48 weeks is relatively safe in healthy, normative-aging adults, and was associated with significant improvements in lean tissue mass and pain in women. Future work will evaluate benefits of a broader range of rapamycin doses on healthspan metrics for longevity, and will aim to more comprehensively establish efficacy.

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PREPRINT

ElixirSeeker:A Machine Learning Framework Utilizing Attention-Driven Fusion of Molecular Fingerprints for the Discovery of Anti-Aging Compounds

Yan Pan, Hongxia Cai, Fang Ye, Wentao Xu, Zhihang Huang, Jingyuan Zhu, Yiwen Gong, Yutong Li, Anastasia Ngozi Ezemaduka, Shan Gao, Shunqi Liu, Guojun Li, Hao Li, Jing Yang, Junyu Ning, Bo Xian

Despite the growing interest in anti-aging drug development, high cost and low success rate pose a significant challenge. We present ElixirSeeker, a new machine-learning framework designed to help speed up the discovery of potential anti-aging compounds by utilizing the attention-driven fusion of molecular fingerprints. Our approach integrates molecular fingerprints generated by different algorithms and utilizes XGBoost to select optimal fingerprint lengths. Subsequently, we assign weights to the molecular fingerprints and employ Kernel Principal Component Analysis (KPCA) to reduce dimensionality, integrating different attention-driven methods. We trained the algorithm using DrugAge database. Our comprehensive analyses demonstrate that 64-bit Attention-ElixirFP maintains high predictive accuracy and F1 score while minimizing computational cost. Using ElixirSeeker to screen external compound databases, we identified a number of promising candidate anti-aging drugs. We tested top 6 hits and found that 4 of these compounds extend the lifespan of *Caenorhabditis elegans*, including Polyphyllin VI, Medrysone, Thymoquinone and Medrysone. This study illustrates that attention-driven fusion of fingerprints maximizes the learning of molecular activity features, providing a novel approach for high-throughput machine learning discovery of anti-aging molecules.

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PREPRINT

Longitudinal Multi-omic Immune Profiling Reveals Age-Related Immune Cell Dynamics in Healthy Adults

The generation and maintenance of protective immunity is a dynamic interplay between host and environment that is impacted by age. Understanding fundamental changes in the healthy immune system that occur over a lifespan is critical in developing interventions for age-related susceptibility to infections and diseases. Here, we use multi-omic profiling (scRNA-seq, proteomics, flow cytometry) to examined human peripheral immunity in over 300 healthy adults, with 96 young and older adults followed over two years with yearly vaccination. The resulting resource includes scRNA-seq datasets of >16 million PBMCs, interrogating 71 immune cell subsets from our new Immune Health Atlas. This study allows unique insights into the composition and transcriptional state of immune cells at homeostasis, with vaccine perturbation, and across age. We find that T cells specifically accumulate age-related transcriptional changes more than other immune cells, independent from inflammation and chronic perturbation. Moreover, impaired memory B cell responses to vaccination are linked to a Th2-like state shift in older adults' memory CD4 T cells, revealing possible mechanisms of immune dysregulation during healthy human aging. This extensive resource is provided with a suite of exploration tools at https://apps.allenimmunology.org/aifi/insights/dynamics-imm-health-age/ to enhance data accessibility and further the understanding of immune health across age.

PATENT

Title: **Plasma metabolome as a predictor of biological aging**

Document Type and Number: United States Patent 12080432

Abstract: Chronological age is an important predictor of morbidity and mortality, however it is unable to account for heterogeneity in the decline of physiological function and health with advancing age. Several attempts have been made to instead define a "biological age" using multiple physiological parameters in order to account for variation in the trajectory of human aging; however, these methods require technical expertise and are likely too time-intensive and costly to be implemented into clinical practice. Accordingly, a metabolomic signature of biological aging was developed that can predict changes in physiological function with the convenience of a blood sample. A weighted model of biological age was generated based on multiple clinical and physiological measures in a large group of healthy adults and was then applied to a cohort of healthy older adults who were tracked longitudinally over a 5-10 year timeframe. Plasma metabolomic signatures were identified that were associated with biological age, including some that could predict whether individuals would age at a faster or slower rate. These results not only have clinical implications by providing a simple blood-based assay of biological aging, but also provide insight into the molecular mechanisms underlying human healthspan.

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Stochasticity in Dietary Restriction-Mediated Lifespan Outcomes in *Drosophila*

Olivia L. Mosley, Joel A. Villa, Advaitha Kamalakkannan, Eliyashaib James, Jessica M. Hoffman, Yang Lyu

Dietary restriction (DR) is widely considered to be one of the most potent approaches to extend healthy lifespan across various species, yet it has become increasingly apparent that DR-mediated longevity is influenced by biological and non-biological factors. We propose that current priorities in the field should include understanding the relative contributions of these factors to elucidate the mechanisms underlying the beneficial effects of DR. Our work conducted in two laboratories, represents an attempt to unify DR protocols in *Drosophila* and to investigate the stochastic effects of DR. Across 64 pairs of survival data (DR/ad libitum, or AL), we find that DR does not universally extend lifespan. Specifically, we observed that DR conferred a significant lifespan extension in only 26.7% (17/64) of pairs. Our pooled data show that the overall lifespan difference between DR and AL groups is statistically significant, but the median lifespan increase under DR (7.1%) is small. The effects of DR were overshadowed by stochastic factors and genotype. Future research efforts directed toward gaining a comprehensive understanding of DR-dependent mechanisms should focus on unraveling the interactions between genetic and environmental factors. This is essential for developing personalized healthspan-extending interventions and optimizing dietary recommendations for individual genetic profiles.

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Isolating the Direct Effects of Growth Hormone on Lifespan and Metabolism

Alexander Tate Lasher, Kaimao Liu, Michael Fitch, Liou Y. Sun

Prior studies show that disrupting somatotropic axis components extends laboratory mouse lifespan, but confounding effects of additional genes and hormones obscure the specific impact of growth hormone (GH) on longevity. We address this issue by using mice with a specific knockout of the GH gene, revealing that disrupting GH alone substantially increases lifespan. The longevity effects are accompanied by altered metabolic fuel utilization, directly linking GH action to aging mechanisms.

C. elegans aging research

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A rapid in vivo pipeline to identify small molecule inhibitors of amyloid aggregation

Muntasir Kamal, Jessica Knox, Robert I. Horne, Om Shanker Tiwari, Andrew R. Burns, Duhyun Han, Davide Levy, Dana Laor Bar-Yosef, Ehud Gazit, Michele Vendruscolo & Peter J. Roy

Amyloids are associated with over 50 human diseases and have inspired significant effort to identify small molecule remedies. Here, we present an in vivo platform that efficiently yields small molecule inhibitors of amyloid formation. We previously identified small molecules that kill the nematode *C. elegans* by forming membrane-piercing crystals in the pharynx cuticle, which is rich in amyloid-like material. We show here that many of these molecules are known amyloid-binders whose crystal-formation in the pharynx can be blocked by amyloid-binding dyes. We asked whether this phenomenon could be exploited to identify molecules that interfere with the ability of amyloids to seed higher-order structures. We therefore screened 2560 compounds and found 85 crystal suppressors, 47% of which inhibit amyloid formation. This hit rate far exceeds other screening methodologies. Hence, in vivo screens for suppressors of crystal formation in *C. elegans* can efficiently reveal small molecules with amyloid-inhibiting potential.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Artificial intelligence for the study of human ageing: a systematic literature review

As society experiences accelerated ageing, understanding the complex biological processes of human ageing, which are affected by a large number of variables and factors, becomes increasingly crucial. Artificial intelligence (AI) presents a promising avenue for ageing research, offering the ability to detect patterns, make accurate predictions, and extract valuable insights from large volumes of complex, heterogeneous data. As ageing research increasingly leverages AI techniques, we present a timely systematic literature review to explore the current state-of-the-art in this field following a rigorous and transparent review methodology. As a result, a total of 77 articles have been identified, summarised, and categorised based on their characteristics. AI techniques, such as machine learning and deep learning, have been extensively used to analyse diverse datasets, comprising imaging, genetic, behavioural, and contextual data. Findings showcase the potential of AI in predicting age-related outcomes, developing ageing biomarkers, and determining factors associated with healthy ageing. However, challenges related to data quality, interpretability of AI models, and privacy and ethical considerations have also been identified. Despite the advancements, novel approaches suggest that there is still room for improvement to provide personalised AI-driven healthcare services and promote active ageing initiatives with the ultimate goal of enhancing the quality of life and well-being of older adults.

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A Pragmatic Approach to Introducing Translational Geroscience Into the Clinic: A Paradigm Based on the Incremental Progression of Aging-Related Clinical Research

FREE

Daniel E Forman, MD ✉, Robert J Pignolo, MD, PhD ✉

Geroscience posits that molecular drivers underlie the aging process. Gerotherapeutics entail strategies to counter molecular drivers of aging to reduce the chronic diseases and geriatric syndromes they trigger. Although the concept of gerotherapeutics for prevention has generated much excitement, the implications of prescribing potentially harmful medications to older adults who are "healthy" have been associated with many delays. Concerns regarding safety and valid endpoints have contributed to holdups. In contrast, it has been relatively easier to implement trials of medications with gerotherapeutic properties as novel approaches to remedy disease. In these applications, the risks of the medications are easier to justify when therapeutic benefits are perceived as outweighing the harms of the disease. Likewise, metrics of effective disease treatments are often seen as more reliable and quantifiable than metrics of health prolongation. Overall, clarifying geroscience mechanisms in disease therapeutic applications provides key opportunities to advance translational geroscience, especially as preventive geroscience trials are often encumbered. In this review, gerotherapeutic benefits of canakinumab, cholchicine, and zoledronic acid as parts of disease management are considered. Longevity Clinics and other opportunities to advance translational geroscience as parts of contemporary care are also discussed.

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Integrating Machine Learning with Multi-Omics Technologies in Geroscience: Towards Personalized Medicine

by Nikolaos Theodorakis [1,2], Georgios Feretzakis [3], Lazaros Tzelves [4], Evgenia Paxinou [3], Christos Hitas [1], Georgia Vamvakou [1], Vassilios S. Verykios [3,*] and Maria Nikolaou [1]

Aging is a fundamental biological process characterized by a progressive decline in physiological functions and an increased susceptibility to diseases. Understanding aging at the molecular level is crucial for developing interventions that could delay or reverse its effects. This review explores the integration of machine learning (ML) with multi-omics technologies—including genomics, transcriptomics, epigenomics, proteomics, and metabolomics—in studying the molecular hallmarks of aging to develop personalized medicine interventions. These hallmarks include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis. Using ML to analyze big and complex datasets helps uncover detailed molecular interactions and pathways that play a role in aging. The advances of ML can facilitate the discovery of biomarkers and therapeutic targets, offering insights into personalized anti-aging strategies. With these developments, the future points toward a better understanding of the aging process, aiming ultimately to promote healthy aging and extend life expectancy.

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Therapeutic targeting of senescent cells in the CNS

Markus Riessland, Methodios Ximerakis, Andrew A. Jarjour, Bin Zhang & Miranda E. Orr

Senescent cells accumulate throughout the body with advanced age, diseases and chronic conditions. They negatively impact health and function of multiple systems, including the central nervous system (CNS). Therapies that target senescent cells, broadly referred to as senotherapeutics, recently emerged as potentially important treatment strategies for the CNS. Promising therapeutic approaches involve clearing senescent cells by disarming their pro-survival pathways with 'senolytics'; or dampening their toxic senescence-associated secretory phenotype (SASP) using 'senomorphics'. Following the pioneering discovery of first-generation senolytics dasatinib and quercetin, dozens of additional therapies have been identified, and several promising targets are under investigation. Although potentially transformative, senotherapies are still in early stages and require thorough testing to ensure reliable target engagement, specificity, safety and efficacy. The limited brain penetrance and potential toxic side effects of CNS-acting senotherapeutics pose challenges for drug development and translation to the clinic. This Review assesses the potential impact of senotherapeutics for neurological conditions by summarizing preclinical evidence, innovative methods for target and biomarker identification, academic and industry drug development pipelines and progress in clinical trials.

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Selective autophagy: a therapeutic target for healthy aging?

Manastireanu, Denisa Mihaela[#]; Salazar, Nicolle Andrea[#]; Bejarano, Eloy[*]; Nieto-Torres, José Luis[*]

At the molecular level, aging is characterized by the accumulation of unresolved damage to essential components of cells, such as DNA, proteins, and organelles, which over time contributes to cellular malfunction and the onset of age-associated diseases. To counteract this detrimental process, cells are equipped with protective mechanisms that prevent or reverse molecular damage. Arguably, the cellular recycling process of autophagy is one of the most versatile repair pathways that cells display. Autophagy allows the degradation and recycling of surplus and/or damaged cytosolic components, which otherwise may pose a threat to cellular homeostasis. This is achieved via the delivery of cytoplasmic components to lysosomes, which are organelles equipped with a sophisticated set of degradative enzymes that eliminate cellular waste and transform it into building blocks to maintain cellular function. There are different autophagic routes, known as macroautophagy, microautophagy, and chaperone-mediated autophagy, via which a variety of cellular components, ranging from organelles, DNA, proteins, and lipids, can be delivered to lysosomes for proper turnover. While these autophagy pathways operate to maintain cellular homeostasis over time, an overall deficit in autophagic function leads to aging acceleration and is correlated with the onset of age-related diseases. However, the extent to which specific autophagic pathways and the selective degradation of cellular components contribute to aging, as well as the molecular interplay among the different routes, remain elusive and constitute a main research direction. This narrative review summarizes the implications of autophagy subtypes in aging, focusing on the contributions of each pathway to select cargo degradation and their interaction, and highlights future lines of research toward identifying potential therapeutic routes for the amelioration of selective autophagy to promote healthy aging.

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Oxygen, the Paradox of Life and the Eye

Dario Rusciano [1], Paola Bagnoli [2]

Oxidative stress, caused by the formation of free radicals, such as reactive oxygen species (ROS), leads to cell and tissue degradation, contributing to various diseases and aging. While oxygen is essential for aerobic organisms, it inevitably causes oxidative stress. Antioxidants protect against damage from free radicals, and oxidative stress arises when an imbalance occurs between free radical production and antioxidant defenses. However, when investigating whether an excess of antioxidants, almost eliminating oxidative stress, could benefit aging and disease susceptibility, it was observed that a basic level of oxidative stress appears necessary to maintain the correct homeostasis of tissues and organs and life in general. Therefore, this review aimed to compile the most significant and recent papers characterizing and describing the dual role of oxygen as a molecule essential for life and as a precursor of oxidative stress, which can be detrimental to life. We conducted targeted searches in PubMed and Google browsers to gather all relevant papers. We then focused on the eye, an organ particularly vulnerable due to its high metabolic activity combined with direct exposure to light and environmental pollutants, which produces a substantial number of free radicals (mainly ROS). We present a curated selection of relevant literature describing the main ocular pathologies of the posterior and anterior segments of the eye, highlighting oxidative stress as a significant contributing factor. Additionally, we report how endogenous and exogenous antioxidants can mitigate the development and progression of these diseases. Finally, we consider a frequently overlooked aspect: the balance between oxidants and antioxidants in maintaining the homeostatic equilibrium of tissues and organs. It is widely recognized that when oxidants overwhelm antioxidants, oxidative stress occurs, leading to negative consequences for the organism's homeostasis. However, we emphasize that a similarly dangerous situation can arise when the presence of antioxidants overwhelms the production of free radicals, drastically reducing their amount and adversely affecting aging and longevity. Unfortunately, no specific studies have addressed this particular situation in the eye.

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The role of mitochondria in cytokine and chemokine signalling during ageing

Maria Kalykaki [a], Teresa Rubio-Tomás [a], Nektarios Tavernarakis [a b]

Ageing is accompanied by a persistent, low-level inflammation, termed "inflammageing", which contributes to the pathogenesis of age-related diseases. Mitochondria fulfil multiple roles in host immune responses, while mitochondrial dysfunction, a hallmark of ageing, has been shown to promote chronic inflammatory states by regulating the production of cytokines and chemokines. In this review, we aim to disentangle the molecular mechanisms underlying this process. We describe the role of mitochondrial signalling components such as mitochondrial DNA, mitochondrial RNA, N-formylated peptides, ROS, cardiolipin, cytochrome c, mitochondrial metabolites, potassium efflux and mitochondrial calcium in the age-related immune system activation. Furthermore, we discuss the effect of age-related decline in mitochondrial quality control mechanisms, including mitochondrial biogenesis, dynamics, mitophagy and UPR^{mt}, in inflammatory states upon ageing. In addition, we focus on the dynamic relationship between mitochondrial dysfunction and cellular senescence and its role in regulating the secretion of pro-inflammatory molecules by senescent cells. Finally, we review the existing literature regarding mitochondrial dysfunction and inflammation in specific age-related pathological conditions, including neurodegenerative diseases (Alzheimer's and Parkinson's disease, and amyotrophic lateral sclerosis), osteoarthritis and sarcopenia.

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c-Jun N-terminal kinase signaling in aging

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Klaudia Jomova[5] Marian Valko[6]  Qinghua Wu[1,3*] Kamil Kuca[3,7*]

Aging encompasses a wide array of detrimental effects that compromise physiological functions, elevate the risk of chronic diseases, and impair cognitive abilities. However, the precise underlying mechanisms, particularly the involvement of specific molecular regulatory proteins in the aging process, remain insufficiently understood. Emerging evidence indicates that c-Jun N-terminal kinase (JNK) serves as a potential regulator within the intricate molecular clock governing aging-related processes. JNK demonstrates the ability to diminish telomerase reverse transcriptase activity, elevate β-galactosidase activity, and induce telomere shortening, thereby contributing to immune system aging. Moreover, the circadian rhythm protein is implicated in JNK-mediated aging. Through this comprehensive review, we meticulously elucidate the intricate regulatory mechanisms orchestrated by JNK signaling in aging processes, offering unprecedented molecular insights with significant implications and highlighting potential therapeutic targets. We also explore the translational impact of targeting JNK signaling for interventions aimed at extending healthspan and promoting longevity.

OTHER RESEARCH & REVIEWS

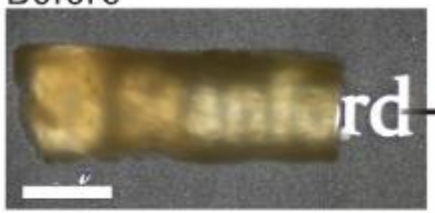
Achieving optical transparency in live animals with absorbing molecules

Optical imaging plays a central role in biology and medicine but is hindered by light scattering in live tissue. We report the counterintuitive observation that strongly absorbing molecules can achieve optical transparency in live animals. We explored the physics behind this observation and found that when strongly absorbing molecules dissolve in water, they can modify the refractive index of the aqueous medium through the Kramers-Kronig relations to match that of high-index tissue components such as lipids. We have demonstrated that our straightforward approach can reversibly render a live mouse body transparent to allow visualization of a wide range of deep-seated structures and activities. This work suggests that the search for high-performance optical clearing agents should focus on strongly absorbing molecules.

Achieving optical transparency in live animals with absorbing molecules

Ex vivo chicken breast tissue

Before



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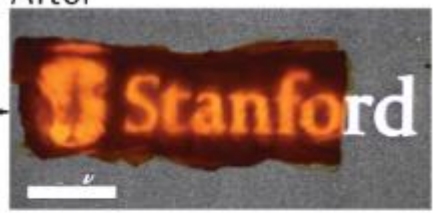
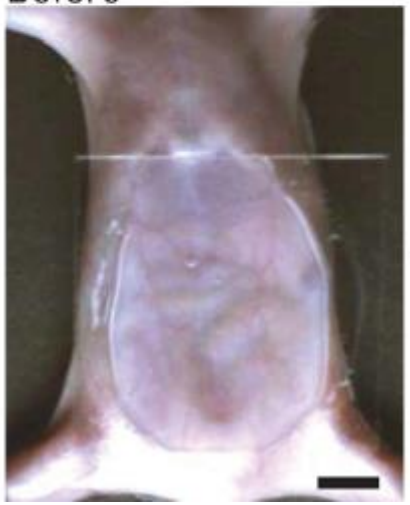


In vivo imaging of internal organs

Before



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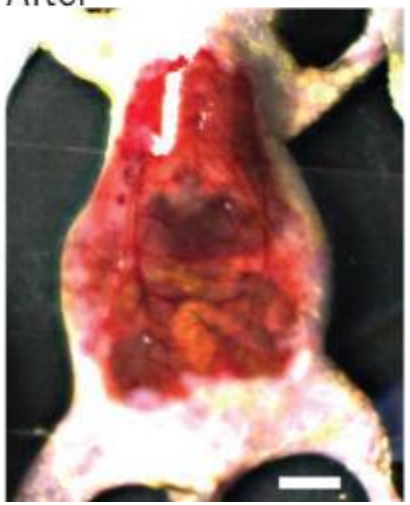

Spaceflight-induced contractile and mitochondrial dysfunction in an automated heart-on-a-chip platform

Devin B. Mair, Jonathan H. Tsui, Ty Higashi, +9, and Deok-Ho Kim Authors Info & Affiliations

With current plans for manned missions to Mars and beyond, the need to better understand, prevent, and counteract the harmful effects of long-duration spaceflight on the body is becoming increasingly important. In this study, an automated heart-on-a-chip platform was flown to the International Space Station on a 1-mo mission during which contractile cardiac function was monitored in real-time. Upon return to Earth, engineered human heart tissues (EHTs) were further analyzed with ultrastructural imaging and RNA sequencing to investigate the impact of prolonged microgravity on cardiomyocyte function and health. Spaceflight EHTs exhibited significantly reduced twitch forces, increased incidences of arrhythmias, and increased signs of sarcomere disruption and mitochondrial damage. Transcriptomic analyses showed an up-regulation of genes and pathways associated with metabolic disorders, heart failure, oxidative stress, and inflammation, while genes related to contractility and calcium signaling showed significant down-regulation. Finally, in silico modeling revealed a potential link between oxidative stress and mitochondrial dysfunction that corresponded with RNA sequencing results. This represents an in vitro model to faithfully reproduce the adverse effects of spaceflight on three-dimensional (3D)-engineered heart tissue.